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CASE REPORTS

EDITORIAL

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Toxicological services in the Sri Lankan context: burden, challenges and way forward

Manilgama SR[1], Hettiarachchi NM[2], Liyanage ADMD[3]

Preamble

Toxicology is a crucial yet often overlooked discipline that plays a vital role in healthcare, particularly in countries like Sri Lanka, where acute poisoning poses a significant public health challenge. Exposure to toxins or toxic doses of substances contribute significantly to emergency admissions, intensive care unit (ICU) utilisation and mortality. The use of pesticides in agriculture, easy access to widely known toxic plants such as yellow oleander, high incidence of snake envenomation, increasing incidence of pharmaceutical drug overdose and substance abuse make toxicology a priority area when expanding healthcare services.(1-3)

Toxicological services refer to specialised medical, laboratory, and advisory services dedicated for the prevention, diagnosis, management, and research of toxic exposures and poisoning. These services play a critical role in clinical care, public health, forensic investigations and environmental safety.

Burden and impact on healthcare due to toxic exposures and poisoning

Sri Lanka has one of the highest rates of self-poisoning in South Asia. Studies indicate that pesticide ingestion is the most common method of self-harm in rural communities.The use of organophosphate (OP) pesticides like chlorpyrifos and dimethoate has been linked to a significant proportion of poisoning-related deaths. The toxic effects of these substances include cholinergic crisis, respiratory failure, and cardiovascular instability, requiring intensive medical care.(4)

A study by Noghrehchi et al. which explored the association of pesticide bans with pesticide self-poisonings and in-hospital deaths in Sri Lanka, included 79 780 patients with self-poisoning from 2002 to 2019. They demonstrated that pesticide ingestion accounted for 36.8% of all the admissions and 72.9% of all deaths.(2)

In addition to self-poisoning, accidental poisoning is a concern, particularly among children. Household chemicals, improperly stored pesticides, and toxic plants contribute to unintentional exposures. The ingestion of yellow oleander (*Thevetia peruviana*) seeds, which contain potent cardiac glycosides, is a well-documented cause of life-threatening arrhythmias in Sri Lanka, notorious for self-harm attempts as well as accidental poisoning. A multicentre study in Sri Lanka which involved 1621 children who received in-ward treatment for acute poisoning revealed that the majority were in the preschool age group. Household chemicals were incriminated in 30.6% of the poisonings and mortality was 0.4%.(5)

Occupational exposure to toxic substances, especially among farmers and industrial workers, is another issue. Many farmers handle pesticides without adequate personal protective equipment (PPE), leading to chronic toxicity or acute poisoning.(6)

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A systematic review on the global distribution of unintentional acute pesticide poisoning estimated that about 385 million non-fatal cases and 11 000 deaths occur per year. (7) Although country specific data is not available, reasonable assumptions could be made on the magnitude of the burden in Sri Lanka, considering its agricultural background.

Similarly, industrial workers exposed to heavy metals, solvents, and insecticides are at risk of developing long-term health complications, including neurotoxicity and organ damage.(8)

Snake envenomation remains a major contributor to poisoning-related morbidity and mortality in Sri Lanka. A study in 2016 revealed over 80 000 bites, 30,000 envenomations and 400 deaths in the preceding 12 months. Species such as Russell's viper (*Daboia russelii*), the cobra (*Naja naja*), and the krait (*Bungarus caeruleus*) are the predominantly incriminated species. These bites can cause severe complications, including systemic bleeding, paralysis, renal failure, and respiratory distress.(9)

While pesticide poisoning has traditionally been the leading cause of poisoning-related hospital admissions, a growing concern is the increasing incidence of medication overdoses. This shift reflects broader societal changes, including the widespread use of pharmaceuticals without sufficient regulation and growing patterns of self-medication, particularly among young adults. Overdoses involving common medications such as paracetamol, benzodiazepines, antidepressants, and opioids have been on the rise, contributing to a significant number of emergency department visits and admissions in both urban and rural settings.(10,11)

Prolonged hospital stays for poisoning cases also increase healthcare costs and strain hospital resources. Patients with toxin-induced kidney failure may require dialysis, while those with severe cardiotoxicity (e.g., from yellow oleander poisoning) may need continuous cardiac monitoring and advanced interventions. Given the already limited number of ICU beds in Sri Lanka, the high demand for critical care due to poisoning cases significantly affects the healthcare system's ability to treat other critically ill patients. A study by Wickramasinghe et al. to estimate the direct financial costs to the Sri Lanka Ministry of Health for treating patients after self-poisoning, particularly from pesticides, demonstrated that the cost of treating self-poisoned patients in all of Sri Lanka in 2004 was US$ 866,304.(12) Another study showed that the average per patient cost of treating pesticide self poisoning at a government hospital in Sri Lanka amounted to US$ 85.3 in 2016. (10)

Toxicological services in Sri Lanka

Toxicological services in Sri Lanka are yet to develop in terms of structure and organised delivery if it is to effectively tackle the full volume of service needs. The high incidence of toxic exposures and high proportion of patients requiring intensive care have increased the burden on an already strained healthcare system. Many hospitals lack essential diagnostic tools, standardised treatment protocols, and a reliable supply of antidotes.

National Poisons Information Centre

The National Poisons Information Centre (NPIC) at the National Hospital of Sri Lanka (NHSL) is the country's primary toxicology information resource. It provides 24-hour guidance to healthcare professionals on poisoning management.(13)

In addition, Sri Lanka has a 24-hour National Poisons Information Centre hotline (011-2686143), which provides real-time medical advice on poisoning management. The hotline assists both medical professionals and the general public in handling poisoning emergencies, offering guidance on first aid measures, antidote administration, and hospital referrals. Despite its availability, public utilisation of this vital service remains low due to a lack of awareness. More efforts are needed to promote this resource and encourage its use in cases of suspected poisoning.

"Management of Poisoning" authored by Professor Ravindra Fernando is a renowned publication of the National Poison Information Centre that serves as a handbook in hospitals nationwide.

Toxicology Unit at Teaching Hospital Peradeniya

The Toxicology Unit at Teaching Hospital Peradeniya offers a dedicated ward, high dependency unit (HDU) and intensive care unit (ICU) to toxicology patients. This unit serves as the national referral unit for managing complex toxicology cases, offering expert consultations for healthcare providers and direct care for patients suffering from severe poisonings. As an additional service the Unit has launched a National Poison Information Hotline to provide expert guidance on poisoning cases.

Toxicology laboratory services

Toxicology laboratory services are limited in Sri Lanka. Routine toxicological screening is not widely available in most hospitals, and confirmatory tests for substances such as pesticides, plant toxins, and pharmaceuticals are mainly conducted at research institutions rather than clinical settings. This lack of real-time toxicology testing hinders rapid diagnosis and treatment.

Antidote Availability

Atropine, activated charcoal, and pralidoxime are available at tertiary care hospitals while smaller hospitals often face shortages due to irregular supplies. There is a supply of N-acetylcysteine (NAC) for paracetamol poisoning and chelating agents for heavy metal poisoning, although inconsistent.

Training and Expertise

Sri Lanka has very few trained clinical toxicologists. However there are learning opportunities offered at the Postgraduate Institute of Medicine (PGIM) Colombo; Postgraduate diploma in toxicology and Msc in Medical Toxicology. Recently a diploma in forensic medicine and toxicology has been introduced by the Forensic Medicine Department of the Faculty of Medical Sciences, University of Sri Jayewardenepura for GCE advanced level qualified students. This highlights the emerging interest and recognition of the training needs in toxicology.

Challenges in prevention, diagnosis and management

One of the biggest challenges in toxicology management in Sri Lanka is the lack of point-of-care toxicology testing. Most hospitals do not have access to rapid diagnostic tests that can detect specific toxins in biological samples. This results in delays in identifying the toxic agent and can lead to inappropriate treatment, increasing the risk of complications.

Another major issue is the limited availability of antidotes. While some tertiary hospitals stock essential antidotes, many district and peripheral hospitals face frequent shortages. This is particularly problematic for organophosphate poisoning, where atropine and pralidoxime (PAM) are critical for treatment. Inconsistent supply chains also affect the availability of anti-snake venom (ASV), leading to delays in treatment, particularly in rural areas where snakebites are most common.

Management of poisoning cases also varies widely between hospitals, with some institutions lacking standardised treatment protocols. This inconsistency in clinical management leads to different outcomes depending on the location of the hospital and the expertise of the attending physician. The most challenging aspect of all remains the approach to a patient with unknown poisoning. This has been methodically addressed in “a clinical guide to identifying toxidromes” algorithm presented in Essential Clinical Toxicology published by Sri Lanka College of Internal Medicine in collaboration with the Ministry of Health Sri Lanka.(14)

Regional poison information centers are lacking, making it difficult for peripheral hospitals to access real-time toxicology advice. Establishing regional poison centers would improve poisoning case management in rural and underserved areas.

A significant challenge in Sri Lanka is the general lack of public awareness regarding the handling of toxic substances and response to exposures. An unfortunate example can be drawn from how inadequate information about fumigation safety protocols and lack of clear public warnings led to the recent fatal cases of suspected phosphine gas poisoning among tourists in Colombo. The general public, including hospitality sector workers and residents, often remain uninformed about the risks posed by certain chemicals and the necessary precautions to take in case of exposure.

Gaps in regulation and easy access to over-the-counter and prescription medications, including paracetamol, benzodiazepines, and antidepressants, commonly lead to misuse, especially in attempts at deliberate self harm, increasing the burden on the healthcare system.

A major gap is observed in providing mental health services which is crucial in preventing attempts at deliberate self harm and suicide. It is beyond the scope of this article to elaborate on the matter further. However, it should be borne in mind that mental health services have a direct bearing on the strain on toxicological services.

Lack of updated research in the local context significantly impedes development in toxicological services. Insufficient data to support policy decisions could curb optimal resource allocations to enhance these services.

Recent developments and initiatives

The National Poison Centre regularly develops IEC (information, education and communication) material for the public and information booklets to disseminate knowledge to healthcare professionals.

The Ministry of Health, Sri Lanka is currently in the process of developing a country specific first-aid guideline for the public in native languages, which has a dedicated component on toxicology.

Professional Colleges such as Sri Lanka Medical Association (SLMA) and Sri Lanka College of Internal Medicine (SLCIM) have undertaken many initiatives in the interest of furthering knowledge of medical officers in toxicology.

The SLMA has published a guideline on management of snake bites in 2021, titled, "Guidelines for the management of snake bites in hospitals".

The SLCIM has taken several initiatives:

1. A lecture series has been initiated to train pre-intern doctors in essentials of clinical toxicology.
2. Recently the college launched an essential clinical toxicology textbook which could serve as a handbook for medical officers of all grades
3. CME activities and webinars in toxicology are carried out frequently to educate medical officers and postgraduate trainees.
4. Materials are currently being developed by the college for a new toxicology training module targeting senior registrars in internal medicine in collaboration with the PGIM.
5. Efforts are being made to standardise existing clinical protocols across the country

The way forward

The decrease in case fatality due to self-ingestion of pesticides observed after the ban on highly hazardous pesticides in Sri Lanka demonstrates a successful instance in implementation of policies on pesticides.(2)

Strategic policy decisions are needed to enhance emergency response, clinical management, public health interventions, and regulatory oversight. Establishing a national poison control network, strengthening clinical toxicology units, and developing state-of-the-art toxicology laboratories are crucial steps. Policies should also focus on occupational and environmental toxicology, ensuring strict chemical safety regulations and effective public health awareness programmes. Policy guidelines for safe pharmaceutical and household chemical disposal are also crucial.

Sri Lanka should strive to achieve an environment conducive to research with upgraded infrastructure and secure funds to generate data relevant to local context, to inform policy decisions in toxicology.

Conclusion

Toxicology remains a critical yet underappreciated component of healthcare in Sri Lanka, with acute poisoning cases contributing significantly to healthcare burden. While pesticide poisoning, toxic plant ingestions, and snake envenomation have long been the primary concerns, recent trends indicate a rise in medication overdoses and other chemical exposures. These shifts underscore the urgent need for improved public awareness and education on toxicology-related risks. Toxicology should be prioritised as a public health necessity, requiring urgent attention from policymakers and healthcare stakeholders.

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Physical signs of yesteryear; forgotten or forgiven

Lekamwasam S*

Introduction

Medical history and physical examination have been the cornerstone in patient evaluation and despite many advances in medicine and therapeutics, the relevance of these two components has not diminished. At a time when investigations were unavailable, delayed and very primitive, clinicians have saved many lives, entirely based on the information obtained from these two elements. Eliciting information from medical history and physical examination requires patience, dedication and sharp clinical acumen. Clinicians of yesteryear were equipped with these qualities abundantly.

The Ancient physicians such as Hippocrates, Vesalius, and Osler had no option other than detailed clinical information and it is astonishing how they observed subtle physical signs differentiating one disease from another. Compared to clinical history, physical signs are more reliable and dependable as they are more objective and reproducible. In contrast, stable angina first described by William Heberden in 1768, however, has stood the test of time and no advanced medical technology has yet replaced it.(1)

Current undergraduate and postgraduate training places less emphasis on the development of clinical skills as current clinicians including trainers rely more on technology-based diagnosis. This has led to a decreased interest in physical examination.(2) The observation made by Crombie in 1963 that 88% of all diagnoses in primary care were established by obtaining a detailed medical history and performing a complete physical examination, is probably still valid. (3,4) Subsequent studies, however, have illustrated the limitations, biases (5) and poor inter-rater agreement of physical examination (5) and a comprehensive analysis of those studies is beyond the scope of this article.

At present medicine is practiced more as a science than an art. To me, however, medicine is both an art and a science and they are interdependent and inseparable. The component of the art of medicine is more relevant as clinicians have to deal with human beings consisting of body, mind and soul. It is a bit disappointing to note that current patient evaluation is more technical and has lost the humane touch.

Physical signs described in this article have been used by clinicians at different time points. With the advancement of medicine and science, some physical signs have disappeared either because newer technologies became more accurate and informative or due to their low accuracy. Hence they are either forgotten or forgiven.

Of thousands of physical signs described in the literature, those included here were selected because I have used them either as a medical undergraduate or during my professional life expanding nearly 40 years. They are, however, not lined up in a particular order. Furthermore, this is not an attempt to persuade the current generation of clinicians to incorporate them into medical practice but merely to inform those who still enjoy the history of medicine and appreciate the artistic component of medicine, like me.

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Kronig's Isthmus

Kronig's isthmus was a popular physical sign in the pre-radiography era in detecting pathological changes in lung apices. In an era when pulmonary tuberculosis and sarcoidosis were rampant, clinicians paid more attention to the abnormalities in lung apices as they were the common sites of predilection. They heavily relied on this particular physical sign to detect early apical involvement before diseases involved other areas of the lung.

Kronig's isthmus is a band of resonance of about 2-3 finger breadths in the supraclavicular area between the shoulder tip and the side of the neck. It is bound medially by the scalenus muscle, laterally by acromion process of scapula, anteriorly by clavicle and posteriorly by trapezius muscle. Basically clinician has to compare the width of the resonant band in the two sides to detect the diseases affecting the apices.(6,7) This sign was used to detect tumors involving lung apices such as Pancoast tumor as well.

d'Espine sign

This physical sign, apparently named after Swiss pediatrician Jean-Henri-Adolphe d'Espine (1846-1930), was used, again in pre-radiography era, to detect abnormalities involving the middle mediastinum such as tumors and mediastinal lymph nodes. When auscultating posteriorly, one can hear bronchial breathing over the trachea until its bifurcation which is surface marked by the 4th thoracic spinous process (easily located using the C7 prominence). The continuation of bronchial breathing below the 4th thoracic spinous process is considered abnormal, indicative of a mass lesion in the middle mediastinum.(8,9)

Puddle sign

Puddle sign that was used to detect early ascites disappeared with the introduction of ultrasonography to clinical practice. For the other physical signs of free fluid in the abdominal cavity such as horse-shoe dullness and shifting dullness to be positive, the amount of fluid in the abdomen needs to be in the range of 0.5 to 1 liter and the Puddle sign can detect ascites smaller than 0.5 liters (even 120 ml).

To elicit the Puddle sign, the examiner needs to first percuss the abdomen in supine position and ensure the presence of the tympanic sound in the midline around the umbilicus. Then the patient is placed in the knee-elbow position for 5 minutes until the fluid gets gravitated to the most dependent position, umbilicus. If fluid is present, the previously resonant umbilical region becomes dull. This can be further confirmed by auscultating. Examiner should place the diaphragm of the stethoscope near the umbilicus and while listening, the examiner repeatedly should flick one point in the abdomen, preferably the loin area. While doing this the examiner should move the stethoscope laterally and look for the point where the sound increases and this demarcates the edge of the fluid collection.(10,11)

Pulsating varicose veins

A rare physical sign, I have seen only twice in my long medical career. Primary varicose veins which are not pulsatile can become pulsatile, mainly due to cardiac causes and the two cases I came across were due to severe tricuspid regurgitation. In both patients varicose veins were very prominent and extensive. The pulsations were due to the severe and long standing back pressure generated by leaking the tricuspid valve transmitted via the inferior vena cava. (12,13)

Hamman's sign (or Hammond's sign)

I still recall the first time I heard this in a 25-year-old woman who presented with acute left sided chest pain. The systolic click was clear and distinct. With the few Marfanoid features she had, the possibility of mitral valve prolapse was high. Chest radiograph, however, showed a partial spontaneous pneumothorax on the left side.

Hammond's sign is described as a click or crunch heard over the precordium, synchronised with heartbeat. The intensity of the click changes with posture (increased when turning to left) and respiration (increases with inspiration). It is associated with partial left sided pneumothorax as well as mediastinal emphysema. Originally, Louis Hamman reported this sign in 1939 in mediastinal emphysema and since then this has been described differently as rasping, crunching, bubbling, crepitant, crackling, clicking, or popping sound. Although uncertain, the origin of the sound is thought to be due to the compression of mediastinal tissue between the heart and anterior chest wall.(14-16)

Homans' sign

This relates to the severe pain in calf muscles on squeezing or on forceful dorsiflexion of the foot. The positive test was considered a sign of underlying deep vein thrombosis. According to history, American surgeon, John Homans in 1941 introduced the dorsiflexion sign, defined as "discomfort behind the knee on forced dorsiflexion of the foot," and it was considered a sign of calf thrombi. The accuracy of the sign came under scrutiny and, although this sign appeared in textbooks for several decades, the high proportions of false positives and false negatives compromised the credibility of the test.(17,18) The story is that although Homans introduced the "dorsiflexion sign" it was his contemporary surgeons who coined the name "Homans sign". Eventually, Homans became unconvinced about the sign and has been quoted as saying "if you wanted to name a sign after me, why didn't you pick a good one?"

Relative bradycardia

At a time when infectious diseases were rampant and diagnostic tools were primitive, we used to look for subtle telltale signs that helped to narrow down the possibilities. The concept of relative bradycardia is based on the physiological relationship between pulse and temperature and some believe that this can be applied only when temperature rises above 102^0F. It assumes that an increase in body temperature by 1^0F is associated with an increase of 10 heart beats per minute and when a patient's resting heart rate is below the expected value for the temperature recorded simultaneously, relative bradycardia is confirmed. Apart from infective causes, several non-infective causes also can lead to this phenomenon. These include factitious fever, beta blocker therapy, CNS lesions and drug fever.(19) Other infective causes of relative bradycardia include legionella, Psittacosis, Rocky Mountain Spotted fever, Q fever and dengue. In 1996 Ostergaard et al stated that relative bradycardia as a clinical sign has no predictive value for a specific infection, but this phenomenon is seen in typhoid fever, Legionnaires disease, and pneumonia caused by *Chlamydia* sp.(20) Although there were many possibilities, most of the infections in the list were not found in the country then and the most likely possibility was typhoid. For this reason, relative bradycardia was considered supportive of the diagnosis of typhoid fever.

Tidal percussion

This particular sign was used to detect paralysis of the diaphragm on one side. When a patient is in the seated position, one has to find the lowest level of the resonance on the posterior side of the chest and particularly the point where percussion changes from resonant to dull. Then the patient is asked to take a deep breath and hold in inspiration and percussion is continued below the point detected earlier. When diaphragmatic movements are normal, the resonance extends 3-5 cm below the point. Negative response indicates possible paralysis of the diaphragm on that side.(21) Widespread availability of imaging made the use of this sign obsolete.

Poor man's stress test

Although not a physical sign, this particular abnormality seen in 12 lead resting ECG has been debated for some time. The T wave inversion in the first sinus beat following a ventricular extrasystole (PE-T) was first described in 1951 and considered a surrogate of underlying coronary artery disease (22,23). It was realized later that the T wave represents ventricular repolarization and it is sensitive to many extracardiac causes such as medications and electrolyte abnormalities. Furthermore, Engel et al in 1977, analyzing coronary angiography, were unable to demonstrate an association between this PE-T and coronary artery disease (24).

Double and triple cardiac apical impulses

Ancient Chinese, Egyptian, and Hebrew texts provide a fascinating description of chest impulses caused by the beating heart. We, however, are guided by the observations made by vigilant clinicians over many centuries and recorded in medical texts.(25) Precordial examination is not complete without detecting the location and character of the maximum cardiac impulse in the apical area. In a healthy heart it is only a single outward impulse representing left ventricular contraction during systole. Detecting a second impulse after the first requires anticipation and concentration. The second apical impulse occurs due to the forceful contraction of the hypertrophied left atrium and this phenomenon can be seen in hypertrophic cardiomyopathy and severe aortic stenosis. Detecting triple apical impulses need more focus and this rare phenomenon is considered to be pathognomonic of hypertrophic cardiomyopathy.(25)

Post-tussive suction

This sign is elicited when a lung cavity is suspected. First the patient should attempt to empty the lung cavity by forceful expiration after repeated coughing. With the diaphragm of the stethoscope a hissing sound can be heard over the cavity due to the rapid gush of air into the empty cavity during inspiration. (26) This sign can be absent when the cavity is small, located deep in the lung or when not connected with a patent bronchus.

Dancing brachial artery ("Locomotor brachialis or Locomotor brachii")

Locomotor brachii is a thickened, dilated, tortuous, and pulsatile brachial artery seen in the cubital fossa. It is mostly seen in older adults and considered a surrogate of underlying atherosclerosis or systemic hypertension. Locomotor brachii is an evidence-based superficial clinical marker of cardiovascular disease, stroke, renal, and peripheral vascular disease. Also it can be seen in aortic regurgitation which is severe enough to lead to peripheral signs. Apart from older adults, it can be seen in younger patients with severe coronary and cerebral ischemic events.(27,28)

Palmomental reflex

It is the involuntary twitch of the mentalis muscle of the chin caused by stroking the palm, especially the thenar eminence. Although not fully reliable, the positive sign alerts the clinician to the possibility of cerebral pathology. It is a primitive reflex reappearing in old age especially in those with cerebral atrophy. The sensitivity and specificity of the sign are low and the reflex can sometimes be seen in normal people. Unilateral reflex, a strong and easily repeatable reflex and the reflex that can be elicited by stimulation of areas other than the palm are more likely to indicate cerebral damage.(29)

Pulsation of intercostal arteries

Although not as popular as the radio-femoral delay, pulsation of intercostal arteries was a sign used to detect the coarctation of aorta. Abnormal pulsations due to the establishment of accessory arterial channels can be seen in the upper part of the chest, posteriorly, when the patient bends forward.(30) Advanced imaging techniques, again, have made the use of this physical sign obsolete.

Final remarks

Advanced medical technology has come to the forefront of patient care making early detection of diseases and high risk individuals possible. Furthermore, newly qualified doctors with technology-based training rely more on modern diagnostic algorithms which are built on these technologies and pay less emphasis on clinical information. Although this approach appears more efficient, how patients react to this kind of care pathways is not adequately analysed. We are not certain whether a patient feels satisfied when a doctor makes a decision after checking his ultrasonography report or does he still expect the doctor to examine his abdomen.

As stated earlier, my intention is not to bring back these physical signs to the current clinical practice. On our journey to modern medicine, we have both rejected and discarded many treatment options that were popular at different time periods. Some of them such as maggot therapy, however, have made a strong comeback. With the rapid advances in medical technology, evidence-based medical practices, health economics and patient expectations, what future doctor-patient relationship will demand is an area of uncertainty.

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RESEARCH

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Factors influencing first-time fathers' involvement in their wives' pregnancy and childbirth; descriptive cross-sectional study at a selected maternity hospital, Sri Lanka

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Abstract

Introduction: Pregnancy is a significant phase, bringing both pleasure and stress to women. Balancing these aspects is crucial for the well-being of both the mother and the developing baby. A partner's involvement during a pregnancy is multidimensional, encompassing emotional, practical, and active support throughout the prenatal, labour, and postpartum periods. This comprehensive involvement not only strengthens the bond between partners but also contributes to better health outcomes for both the mother and the baby. This study determined the first-time fathers' involvement during pregnancy and childbirth, assessed the informational support they received, and explored the factors influencing their level of involvement.

Methods: We conducted a descriptive cross-sectional study at the obstetric wards of De Zoya Maternal Hospital (DMH) on a convenient sample of 200 first-time fathers. The study setting was the obstetric wards of DMH. Data were collected through a pretested interviewer-administered questionnaire, including the validated "Father's Involvement in Pregnancy and Childbirth" instrument with the author's permission. The data were analysed using descriptive statistics and inferential statistics.

Results: Most participants (76.5%, n=153) were 22–31 years of age, all were employed, with a majority (57%, n=114) working an 8-hour shift daily. Additionally, 84.5% (n=169) attended antenatal education sessions. Results indicated varying levels of involvement; poor (11.5%, n=23), moderate (50%, n=100), and good (38.5%, n=77). Factors significantly impacting involvement included working hours per day and attendance at antenatal education sessions.

Conclusions: Given the suboptimal involvement observed, interventions addressing associated factors are necessary to enhance fathers' participation in their partners' pregnancy and childbirth.

Keywords: Antenatal care, first-time fathers, pregnancy and childbirth

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Introduction

Pregnancy marks one of a woman's most joyful and significant phases. Pregnant women may experience numerous changes, not only physical but mental, social and psychological changes.(1) The well-being of women during pregnancy profoundly impacts foetal health, delivery outcomes, and successful breastfeeding.(2) First-time mothers often struggle with the novel experiences brought about by pregnancy, making them more susceptible to emotional disturbances.(3) Furthermore, first-time mothers may lack the prior experience and knowledge to navigate the challenges of pregnancy with confidence.(4) Moreover, societal expectations and cultural norms surrounding pregnancy and motherhood may also impact first-time mothers' experiences.(5) The support and involvement of partners, family members, and healthcare providers play a crucial role in helping first-time mothers direct the emotional ups and downs of pregnancy.(6) The active participation of fathers during pregnancy significantly contributes to the mother's overall health.(7) A supportive and understanding partner can provide reassurance, practical assistance and emotional support, which can help alleviate stress and promote emotional well-being during this transformative period, especially for first-time pregnant women.(8)

In Asian countries, including Sri Lanka, traditionally, the focus has primarily been on maternal care, with fathers playing a secondary role.(9) With the recognition of the importance of paternal involvement for maternal and infant health outcomes, there's a growing interest in understanding the factors that influence fathers' engagement during pregnancy and childbirth. Despite this growing interest, there needs to be more research specifically focusing on the role of first-time fathers in maternal health within the Sri Lankan context. Most studies tend to prioritise maternal perspectives, overlooking the experiences and contributions of fathers. This knowledge gap hinders the development of targeted interventions and support services to involve fathers in the maternal health journey.

Therefore, this study aimed to determine first-time fathers' involvement during pregnancy and childbirth, assess the informational support they received, and explore the factors influencing their level of involvement.

Methods

A descriptive cross-sectional study was conducted at the obstetric wards of De Zoya Maternal Hospital (DMH), the primary referral centre for maternity care in Sri Lanka. First-time fathers visiting their wives in the obstetric wards at DMH who consented for participation in the study were included. The first-time fathers who had experienced stillbirth were excluded. A convenient sample was obtained. The sample size for this study was 200 participants, determined using Daniel's formula.(10) Data were collected using an interviewer-administered questionnaire.

Assessment of fathers' involvement in their wives' pregnancy and childbirth was carried out using a tool developed by Xue et al.(11) Permission to utilise this questionnaire was obtained from the authors before data collection. Section A of the questionnaire assessed the socio-demographic characteristics of the participants. Section B evaluated participants' involvement during their wives' pregnancy and childbirth through a scoring-based approach, consisting of 13 questions. Key areas of assessment included support for ultrasound scans and other medical tests, obtaining information about different stages of pregnancy, managing household responsibilities, providing emotional support to their wives, and maintaining communication with healthcare providers. Participants were required to indicate their involvement in each item using a binary response scale, where "yes" was scored as 2, and "no" or "not applicable" was scored as 0. The total scores ranged from 0 to 26, with higher scores reflecting greater levels of involvement during pregnancy and childbirth. These scores were subsequently categorised into three groups based on cut-off points; fathers who scored 20 or above were classified as having good involvement (highly involved, >75%), scores between 13 and 19 indicated moderate involvement (75%-50%), and scores of 12 or below were considered as poor involvement (<50%).(11)

Section C of the questionnaire focused on assessing the levels of informational support received by participants during pregnancy and childbirth. Participants were asked to rate their agreement with each item using a 3-point Likert scale, where 1 represented "strongly disagree" and 3 represented "strongly agree." The total scores ranged from 12 to 36, with higher scores indicating greater levels of informational support.

The total score was subsequently categorised into three groups based on predetermined cut-off points. A score of 27 or higher indicated the father had received sufficient information (>75%). Scores ranging from 18 to 26 reflected moderate informational support (50%-75%), while scores of 18 or lower were considered to be insufficient.(<50%).(11)

The data were analysed using descriptive statistics, including frequencies and percentages, and inferential statistics, specifically the chi-square test. SPSS Version 25 (Statistical Package for the Social Sciences) was used as an analytical tool.

Ethical approval was granted by the Ethics Review Committee at KIU (KIU/ERC/21/218). Additionally, approval was obtained from the Ethics Review Committee at DMH (DMH/ERC/22/010), and permission was obtained from the relevant authorities. Informed written consent was obtained from the participants.

Results

Participant recruitment

A total of 224 first-time fathers were invited; however, 23 individuals did not consent and 1 was excluded due to a stillbirth. Therefore the study sample was reduced to 200 participants.

Sociodemographic features of the sample

The mean age of first-time fathers in this study was 28 years. Most participants (n= 153, 76.5%) belonged to the 22–31 age group. Over half of the participants (n=135, 67.5%) identified as Sinhalese, while 11% (n=22) identified as Tamil and 21.5% (n=43) as Muslim. A considerable portion of the sample demonstrated a strong educational background, with 27.5% (n=55) having completed secondary school, 32.5% (n=65) holding diplomas, and another 32.5% (n=65) having university degrees. Among the participants, 69.5% (n=139) were full-time employees. Over half of the sample (n=114, 57%) reported having an 8-hour workday. Regarding marital status, 65% of participants had been married for less than one year, while only 14.5% (n=29) had been married for more than two years. Regarding pregnancy, 68% (n=136) of participants had planned their pregnancies, while 32% (n=64) experienced unplanned pregnancies.

Majority of the wives of first-time fathers (n=187, 93.5%) had attended antenatal clinics, while a smaller proportion (n=13, 6.5%) had not. Notably, only 41% (n=82) of first-time fathers had accompanied their wives to these clinic visits. Table 1 shows the sociodemographic features of the study sample.

Fathers' involvement in their wives' pregnancy and childbirth

Based on the findings, it was determined that 50% (n=100) of participants exhibited a moderate level of involvement, while 38.5% (n=77) demonstrated very good participation according to scoring criteria.

Factors associated with involvement in their wives' pregnancy and childbirth

There was a significant association of first-time fathers' involvement in their wives' pregnancy and childbirth with working hours per day and attendance at antenatal clinics. Associated factors are depicted in table 2.

First-time father’s informational support and sources of support

Based on findings, 46% (n=92) of the participants acquired sufficient information, 45% (n=90) obtained a moderate level, and 9% (n=18) did not receive an adequate amount of information regarding pregnancy and childbirth. The study revealed that participants obtained information from various sources, including the internet (n=188, 94%), doctors (n=184, 92%), wives (n=180, 90%), nurses (n=178, 89%) and friends (n=96, 48%). However, only 30% (n=60) acquired information regarding pregnancy and childbirth from books, magazines, and newspapers.

Discussion

This research investigated the extent of fathers' engagement during their partner's pregnancy and childbirth and the factors influencing it. The average age of first-time fathers in this study was 28 years old, aligning closely with findings from a prior study carried out in the United States (27 years).(11) The results of the present study indicated that first-time fathers were engaged in their wives' pregnancy and childbirth. However, less than half (38.5%) of the participants exhibited a high level of involvement, which aligns with findings from a study conducted in Singapore, where only 35.2% of participants were highly engaged in their partner's pregnancy and childbirth.(12) Demands from work or career responsibilities may limit fathers' availability to

Table 1 - Sociodemographic features of the study sample (n=200)

Serial No	Variables	Frequency(n)	Percentage (%)
1	**Age Category**		
	41-32	45	22.5
	31-22	153	76.5
	21-12	2	1.0
	Total	200	100.0
2	**Ethnicity**		
	Sinhalese	135	67.5
	Tamil	22	11.0
	Muslim	43	21.5
	Total	200	100.0
3	**Highest Educational Level**		
	Primary School	15	7.5
	Secondary School	55	27.5
	Diploma	65	32.5
	University (bachelor's degree and above)	65	32.5
	Total	200	100.0
4	**Current Employment Status**		
	Self Employed	48	24.0
	Full-time employee	139	69.5
	Part-time employee	13	6.5
	Total	200	100.0
5	**Working hours per day**		
	5 Hr	4	2.0
	6 Hr	31	15.5
	8 Hr	114	57.0
	12 Hr	32	16.0
	24 Hr	19	9.5
	Total	200	100.0

Table 1 - Sociodemographic features of the study sample (n=200) continued...

Serial No	Variables	Frequency(n)	Percentage (%)
6	**Average Income per month**		
	Rs.5000 - Rs. 20000	24	12.0
	Rs.20000 - Rs.40000	18	9.0
	Rs.40000 - Rs.60000	90	45.0
	Rs.60000 - Rs.100000	39	19.5
	More than Rs.100000	29	14.5
	Total	200	100.0
7	**Duration of the marriage**		
	0 - 1 year	130	65.0
	2 years	41	20.5
	More than 2 years	29	14.5
	Total	200	100.0
8	**Pregnancy was planned or not**		
	Planned	136	68.0
	Unplanned	64	32.0
	Total	200	100.0
9	**Mode of delivery**		
	Normal Vaginal Delivery	120	60.0
	Assisted Delivery	2	1.0
	Caesarean Delivery	78	39.0
	Total	200	100.0
10	**Duration of the pregnancy**		
	24 Weeks -28Weeks	3	1.5
	28 weeks - 32 weeks	50	25.0
	32 weeks - 36 weeks	74	37.0
	36 weeks - 40 weeks	73	36.5
	Total	200	100.0

Table 2 - Factors associated with involvement level of first-time fathers

Factors	Chi-square value (χ^2)	p value
Age of the first-time fathers 41-32 31-22 21-12	4.61	0.100
Ethnicity of the first-time fathers Sinhalese Tamil Muslim	3.49	0.175
Education level of first-time fathers Primary school Secondary school Diploma University	2.32	0.508
Employment status of the first-time fathers Self employed Full-time employee Part-time employee	1.91	0.385
Working hours per day of the first-time fathers* 5 Hr 6 Hr 8 Hr 12 Hr 24 Hr	13.8	0.000
Average monthly income Rs.5000 - Rs. 20000 Rs.20000 - Rs.40000 Rs.40000 - Rs.60000 Rs.60000 - Rs.100000 More than Rs.100000	8.81	0.066
Duration of marriage 0 - 1 year 2 years More than 2 years	5.50	0.064
Attendance for antenatal clinics (accompanied their wives)* Yes No	6.47	0.011

*$p \leq 0.05$, confidence level (CI)= 95% , *significant*

attend appointments or participate in activities related to pregnancy and childbirth.(13) Additionally, a lack of awareness regarding the significance of their involvement or uncertainty about how to contribute effectively may contribute to their reduced participation.(14)

In the present study, it was found that both the number of working hours per day and attendance at antenatal clinics were significantly linked to fathers' involvement in their wives' pregnancy and childbirth. A study conducted in the United States also found a positive relationship between work conflict and fathers' involvement during the transition to parenthood, which includes the pregnancy period. (15) Fathers working long hours may experience higher levels of stress and fatigue, which can impact their ability to engage actively in pregnancy-related tasks and provide emotional support to their partners. Moreover, balancing work and family responsibilities can become challenging for fathers with long working hours, leading to conflicts between work and family roles. This conflict may result in less involvement in pregnancy-related activities.

In the current study, fewer first-time fathers participated in antenatal clinics with their partners. Attending antenatal clinics allows fathers to receive sufficient information about pregnancy, childbirth, and infant care directly from healthcare professionals. This shared knowledge enables fathers to provide support to their partners.(16) Further, current study findings reveal that less than half of the participants acquired sufficient information regarding pregnancy and childbirth and most participants had received information about pregnancy and childbirth from healthcare professionals. Antenatal educational programmes in Sri Lanka are designed for expectant mothers and focus on maternal health, childbirth preparation, and newborn care. While these programmes are valuable for mothers, they often overlook the role of fathers in the process. The lack of facilities offering antenatal educational programmes tailored explicitly for fathers is a significant gap in the healthcare system.(9) Fathers may feel uninformed and unprepared to provide adequate support to their partners during pregnancy and childbirth. This gap contributes to a lack of involvement by fathers in the process of childbirth and can impact maternal and infant health outcomes.

Limitations of the study

This was a single centre study where a convenience sampling method was used; only fathers who were present in the obstetric wards during their wives' pregnancies were recruited.

Conclusion and recommendations

The study revealed that only a small proportion of first-time fathers established a high level of involvement during their wives' pregnancies. Key factors influencing paternal involvement included long working hours and limited attendance at antenatal clinics. To address these challenges, future research should investigate additional determinants that were not explored in this study, including cultural norms, psychological readiness, and access to family support systems. This would provide a more comprehensive understanding of fathers' knowledge, attitudes, and barriers to engagement.

Policymakers are encouraged to implement measures that promote workplace flexibility and support for first-time fathers, enabling them to actively participate in caregiving responsibilities during and after pregnancy. Initiatives such as paternity leave policies, flexible working arrangements, and workplace education programmes may significantly enhance paternal involvement. Additionally, healthcare providers should consider introducing tailored educational sessions and support services specifically designed for fathers, offered through antenatal clinics and community programmes. Enhancing accessibility to such resources, including telehealth options, could further encourage fathers to take an active role in supporting their wives throughout pregnancy and childbirth.

Declarations

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Author contributions
All authors have substantially contributed to the conception and design of the study. HHNDD drafted the manuscript. All authors of the paper have revised the content and approved the final version to be published. All authors are accountable for all aspects of the work.

Conflicts of Interests
The authors declare that there is no conflict of interest regarding the publication of this article.

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RESEARCH

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Intravenous lidocaine and ketamine combined infusion in chronic pain relief: a follow-up study

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Abstract

Introduction: Chronic pain is a common problem worldwide. It is a significant cause of disability and is challenging to treat. Intravenous lidocaine and ketamine combined infusion is a novel treatment strategy. Data on the efficacy and acceptability of this in South Asia is sparse. We studied the same in a cohort of Sri Lankans with chronic pain resistant to usual medications.

Methods: We studied all the patients with chronic pain who were not responding to routine oral analgesic medications and underwent the above treatment at the Pain Clinic of Colombo North Teaching Hospital Ragama from March to August 2022. We followed them up from the intervention date (baseline) to 1-month post-intervention at 24-hours, 2-week, and 1-month intervals. Patients were interviewed by a medical graduate using an interviewer-administered questionnaire. Data on demographics, past medical history, and pain intensity were gathered at baseline. Pain intensity was measured at baseline and 24 hours, 2 weeks, and 1 month post-intervention, while physical and psychosocial deficits were assessed at baseline and 1-month using Brief Pain Inventory Short Form (BPISF) and compared.

Results: A total of 29 patients, 8(27.6%) of them males, with a mean age (±SD) of 53±13.3 years were studied. The mean pain score at baseline, 7 ±1.5, reduced to 3 ±1.5 at 1 month (p = 0.001). The change in BPISF parameters from baseline to 1-month post-intervention were as follows: physical deficit 5±2.0 to 3±1.9(p= 0.001), sleep 6±2.3 to 3±1.9 (p= 0.001), enjoyment of life 5±2.1 to 3±1.9(p=0.001), mood 5±2.0 to 3±1.8 (p=0.001) and sexual relationship 5±2.1 to 3±1.9 (p =0.001). There were no major adverse effects of treatment. The majority, 24(80%) were satisfied with the intervention.

Conclusion: Intravenous ketamine and lidocaine combined infusion maintained sustained pain relief and improved related parameters in the majority of this Sri Lankan cohort with resistant chronic pain.

Keywords: Ketamine, lidocaine, chronic pain relief, analgesia, local anesthetics

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Introduction

Chronic pain is a common health problem worldwide. It is a significant cause of morbidity. Morbidity due to pain affecting day-to-day life, including physical, social and psychological well-being, makes people severely debilitated.(1) It has multiple aetiologies requiring multimodal treatment, which makes it difficult to treat.(1) The overall prevalence of chronic pain globally in young adults is 11.6%, and approximately one in every nine young adults experiences chronic pain worldwide.(2) The prevalence of chronic pain among Asian adults ranges from 7.1% (Malaysia) to 61% (Cambodia and Northern Iraq). The prevalence of chronic pain is even higher among the Asian geriatric population and ranges from 42% to 90.8%.(3) However, the prevalence of chronic pain among Sri Lankans is not documented.

Intravenous (IV) lidocaine and ketamine combined infusion for chronic pain management came into practice in the 1940s in Western countries.(4) Ketamine and lidocaine doses well below the doses used in anaesthesia and treatment of arrhythmias are used as a combined infusion for relief of chronic pain under this treatment. The dose of ketamine 0.5mg/kg and lidocaine 2 mg/kg provide a synergistic effect in pain management, minimising the adverse effects.(4) The usual starting dose of lidocaine is 4 mg/kg and ketamine 0.5mg/kg and is titrated up depending on the side effect profile and improvement in pain.(4) Ketamine and lidocaine infusion has been shown to reduce chronic pain by 30% and is an accepted treatment for chronic pain in high-income countries.(5–11) No significant drug interactions have been reported with this combined infusion in the literature.(11,12)

This treatment was introduced to Sri Lanka in 2015 and is now being trialled in a few centres specialising in pain management in Sri Lanka; Colombo North Teaching Hospital, Teaching Hospital Karapitiya, Teaching Hospital Kandy, and National Hospital of Sri Lanka, but is not well established. Reports on the efficacy and acceptability of this treatment in chronic pain are scarce from South Asia, and there are no reports from Sri Lanka.(10,13)

Therefore, we aimed to study the efficacy and acceptability of lidocaine and ketamine combined infusion in the management of chronic pain in a cohort of Sri Lankans.

Methods

We conducted a cohort study at the pain clinic of the Colombo North Teaching Hospital Ragama from March 1, 2022 to August 31, 2022. A convenient sample of all patients with chronic pain, not responding to routine oral analgesics, who were offered the above treatment at the pain clinic for the first time and consented for the study were recruited.

Data on demographics, past medical history and pain intensity were gathered using an interviewer-administered questionnaire. The Sinhala-validated version of the Brief Pain Inventory Short Form (BPISF) was used to assess pain intensity and its impact on life.(14) BPISF is a universally accepted pain assessment tool used worldwide. It contains separate numerical scales for the assessment of pain, the degree to which that pain interferes with sleep, mood, enjoyment of life, and sexual life. Patient satisfaction was measured using a visual scale ranging from 0 to 10, with 10 being the highest satisfaction level. A satisfaction rating of 7 or more was taken as having been satisfied with the intervention.

In the clinic, all patients were given lidocaine 4 mg/kg and ketamine 0.5 mg/kg single dose, and we followed up for 4 weeks. Lidocaine and ketamine were combined and administered as a slow infusion over 4 hours under close observation by an anaesthetist. The patient was attached to a multipara monitor, and his/her vital signs, including blood pressure, heart rate, respiratory rate, and oxygen saturation were monitored by a pain nurse. Patients were observed for 4 hours post intervention before discharge.

Pain intensity was studied before the intervention (baseline) and 24 hours, 2 weeks, and 1 month post-intervention. Physical deficit (in the ability to perform activities of daily living such as walking, washing, brushing, climbing stairs) and psychosocial deficit (in enjoyment of life, mood, relationship with family members, sexual life and employment) were measured at baseline and 1-month post-intervention. The patients' satisfaction was assessed one month after the intervention. Adverse effects of the intervention were monitored during the intervention and follow-up.

Ethics approval for the study was obtained from the Ethics Review Committee of the Postgraduate Institute of Medicine, University of Colombo, Sri Lanka (ERC/PGIM/2021/229). Informed written consent was obtained from all the patients.

Data were analysed using the Statistical Package for Social Sciences 23.0. We compared the mean pain scores from baseline to 24 hours and baseline to 1 month post-intervention using the student t-test. We also compared the mean scores related to physical and psychosocial deficits at baseline and 1-month.

Results

A total of 29 patients, 8(27.6%) males, of mean age (±SD) 53 (±13.3) years with chronic pain, who underwent the intervention were studied. The baseline data of the study sample is shown in table 1. Back pain was the most common cause of chronic pain; 11(38%). All had pain scores ≥5 with a mean (±SD) of 7.5 (±1.46). A third of patients, 10 (34.5%), had a pain score of 10/10. Physical activity, sleep, mood and income were affected due to chronic pain in 28 (96.6%), 24 (82.8%), 24 (82.8%) and 16 (55.2%) respectively. Enjoyment and sexual life were affected in 20 (69.0%) and 14 (48.3%).

The outcome of the intervention at different points in time is shown in table 2**.** The mean pain score at baseline, 7±1.5, reduced to 3±1.5 at 1 month (p=0.001). BPISF parameters changed from baseline to 1-month post-intervention; physical deficit 5±2.0 to 3±1.9(p= 0.001), sleep 6±2.3 to 3±1.9(p=0.001), enjoyment of the life 5±2.1 to 3±1.9(p=0.001), mood 5±2.0 to 3±1.8 (p=0.001) and sexual relationship 5±2.1 to 3±1.9 (p=0.001), respectively.

The known adverse effects of the intervention are high blood pressure, tachyarrhythmia, breathing problems and drowsiness. In our study only 1 patient (3.5%) experienced an adverse effect, which was drowsiness, immediately following the intervention.

Regarding patient satisfaction and feedback, 24 (79.4%) rated the intervention as good, 3 (6.9%) had no improvement, and 1 (3.5%) did not comment on the treatment.

Discussion

We observed that intravenous ketamine and lidocaine combined infusion maintained sustained pain relief and related parameters in the majority of this cohort of patients at one month. Most patients were satisfied with the intervention and had no serious side effects.

Our findings are in keeping with the literature. A double-blind, randomised control trial carried out in Indonesia on patients with chronic low back pain also reported improvement in numeric pain rating scale as well as significant functional pain scale changes after a month.(15) The randomised, double-blind, placebo-controlled clinical trial by Gottrup et al. randomised patients with neuropathic pain to receive 0.24 mg/kg ketamine, 5 mg/kg lidocaine, or saline infusion, and the impact on ongoing or evoked pain (brush or pin-prick) showed that lidocaine reduced prick-evoked pain while ketamine reduced both ongoing and evoked pains.(16) Several other studies have found that the use of ketamine and/or lidocaine as adjuncts to opioids lowers opioid consumption. (17-20). In our study, we compared every component before and after the intervention using the numerical scales and showed a significant improvement in sleep, mood, enjoyment of life, and sexual life. A considerable improvement in all these aspects without significant side effects gives a more remarkable improvement in the quality of life for patients. The standard side effect profile of lidocaine and ketamine hallucinations, memory defects, panic attacks, vomiting, cardiovascular stimulation, and, in rare instances, hepatotoxicity was not seen with this intervention, probably because a lower dose was being used. The only side effect noted in other studies was drowsiness, which we also observed.(21)

Our study is the first report on the use of intravenous ketamine and lidocaine combined infusion in the treatment of chronic pain in Sri Lanka. We showed that this method had high satisfaction levels in addition to its effectiveness. We individually followed up with each patient just before, during, until 1-month post-intervention, which is an accurate real-world experience of the intervention. However, the study has a few limitations to acknowledge. The sample size was small, and long-term follow-up beyond 1 month was not studied. Therefore, we plan to conduct a larger study to capture the effects of repeated infusions and long-term efficacy by following them up for an extended period in the future.

Conclusion

Intravenous ketamine and lidocaine combined infusion maintained sustained pain relief and improved related parameters at 1-month post-intervention in the majority of the study sample with chronic pain resistant to the usual treatment. A higher proportion of the participants showed good satisfaction with the treatment. This intervention

Table 1 - Baseline characteristics of the sample

Characteristics	Number (%)
Age (years) (SD)	53 (±13.3)
Male n (%)	8 (27.6%)
Level of education, n (%)	
Up to Ordinary level	12 (41.4%)
Passed Ordinary level	7 (24.1%)
Advanced level	6 (20.7%)
Higher education	4 (13.8%)
Employment status	
Employed	10 (34.5%)
Unemployed	19 (65.5%)
Comorbid conditions, n (%)	
Hypertension	10 (34.5%)
Diabetes mellitus	10 (34.5%)
Ischemic heart disease	2 (6.9%)
Pulmonary diseases	3 (10.5%)
Location of pain, n (%)	
Back pain	15 (51.7%)
B/L Knee joint pain	2 (6.9%)
Trigeminal neuralgia	6 (20.7%)
Shoulder pain	4 (14.0%)
Carpal tunnel syndrome	1 (3.5%)
Phantom limb pain	1 (3.5%)
Intensity of pain [scale of 0 (lowest) to 10 (highest)], n (%)	
5	2(6.9%)
6	2(6.9%)
7	4(13.8%)
8	7(24.1%)
9	4(13.8%)
10	10(34.5%)

Table 1 - Baseline characteristics of the sample (continued...)

Characteristics	Number (%)
Adverse interference of pain in daily functioning, n (%)	
Sleep	24 (82.8%)
Physical activities	28 (96.6%)
Income	16 (55.2%)
Mood	24 (82.8%)
Enjoyment of life	20 (69.8%)
Sexual relationships	14 (48.3%)
Allergy, n (%)	
Food	2 (6.9%)
Drug	7 (24.1%)
Plaster	1 (3.5%)
No food, drug or plaster allergy	19 (65.5%)
Drug history, n (%)	
Paracetamol + codeine phosphate	1(3.5%)
Non-Steroidal Anti-Inflammatory Drugs	25 (86.2%)
Tricyclic Antidepressants	21 (72.4%)
Anti – epileptics	10 (34.5%)
Oral steroids	1 (3.5%)

Table 2 - Outcome following the intervention

Parameter	Brief Pain Inventory (mean)				
	Baseline score	24-hours post-intervention	2-weeks post-intervention	1-month post-intervention	p value*
Average Pain score	7.50	4.24	3.27	3.07	0.001
Physical activity	5.18	...	...	2.96	0.001
Mood	5.21	...	...	2.66	0.001
Sleep	5.90	...	...	2.69	0.001
Sexual life	5.10	...	...	2.66	0.001
Enjoyment of life	5.34	...	...	2.59	0.001

*baseline vs one month

Intravenous ketamine and lidocaine combined infusion maintained sustained pain relief and improved related parameters at 1-month post-intervention in the majority of the study sample with chronic pain resistant to the usual treatment. A higher proportion of the participants showed good satisfaction with the treatment. This intervention seems a plausible option for the treatment of chronic pain in Sri Lankans. However, further studies with adequate power and long-term follow-up are needed to understand the real-world benefits of the intervention in the long run.

Declarations

Conflicts of interest
None

Ethics approval
Ethics Review Committee of the Postgraduate Institute of Medicine, University of Colombo, Sri Lanka (ERC/PGIM/2021/229).

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RESEARCH LETTER

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Student perception and efficacy of simulation-based history taking as a part of early clinical exposure - a qualitative study from a Sri Lankan medical faculty

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Introduction

Simulation-based learning (SBL) has evolved significantly over the past six decades, initially starting with flight simulators and later advancing into medical education through various levels of fidelity simulators.(1,2) While traditional SBL focuses on procedural and technical skills, SB history-taking involves trained human actors portraying patients.(3,4) These actors simulate patient interactions to create a high-fidelity learning environment, offering unique benefits in developing communication and interpersonal skills.(5) In medical education, SBL has been extensively used for acquiring skills related to surgical procedures, clinical assessments, and communication. It is especially beneficial in contexts where real-life practice is risky or unethical. The history of using simulated patients in medical education dates back to the 1960s when Barrows and Abrahamson introduced the concept of the "programmed patient" for assessing neurology students.(6) Over time, the methodology has evolved, incorporating various levels of fidelity in simulation to enhance learning outcomes. High-fidelity simulations, in particular, are capable of mimicking realistic clinical scenarios, including physiological responses and complex interactions.(7,8) At the Faculty of Medicine, University of Moratuwa, the curriculum emphasises student-centered, integrated, and outcome-based learning.(9) This newly established medical faculty focuses on innovative teaching-learning strategies to ensure competency development. As part of this initiative, SB history-taking was introduced early in the curriculum to provide students with hands-on experience and bridge the gap between theoretical knowledge and clinical practice. This study aimed to explore student perceptions of SB history-taking and evaluate its efficacy in early clinical exposure.

Methods

A qualitative research design utilising focus group discussions (FGDs) was employed. The study involved 15 second-year medical students who had participated in SB history-taking sessions. Three FGDs, each consisting of five students, were conducted using a semi-structured interview format. The guiding questions focused on students' perceptions, the relevance of SB history-taking to their curriculum, perceived efficacy, and suggestions for improvement. The sessions were audio-recorded, transcribed, and subjected to thematic analysis. The purposive sampling method ensured representation from both genders, allowing a diverse range of opinions. The thematic analysis approach helped identify common themes and subthemes, providing in-depth insights into the students' experiences and feedback.

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Results

Guiding questions and student perceptions

Students were asked about their feelings, perceived relevance, and the efficacy of SB history-taking sessions. The main themes identified were:

(1) Appropriateness and relevance:

Students found SB history-taking relevant to their curriculum. They expressed that it helped bridge the gap between basic sciences and clinical sciences. Statements like "interviewing a simulated patient helps me link the basic sciences with clinical sciences" and "these sessions make exam preparation easy" highlighted its importance. Additionally, students felt that the sessions aligned well with the integrated nature of their curriculum, where basic science concepts are taught in the context of clinical applications.

(2) Early clinical exposure:

The sessions provided early exposure to clinical environments. Students commented, "taking part in SB sessions allows me to learn to behave as a doctor, even within the limited knowledge I have" and "it's really good to be able to talk to someone mimicking a patient, rather than studying textbooks only." This early exposure is essential for building confidence and familiarity with clinical settings, reducing anxiety when students encounter real patients later in their training.(10)

(3) Student-centered learning:

SB history-taking facilitated student-centered learning, encouraging independent thinking and self-directed study. Remarks such as "when talking to the simulated patient, I have to think for myself what to ask" and "I come across a lot of new terms during SB history-taking, which I have to go back and refer to" underscore this theme. The sessions motivated students to review and expand their knowledge, fostering a proactive approach to learning.

(4) Continuation beyond basic sciences:

Students suggested extending SB history-taking sessions into clinical years, with statements like "I'm sure I will understand what to ask from these patients better when I learn about diseases in future modules." They emphasised the potential benefits of using SB learning to practice complex clinical scenarios and ethical dilemmas, such as end-of-life care and bereavement.(8)

Advantages

- **Skill development:** Students cited improved self-confidence, communication skills, and familiarity with history-taking as key benefits.(7) They noted that repeated practice in a safe environment helped them overcome initial shyness and hesitation.
- **Safe learning environment:** The sessions provided a non-threatening environment for practice, with students feeling more comfortable interacting with trained facilitators than with academic staff.(8) This aspect is particularly important in medical education, where fear of making mistakes can hinder learning.
- **Feedback and observation:** Observing peers and receiving feedback from facilitators were noted as valuable aspects of the learning process. (11) The structured feedback allowed students to identify their strengths and areas for improvement, enhancing their learning experience.

Limitations

- **Limited opportunities:** Some students reported insufficient chances to interact with simulated patients due to time and resource constraints. This limitation is common in SBL, where logistical and financial factors can affect the availability of high-quality simulations.(12)
- **Knowledge gaps:** Conducting sessions early in the module was challenging for students with limited clinical knowledge. They suggested scheduling sessions later in the module to address this issue.
- **Authenticity:** While some students appreciated the realism of simulated patients, others felt that the interactions lacked authenticity. Despite the high fidelity of the simulations, the absence of real clinical signs and symptoms was noted as a drawback by some participants.

Suggestions for improvement

Students proposed:

- Increasing the frequency of sessions.
- Reducing group sizes to enhance individual participation.

- Scheduling sessions toward the end of modules to minimise knowledge gaps.
- Incorporating more complex scenarios to better prepare for real-life clinical encounters.

Discussion

The findings align with existing literature on the benefits of SB history-taking in medical education. Simulation-based methods improve communication skills, self-confidence, and the ability to connect theoretical knowledge with clinical practice.(7,8) Incorporating SB history-taking early in the curriculum enhances students' cognitive and emotional readiness for real patient encounters, as noted by Tayade et al.(11), who emphasised the value of early clinical exposure in linking basic and clinical sciences while reducing student anxiety.

Students suggested extending SB learning into clinical years and incorporating complex scenarios, such as ethical dilemmas and bereavement, which aligns with Sanson-Fisher et al.'s findings on the flexibility of simulated scenarios in preparing students for real-world challenges.(8) In this study, MBBS graduate demonstrators, trained by academic staff to simulate cases, facilitated sessions. Students reported feeling more comfortable and performing better with peer facilitators than with academic staff, supporting evidence on the effectiveness of near-peer learning in improving history-taking skills.(12,13)

The potential of SB learning to enhance communication skills is well-documented. Blackmore et al. indicated that gains in communication from SB learning yield measurable clinical benefits.(14) Additionally, simulating emotionally difficult scenarios, such as terminal illness and bereavement, prepares students for complex interactions.(15)

Conclusion

Students viewed SB history-taking as a highly beneficial educational approach that builds confidence, and communication skills, and bridges basic and clinical sciences. Despite issues with resource availability and session timing, these challenges can be mitigated through curriculum adjustments. Extending SB history-taking into clinical years could further improve students' readiness for real-world practice.

Declarations

Author contribution
All authors have read and approved the manuscript. UMW came out with the research idea and proposal. KTD and NS were involved in coordinating simulation-based history-taking sessions for the students. UMW carried out the focus group discussions, data analysis and development of the research paper.

Data accessibility statement
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Competing interests statement
The authors declare that there are no competing interests.

Permissions statement
Permissions for third-party or restricted content are not relevant to this study.

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MINI REVIEW

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Propanil poisoning, management and challenges faced by health professionals in Sri Lanka

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Abstract

Propanil, being a widely used herbicide in cultivation and a popular agent used for deliberate self-harm, seemingly has less attention from both the public and health sectors. It causes potentially life-threatening end-organ failure as well as death by inducing methaemoglibinaemia when ingested. While intravenous methylene blue remains the drug of choice for propanil poisoning, lack of adequate supplies and proper guidance hinder patient management. The guidelines and management options have been upgraded with the invention of the bedside colour chart but whether it has been used effectively is questionable. This review aims to discuss the clinical features of propanil poisoning, available management options and the challenges in a resource-poor setting.

Key words: Methaemoglibinaemia, methylene blue, propanil poisoning, 3,4 – dichlorophenyl propionanilide

Introduction

Propanil (3,4 – dichlorophenyl propionanilide) is a potent herbicide belonging to the acetanilide group, which is used widely in agriculture, particularly in rice cultivation to control weeds. It is available in around twenty different brand names, usually at a concentration of 36% (w/v).(1-5)

The active metabolite of propanil is 3,4 – dichloroaniline (DCA) which results from hydrolysis of propanil. Both propanil and DCA are lipophilic substances. DCA oxidises into 3,4 – dichlorophenyl hydroxylamine in red blood cells which potently induces the production of methaemoglobin by converting Fe +2 (oxyhaemoglobin) into Fe +3 (methaemoglobin) leading to methaemoglobinaemia. (1-3) Methaemoglibinaemia is defined as elevation of blood methaemoglobin level by more than 1%. Methaemoglibinaemia can be suspected in the presence of an oxygen saturation gap between pulse oximeter readings and arterial blood gas measurements and desaturation that does not improve with oxygen therapy.(6) This will reduce the oxygen-transporting capacity of blood resulting in tissue hypoxia and end-organ dysfunction. Other suggested pathways of toxicity are lipoperoxidation, myelotoxicity, immune dysfunction and direct oxidative damage to red blood cells.(3,7)

Although uncommon and rare, poisoning with propanil may occur accidentally during cultivation or due to intentional ingestion.(1,8) According to literature propanil poisoning accounts for about 2% of all self-poisoning cases admitted to hospitals in Sri Lanka and it is the second most lethal herbicide reported after paraquat. 10 mL of the undiluted compound is the lethal dose for man while ingestion of more than 200 mL of diluted solution of propanil is considered severe poisoning.(2, 3)

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Prior to 2008, self-poisoning with propanil in Sri Lanka was associated with a case fatality rate of approximately 11%.(9,10) Severe propanil poisoning reports severe morbidity and mortality.(3,11) Propanil poisoning-associated morbidity is related to end-organ damage due to methaemoglobinaemia, acidosis and haemolysis resulting in anaemia. Mortality is mostly attributed to prolonged and treatment-resistant methaemoglobinaemia associated with larger ingestions and the most pronounced causes are old age, multiorgan failure, haemolysis, central nervous system (CNS) depression and non-retractable hypotension leading to coma and cardiorespiratory arrest.(1,9) Poor prognosis is usually associated with features of clinical toxicity at the time of presentation while the severity of symptoms, signs, and mortality is mainly related to the level of methaemoglibinaemia.(1,2) A case series from Sri Lanka suggests that sometimes even lower methaemoglobin levels can be associated with fatal outcomes.(8)

Clinical Features (table 1)

Development and onset of tissue hypoxia and related symptoms are proportional to the level of toxicity.(3) Cyanosis appears when the methaemoglobin level is more than 10% (1.5 g/dL) in an individual with a baseline haemoglobin level of 15 g/dL.(6) Gastrointestinal symptoms such as pain and vomiting are caused by gastrointestinal irritation.(4) Symptoms such as anxiety, fatigue, dizziness, headache, tachycardia, arrhythmias, stupor and confusion begin to appear when the level is more than 30%. When the methaemoglobin level is more than 50%, life-threatening consequences of progressive end-organ dysfunction such as respiratory depression, central and peripheral cyanosis, acidosis, bradycardia, hypotension, heart failure, CNS depression, seizures, coma and death can occur and are consistent with severe and prolonged methaemoglibinaemia.(2-6)

Other less common signs include hepatotoxicity/ acute hepatitis and haemolysis.(2,8) Around 1/3 of the poisoned patients will experience haemolytic anaemia. It is suggested that direct oxidative damage to the red blood cells by the poison may be the cause.(3,7)

Pulse oximetry and partial pressure of oxygen (PaO_2) in arterial blood gas analysis (ABG) might be misleading as it does not reflect the tissue oxygenation level in these cases.(3,5)

Management (figure 1)

Supportive care and investigations

Removal of the poison can be achieved by gastric lavage within 2 hours of ingestion. Care must be taken to protect the airway, including intubation of the patient if the conscious level is reduced.(4)

Supportive care must be given with adequate intravenous (IV) fluid replacement and intensive monitoring with fluid balance charts. Strict bed rest is a must.(3,4) Blood glucose levels should be maintained within normal ranges to achieve maximum efficacy of methylene blue.(9) Signs of respiratory depression and cyanosis require 100%

Table 1 - Clinical features of methemoglobinaemia related to the level of blood methaemoglobin concentration

Methaemoglobin concentration in blood	Signs and symptoms
0 – 3 %	No symptoms
10 – 20 %	Mild symptoms (Cyanosis, Gastrointestinal irritation - pain and vomiting) Chocolate brown blood
20- 50 %	Dyspnoea, decreased exercise tolerance, anxiety, fatigue, dizziness, headache, tachycardia, arrhythmias, stupor, confusion
>50 %	Central nervous system hypoxia, coma, respiratory depression, tachypnoea, ischaemia, metabolic acidosis, dysrhythmias, bradycardia, heart failure, seizures
>70 %	Severe hypoxia, death

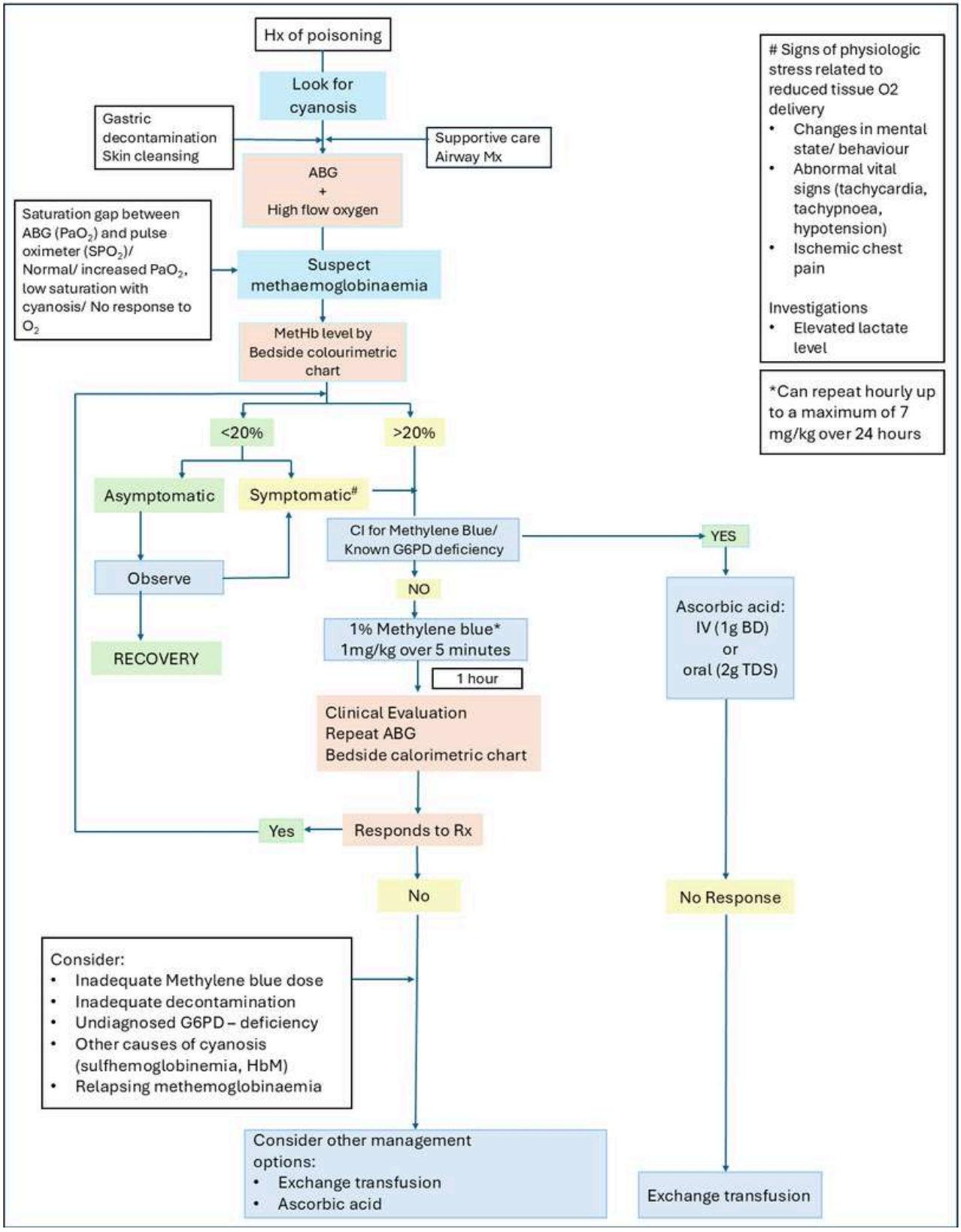

Figure 1 - **Management of methaemoglobinaemia due to the propanil poisoning**

(flow chart for easy use in the emergency setting) *[Hx – history, Mx – management, ABG – arterial blood gas, O2 – oxygen, PaO2 – partial pressure of oxygen in ABG, SPO2 – Pulse oximeter oxygen saturation, MetHb – methemoglobin, G6PD - glucose-6-phosphate dehydrogenase, HbM – haemoglobin M, CI - contraindication]*

oxygen therapy either in the form of a face mask or assisted ventilation.(4)

Arterial methaemoglobin levels should be monitored if facilities are available. 20% or more methemoglobin level is the treatment threshold used in Sri Lankan guidelines.(5,11) The quantitative methaemoglobinaemia bedside test with the graded colour chart can be used to get a methaemoglobinaemia estimation which may range from normal to 80% and this enables the rapid diagnosis of methaemoglobinaemia in resource-poor settings like Sri Lanka.(5,11) The introduction of this simple test has reduced the case fatality from 9.5% to 3.1% with increased use of methylene blue from 10% to 55% of propanil poisoning cases in three tertiary care centres in Sri Lanka. This simple measure has reduced the rate of using ascorbic acid and the need for exchange transfusion.(5)

ABG should be done along with other basic investigations (full blood count, liver and renal functions and coagulatory profile) to detect acidosis, elevated lactate level and saturation gap (>5 is considered abnormal).(3,12)

If haemolysis is suspected, serum bilirubin levels, serum lactate dehydrogenase (LDH) level, blood picture and urinalysis are also indicated.(3) Haemoglobin level should be monitored to both detect and monitor haemolysis and if this results in anaemia, folic acid supplements may be necessary during the recovery phase.(9)

Severe propanil poisoning ideally should be managed in an intensive care unit (ICU) with cardiac monitoring.(4)

Methylene blue

The antidote for propanil poisoning is methylene blue. It reduces blood methaemoglobin levels by converting methaemoglobin into haemoglobin. The dose in both adults and children is IV methylene blue 1 - 2 mg/kg body weight (1% methylene blue 0.1 ml/kg) over 5 minutes. The same dose should be repeated in one hour if the symptoms are not improved.(2-6)

Additional boluses may be required in severe poisoning with large propanil ingestions as methaemoglobinaemia may relapse.(2,4) Doses greater than 7 mg/ kg should be used with caution as haemolysis due to methylene blue toxicity may aggravate the methaemoglobinaemia.(5)

If IV methylene blue is not available or in the case of a mild poisoning, oral preparation can be used, as a 300 mg daily dose.(4,8)

A main enzyme defect that is responsible for haemolysis is glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD deficient red cells have low capacity to produce NADPH which is used as the reducing agent of glutathione. Reduced glutathione is important for protection of red cells against both haemolysis and methaemoglibinaemia. Methylene blue also needs NADPH for successful antidotal action (to reduce methaemoglobin). When there is methaemoglibinaemia in a G6PD deficient red cell, both oxidised glutathione and methylene blue compete with each other for NADPH resulting in methylene blue-induced haemolysis. This can exacerbate methaemoglibinaemia, making the treatment with methylene blue less effective. Also, haemolysis is caused by oxidative stress and can occur with methaemoglibinaemia. However, as the expression of deficiency states is variable, we cannot predict who will respond to the treatment.

There is a considerable prevalence of full or partial G6PD deficiency among the Sri Lankan population, making these individuals more vulnerable to severe adverse outcomes due to antidotal treatment with methylene blue.(13,14)

Ascorbic acid

Alternatively, if any form of methylene blue is not available or if methylene blue is contraindicated (e.g., allergy), ascorbic acid (vitamin C) can be given orally or as IV infusions.(3, 4) It is also the drug of choice in patients with G6PD deficiency. Ascorbic acid can directly reduce Methaemoglobin. It generally requires multiple doses and may take 24 hours or longer to lower Methemoglobin levels. Dosing of ascorbic acid in propanil poisoning is not yet well standardised. Doses in adults have ranged from 0.5 g orally every 12 hours × 16 doses, 1 g orally every 12 hours × 14 doses, 1.5-2 g IV × 3–4 infusions, 5 g orally every 6 hours × 6 doses, or even 10 g orally × one dose.(15)

Exchange transfusion

Exchange transfusion is a life-saving measure in severe propanil poisoning when there is no improvement with methylene blue, it is contraindicated or not available.(3, 6, 8, 12). The total volume to be replaced is calculated according to the patient's body weight and estimated blood volume. It replaces methaemoglobin and improves the oxygen-

carrying capacity of blood by giving new red blood cells.(3) Treatment with exchange transfusion requires extensive monitoring and is ideally done in the ICU set up. There can be a requirement for additional methylene blue doses even after exchange transfusion.(5) There are complications of exchange transfusion such as blood-borne infections, transfusion reactions, venous catheter site infections and electrolyte imbalance.(3)

Venesection-blood transfusion cycles

Arunpriyandan et al. describe manual exchange transfusion as a treatment modality which can be used in a resource-poor setting. Here, they manually removed methaemoglobin-containing blood via venesection and replaced the same amount of blood soon after via blood transfusion, thus providing healthy red blood cells.(2) The number of cycles that need to be run may vary with the clinical condition of the patient and typically follows the regime of exchanging 1 unit every 1 -2 hours until the recovery or patient's death.(9) However, in the reported case, the patient improved with each venesection-blood transfusion cycle, and the pulse oximeter reading became normal after three cycles.(2)

N-acetylcysteine (NAC)

The role of NAC in the treatment of methaemoglibinaemia is unclear and questionable. Although according to in vitro data, it is an antioxidant that can increase depleted intracellular glutathione stores, there is no clinical data to recommend its use in propanil poisoning.(15,16). But it has been suggested for use in patients with G6PD deficiency when there is methaemoglibinaemia.(15) As dose-response studies are not available, NAC can be administered in a dose similar to that used in paracetamol poisoning. The initial dose of NAC is administered over a longer period. The dose in adults starts with IV NAC 150 mg/kg over 4 hours, then 50 mg/kg over 4 hours, followed by an infusion of 100 mg/kg over 16 hours. The last infusion should be repeated until the patient has recovered.(16)

Challenges and recommendations

Sri Lanka despite having a remarkably high standard of health care in the South Asian region faces a lot of challenges as a low-income country.

While methylene blue remains the drug of choice to treat propanil poisoning, we should not hesitate to use repeated doses of methylene blue and exchange transfusion as a life-saving treatment for severe poisoning when the time comes. Unfortunately, exchange transfusions are usually available at tertiary care centres while many poisonings present to peripheral hospitals.

The unavailability of an adequate amount of IV methylene blue in most hospitals for repeated doses, lack of ICU beds, unavailability of exchange transfusion facilities in regional hospitals, and inability to measure methemoglobin levels due to the unavailability of laboratory facilities are some of the challenges we face.

The colour chart for quantitative estimation of clinically significant methaemoglobinaemia is a low-cost bedside test that needs to be popularized among healthcare professionals and distributed in all hospitals.

It is recommended to use the colour chart in the management of propanil poisoning. Use methylene blue according to the methaemoglobinaemia level and arrange early transfer to an exchange transfusion available tertiary care centre and/or commence early exchange transfusion.

The management guidelines indicate that repeated doses of methylene blue may be needed in severe propanil poisoning but the frequency of administering these subsequent doses is unclear. Whether it is also by hourly intervals or beyond that, needs to be evaluated. Clarifying the best timing for exchange transfusion needs further research. However, whether it can be used as a first-line treatment for severe methaemoglobinaemia is questionable.(12) It needs further standardised studies involving uniform exchange transfusion protocols to see the actual efficacy and usefulness of this treatment modality.

Management options to be used in resource-poor settings should be further explored and evaluated so that they can be a guide for physicians managing these cases in the periphery.

The way forward

The National Poison Information Centre of Sri Lanka, established in 1988, serves as a critical resource for both the public and healthcare professionals, offering vital information on toxins and poisonings. This centre plays a pivotal role in addressing inquiries and

providing timely guidance in cases of exposure to harmful substances.(17)

In addition, the Teaching Hospital Peradeniya houses a dedicated Toxicology Unit, featuring 35 beds and 3 ICU beds specifically reserved for toxicology patients. (18) This specialised unit is equipped to handle severe cases of poisoning, ensuring focused care and monitoring. The unit also operates a nationwide hotline, which healthcare teams from across the country rely on to access essential information and expert advice in managing toxicological emergencies. Through this integrated approach, the Toxicology Unit and the Poison Information Centre work hand-in-hand to safeguard public health and support healthcare professionals in providing life-saving interventions.

We need to update the poisoning management guidelines with evidence-based medicine and distribute them in all government hospitals. As an initiative, the Sri Lanka College of Internal Medicine has launched a book on 'Essential Clinical Toxicology' which can be used as a guide in the management of poisonings. Periodic workshops to educate healthcare professionals are also useful in disseminating knowledge. The ministry of health should establish facilities to measure methemoglobin levels as it helps determine the severity of poisoning, response to treatment and make decisions regarding further treatment.

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PRACTICE GUIDELINE

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Managing acute kidney injury in oncology patients: a guidance for the Internist

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Case vignette

A 64-year-old woman, recently diagnosed with diffuse large B-cell lymphoma, presents with increasing fatigue, shortness of breath, nausea, and decreased urine output over the last five days. She recently finished her second cycle of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Her medical history includes hypertension, managed with an angiotensin-converting enzyme inhibitor.

The patient appears lethargic, with low blood pressure (85/50 mmHg) and tachycardia (110 bpm). She has dry mucous membranes, mild peripheral oedema, and reduced skin turgor. There is tenderness in the right flank, but no evidence of bladder distension on palpation.

The patient's laboratory results show a serum creatinine of 3.8 mg/dL (baseline 1 mg/dL), Elevated blood urea nitrogen of 50 mg/dL, and serum potassium of 6.2 mEq/L. Further investigations revealed elevated calcium, LDH, and uric acid levels. Urinalysis showed mild proteinuria and an ultrasound scan showed hydronephrosis of the right kidney.

- What is the cause of acute kidney injury (AKI) in this patient?
- How would you manage this patient?

Introduction

Acute kidney injury (AKI) is a common and serious complication in oncology patients, with a reported incidence ranging from 24% to 52% (1,2), and is associated with increased morbidity and mortality. In patients with malignancies, AKI can arise due to the direct effects of the cancer itself, as a side effect of cancer treatment, or secondary to factors such as infections or dehydration. This condition not only exacerbates morbidity and mortality but also presents a significant clinical challenge due to the complexity of the patient's underlying conditions. Effective management of AKI in oncology patients requires a multidisciplinary approach. Therefore, it is essential for internists to remain up-to-date with evidence-based strategies for understanding, diagnosing, and managing AKI in this unique patient population.

Causes of AKI

As in other general medical patients, the causes can be broadly categorised into pre-renal, intrinsic renal, and post-renal, with specific cancer and treatment-related causes in each category.

(1) Prerenal

- **Dehydration and hypovolemia** are common in patients who are undergoing chemotherapy due to vomiting, diarrhoea, and reduced oral intake. (3,6)
- **Tumour lysis syndrome** is common in patients with haematological malignancies. The cumulative effect of hypovolaemia from dehydration and the effects of electrolyte disturbances (hyperkalemia and hypocalcemia) on the cardiovascular system leads to reduced renal perfusion.(1,7)

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- **Sepsis** is another leading cause of AKI in this group of patients and the disease and treatment-related immunodeficiency plays a key role in pathogenesis.(2,5)

(2) Intrinsic renal causes

- **Nephrotoxicity of chemotherapeutic agents**

As internists, it is very important to be familiar with common chemotherapeutic agents and their mechanisms of nephrotoxicity to identify and manage AKI in oncology patients effectively. Chemotherapy-induced acute kidney injury (AKI) occurs through various mechanisms depending on the drug class as outlined below.(6,9)

- **Thrombotic microangiopathy (TMA)**

TMA results from endothelial injury leading to microvascular thrombosis. This can be a consequence of the malignancy itself or treatment; e.g., chemotherapy (e.g., cisplatin, gemcitabine) or targeted therapies (e.g., VEGF inhibitors). The

Table 1 - Main pharmacological agents causing acute kidney injury (AKI) in oncology patients

Drug Class	Chemotherapy Agent	Mechanism of Nephrotoxicity	Type of AKI
Platinum-based Compounds	Cisplatin	Direct tubular toxicity, oxidative stress, and apoptosis of renal tubular epithelial cells leading to tubular injury and inflammation	Acute tubular necrosis (ATN)
Folate Antagonists	Methotrexate, Pemetrexed	Methotrexate: Precipitates in renal tubules, causing tubular obstruction and direct tubular damage.Pemetrexed: Inhibits folate metabolism, leading to tubular injury	Crystal-induced AKI, ATN
Alkylating Agents	Cyclophosphamide, Ifosfamide	Cyclophosphamide: Toxic metabolites (acrolein) cause haemorrhagic cystitis and obstruction.Ifosfamide: Oxidative stress induces proximal tubular injury	Haemorrhagic cystitis, Post-renal AKI, ATN
Proteasome Inhibitors	Bortezomib	Direct tubular toxicity and may induce thrombotic microangiopathy via proteasomal pathway disruption in renal endothelial cells	ATN, Thrombotic Microangiopathy (TMA)
Anthracyclines	Liposomal Doxorubicin	Oxidative stress and free radical formation leading to proximal tubular damage	ATN
Antibiotics (Cytotoxic)	Mitomycin-C	Endothelial damage leading to thrombotic microangiopathy and glomerular dysfunction	TMA
Immune Checkpoint Inhibitors	Nivolumab, Pembrolizumab	Immune-mediated inflammation of renal interstitium causing acute interstitial nephritis	Acute interstitial nephritis (AIN)
Vascular Endothelial Growth Factor (VEGF) Inhibitors	Bevacizumab	Endothelial damage in glomerular capillaries leads to thrombotic microangiopathy and subsequent AKI	TMA
Drug Class	Chemotherapy Agent	Mechanism of Nephrotoxicity	Type of AKI

microthrombi occlude the renal microvasculature leading to renal ischaemia.(7,9)

- **Radiation Nephropathy**

Interstitial fibrosis and glomerular injury can lead to AKI if the kidneys are directly within the radiation field.(8)

(3) Post renal causes

- **Obstructive Uropathy**

Gynaecological and urological cancers can directly compress or infiltrate the ureters leading to obstructive uropathy.(5)

- **Urolithiasis**

Certain medications like sulphonamides and hyperuricaemia in tumor lysis can lead to the formation of renal stones.(10)

Diagnostic workup

Tables 2 and 3 summarise the important points in clinical assessment (11) and a framework for targeted investigations.(12-14)

Management principles

Once established, the management of AKI is focused on correction of the underlying cause of AKI and providing supportive care.

(1) Supportive care

Fluid resuscitation:

The use of isotonic crystalloids, such as normal saline, is recommended as the first choice for fluid resuscitation. The approach should be tailored to the patient's haemodynamic condition, signs of volume depletion, and the risk of fluid overload, particularly in those with pre-existing conditions like heart failure or respiratory problems.(6,15)

Electrolyte management:

Careful monitoring of electrolyte levels is crucial in oncology patients, particularly in the setting of tumor lysis syndrome (TLS) or sepsis. Timely correction of hyperkalemia, hyperphosphatemia, and hypocalcemia is necessary to prevent serious cardiac and neurological complications.(7)

Dialysis:

Renal replacement therapy (RRT) may be necessary in cases of severe AKI, particularly when patients have persistent hyperkalemia, metabolic acidosis, or fluid overload that does not respond to standard treatments. In critically ill patients, continuous renal replacement therapy (CRRT) is often favoured over intermittent haemodialysis to prevent sudden fluid shifts.(12,15)

Table 2 - Important aspects of clinical assessment

Clinical history
• Type of cancer and stage • Cancer treatments and medications • Hydration status • Symptoms suggestive of obstruction – flank pain, anuria
Physical examination
• Volume status • Palpable bladder • Abdominal masses • Flank tenderness • Signs of uraemia • Oedema

Table 3 - Laboratory and imaging investigations

Investigation	Significance/ use of the investigation
Serum Creatinine and Blood Urea Nitrogen (BUN)	• Serial measurements are essential for assessing the severity of acute kidney injury (AKI) • BUN to creatinine ratio may provide clues regarding prerenal vs intrinsic renal causes of AKI
Electrolytes and Acid-Base Status • Serum electrolytes (potassium, calcium, phosphate, and bicarbonate levels) • pH • Uric acid levels	• To monitor electrolyte and acid-base disturbances associated with tumour lysis syndrome (TLS) or renal failure
Urinalysis and Urine Microscopy	• Examination of urine sediment can help distinguish between prerenal and intrinsic renal causes. ◦ Muddy brown casts → Acute tubular necrosis ◦ Dysmorphic red cells or white cells → glomerulonephritis or interstitial nephritis
Tumour Lysis Syndrome Panel (uric acid, phosphate, calcium, and LDH levels)	• Monitor uric acid, phosphate, calcium, and LDH levels in patients at risk of TLS to detect early signs of TLS-induced AKI.
Ultrasound of the Kidneys and Bladder	• A non-invasive, rapid method for evaluating hydronephrosis, renal stones, or mass lesions causing obstructive uropathy.
CT or MRI	• When ultrasound findings are inconclusive, contrast-enhanced CT or MRI may be required for further evaluation. • Assess risk and take preventive measures for contrast-induced nephropathy.

(2) Management of Specific Causes

- **Tumour Lysis Syndrome**

AKI due to TLS can be anticipated in high-risk patients like in those with haematological malignancies and following preventive methods are recommended. (7,14)

- **Hydration**: aggressive intravenous fluid administration (2–3 L/m^2/day) to maintain high urine output.
- **Allopurinol / Rasburicase**: to prevent hyperuricaemia.
- **Monitoring**: frequent monitoring of electrolytes (potassium, phosphate, calcium, and uric acid), renal function, and fluid balance.

Established TLS will need prompt identification and intervention.(7,14)

- Correction of Electrolyte Imbalances
  - Hyperkalemia: administer calcium gluconate, insulin/ dextrose
  - Hyperphosphatemia: restrict phosphate intake and administer phosphate binders if needed
  - Hypocalcaemia: treat if symptomatic or if calcium levels are critically low
- Renal replacement therapy (RRT): recommended for cases of persistent electrolyte imbalances, oliguria, or fluid overload that do not respond to other treatments.
- Managing uric acid: continue treatment with allopurinol or rasburicase to maintain low uric acid levels.

- **Nephrotoxicity from chemotherapy:**

Management of chemotherapy-induced nephrotoxicity involves several key principles.(9)

  - Pre-treatment assessment: evaluate kidney function and risk factors
  - Hydration: ensure adequate hydration to maintain renal perfusion
  - Dose adjustment: adjust chemotherapy doses based on renal function
  - Avoidance of nephrotoxic agents: avoid co-administration of NSAIDs, aminoglycosides, and contrast agents where possible
  - Monitoring: regular monitoring of renal function and early detection of kidney injury
  - Cytoprotective agents: use agents like mesna (for cisplatin) to reduce nephrotoxicity risk
  - Electrolyte correction: promptly correct imbalances
  - Renal replacement therapy (RRT): may be required in severe cases of renal failure

- **Obstructive uropathy**

Immediate relief of obstruction is critical in managing post-renal AKI. For tumour-related obstructions, procedures like ureteral stenting or percutaneous nephrostomy may be necessary to reestablish urine flow.(10)

As outlined above, preventive measures like hydration protocols, regular monitoring of renal functions, and dose adjustments of nephrotoxic agents can help prevent and minimize the risk of AKI in oncology patients.

Back to the case vignette……

AKI in this patient is likely to be multifactorial, a combination of pre-renal AKI (hypotension and volume depletion, caused by vomiting, diarrhoea, and poor oral intake) worsened by chemotherapy and tumour lysis syndrome (TLS). Elevated uric acid, LDH, and hyperkalemia are consistent with TLS, which can cause crystal deposition in the kidneys, leading to tubular obstruction. Additionally, drug-induced nephrotoxicity, from cyclophosphamide, doxorubicin, and an ACE inhibitor, likely contributed to tubular damage and decreased renal perfusion. The presence of hydronephrosis suggests a component of obstructive AKI, possibly due to tumor compression or retroperitoneal lymphadenopathy.

Principles of management include aggressive intravenous (IV) hydration with normal saline to correct hypotension, treatment of TLS with allopurinol or rasburicase and sodium bicarbonate, monitoring and treating hyperkalemia, discontinuing nephrotoxic drugs like ACE inhibitors, and follow-up renal ultrasound to monitor hydronephrosis and potential obstruction.

Summary

Acute kidney injury (AKI) in oncology patients is a complex and multifaceted condition that greatly affects patient outcomes. The causes of AKI in these patients vary widely, including prerenal factors such as dehydration, intrinsic renal injury from nephrotoxic drugs, and post-renal obstruction. Early detection and timely management, including supportive care, addressing the root cause, and implementing preventive strategies, are key to improving outcomes. Effective management requires a multidisciplinary team involving oncologists, nephrologists, physicians, and other specialists to ensure comprehensive care for these patients.

Declarations

Data accessibility statement
No new datasets were generated or analyzed during the preparation of this article. All referenced data and information are derived from publicly available studies and resources as cited in the manuscript.

Ethics and consent statement
This article does not involve any new research on human participants or animals. The case vignette ensures no patient identifiers are disclosed.

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Dr UM Wariyapperuma conceptualised, wrote, and revised the manuscript.

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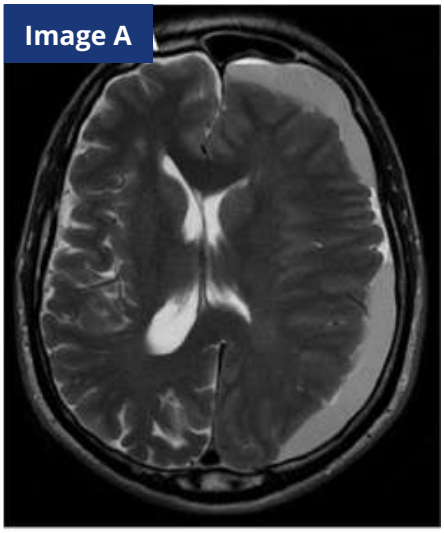
(1) A 64-year-old man presents with altered mental status, characterised by repeated attempts of buttoning and unbuttoning his shirt, new-onset slurred speech, and mild weakness on the right side of his limbs. A non-contrast MRI is performed. (See image: A)

What is the diagnosis?

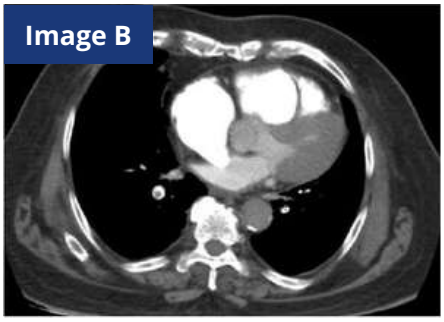
(A) Extradural haemorrhage
(B) Subdural haemorrhage
(C) Subdural empyema
(D) Subdural hygroma
(E) Unilateral cerebral atrophy



(2) A 45-year-old woman presents with gradual onset of shortness of breath for 2-3 hours, sharp and stabbing chest pain aggravated by deep breathing and cough. Based on clinical history, examination, and blood investigations, a computed tomography pulmonary angiogram (CTPA) is performed. (See image: B)

What is the diagnosis?

(A) Aortic dissection
(B) Left ventricular thrombus
(C) Heart failure
(D) Myocardial infarction
(E) Pulmonary embolism

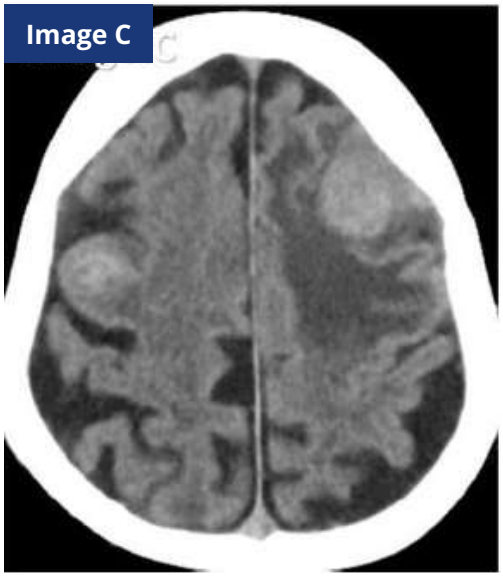


(3) A 65-year-old man presents with a headache and a seizure episode. His past medical history revealed features of severe bladder outflow obstruction for three months and was otherwise unremarkable. A non-contrast CT is performed. (See image: C)

What is the diagnosis?

(A) Brain metastasis
(B) Developing cerebral abscess
(C) Glioma
(D) Haemorrhagic infarction
(E) Meningioma

Image C

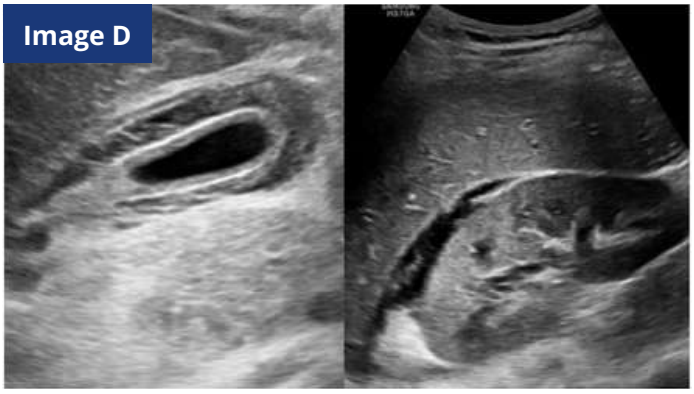


(4) A 45-year-old man presents with generalised abdominal pain and a few episodes of vomiting for one day. Prior to this presentation, he had a fever, headache, and generalised body aches and pains for three days. The physical examination revealed tachycardia of 110/minute and blood pressure of 100/70 mmHg. Point of care ultrasonography (PoCUS) is performed (See image: D)

What is the most possible diagnosis?

(A) Acalculous cholecystitis
(B) Calculous cholecystitis
(C) Decompensated cirrhosis
(D) Dengue haemorrhagic fever
(E) Pancreatitis

Image D

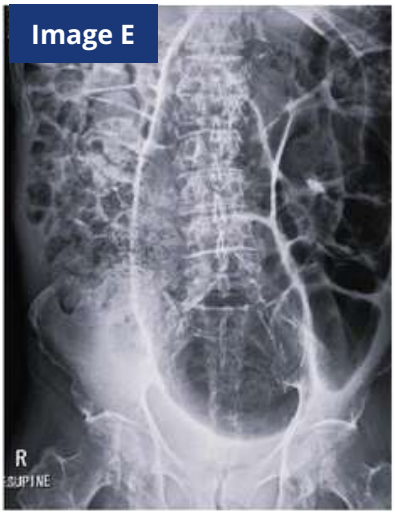


(5) A 75-year-old man from an elderly home, presents with a 6-day history of worsening colicky abdominal pain and vomiting. He has not opened his bowels for four days and is now unable to pass flatus. Supine abdominal X-ray is performed (See image E)

What is the possible interpretation?

(A) Caecal volvulus
(B) Colonic diverticulum
(C) Gastroparesis
(D) Sigmoid volvulus
(E) Toxic megacolon

Image E

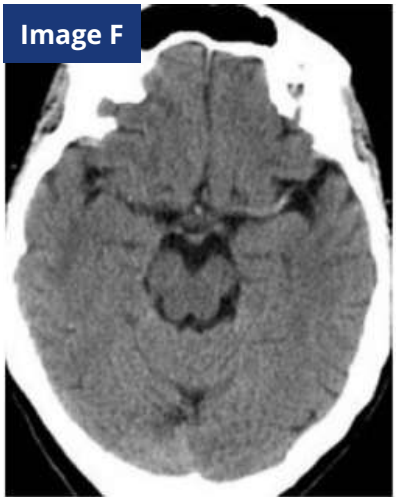


(6) A 60-year-old man presents with acute dysphasia and mild right-sided leg-arm weakness. A non-contrast CT of the brain is performed three hours after the incidence (See image: F)

What is the possible interpretation?

(A) Lacunar infarct
(B) Left dense middle cerebral artery sign
(C) Middle cerebral artery aneurysm
(D) Middle cerebral artery calcification
(E) Subarachnoid haemorrhage

Image F



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N.B.: The above photographs were published with consent from the respective patients.
**Refer the PICTURE QUIZ-KEY; pages 171-174 for answers and explanations.*

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Cerebral T waves in ischaemic stroke: an uncommon yet significant ECG finding

Kajananan S[1], Merjiny S[1], Nalayani J[1], Perananthara jah T[1]

A 62-year-old woman presented with sudden onset of left side face, arm, and leg weakness, raising immediate concern for a cerebrovascular accident. Non-contrast computed tomography of the brain revealed acute infarction involving right basal ganglia and internal capsule with early haemorrhagic transformation (figure 1A). Interestingly, the patient's initial electrocardiogram (ECG) was normal. However, a subsequent ECG performed on the following day revealed diffuse T inversions with striking giant T-wave inversions in the chest leads of V3-V6, accompanied by prolonged QT interval (figure 1B). Troponin I was marginally elevated, and subsequent measurements showed a decreasing trend. However, she did not complain of chest pain. 2D echocardiography showed rheumatic heart disease with mitral stenosis, anterior and lateral wall hypokinesia, and an ejection fraction of 40%. T-wave inversions produced by myocardial infarction are classically narrow and symmetric, while “cerebral T waves” are widespread giant T-wave inversions with QT prolongation.(1) Cerebral T waves and left ventricular dysfunction are uncommon manifestations in acute cerebrovascular events. In a retrospective analysis by Stone et al., only seventeen out of eight hundred patients with acute stroke exhibited cerebral T waves on their ECGs. Notably, they identified three cases where cerebral T waves were associated with left ventricular wall motion abnormalities, all of which were linked to infarcts within the middle cerebral artery distribution; findings that closely parallel our patient’s clinical presentation.(2)

Follow-up ECG demonstrated complete resolution of the T-wave inversions, and a repeat 2D echocardiogram showed no regional wall motion abnormalities with normal left ventricular function, while rheumatic heart disease findings remained unchanged. Additionally, a coronary angiogram was performed and revealed normal coronary arteries.

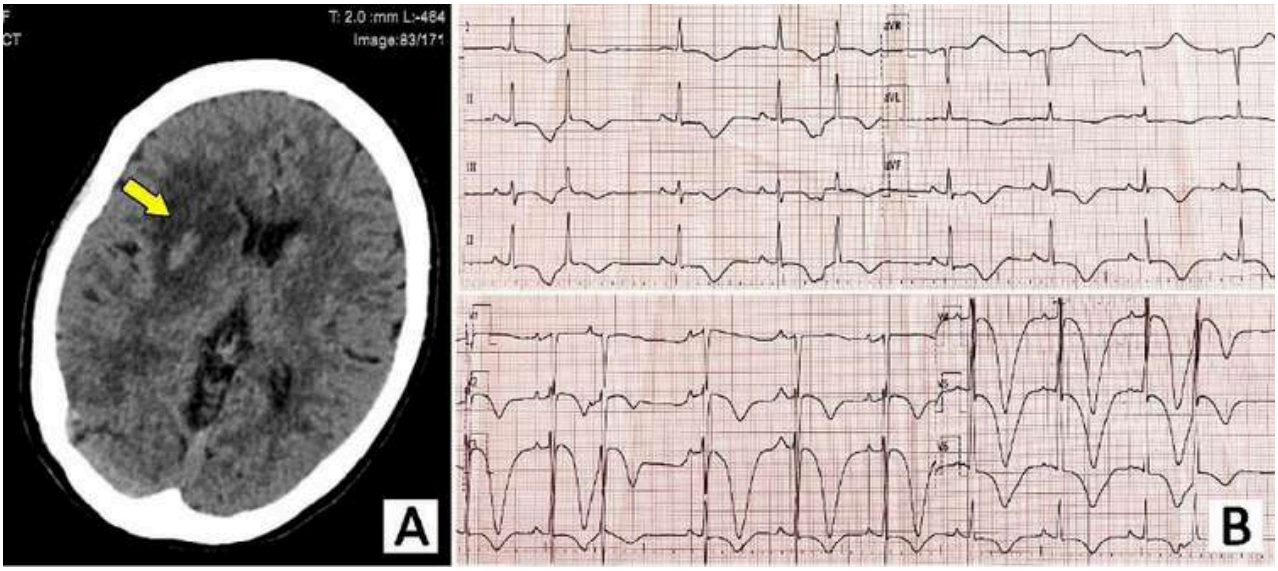

Figure 1 - **Panel A**: Non-contrast computed tomography of the brain showing acute infarction involving right basal ganglia and internal capsule with early haemorrhagic transformation; **Panel B**: ECG showing diffuse T inversions with striking giant T-wave inversions in the chest leads of V3-V6, accompanied by prolonged QT intervals

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Consent for publication was obtained from the patient

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Proptosis leading to unveiling of granulocytic sarcoma in acute myelocytic leukaemia

Kajananan S[1], Merjiny S[1], Nalayani J[1], Perananthara jah T[1]

A 35-year-old man presented with a one-month history of intermittent fever, fatigue, and progressive changes in facial appearance. He also complained of heaviness in head and blurring of vision. On examination, he was found to have bilateral proptosis (figure 1-A), which raised concerns for an underlying systemic condition.

Figure 1 - **Panel A:** photo of the patient showing asymmetrical proptosis (L>R) of the both eyes

Laboratory investigations revealed leucocytosis of 24.1 x 10^9/L, anaemia and thrombocytopenia. Blood picture and bone marrow biopsy with flow cytometry findings were consistent with acute myeloid leukaemia. Non-contrast computed tomography of the brain revealed soft tissue density masses involving bilateral frontal lobes (figure 2-B) and frontal sinuses. Large soft tissuedensity masses involving both orbital cavities leading to proptosis (figure 2-C and 2-D). Overall findings favoured granulocytic sarcoma involving the central nervous system and cranial bone. Granulocytic sarcoma, also known as myeloid sarcoma, is a rare extramedullary tumour composed of immature granulocytic cells. It is a rare condition that is oftenaccompanied with acute myeloid leukaemia.(1) This case emphasises the importance of considering the diagnosis of granulocytic sarcoma in patients presenting with bilateral proptosis, especially when associated with constitutional symptoms, leucocytosis and other cytopenia.

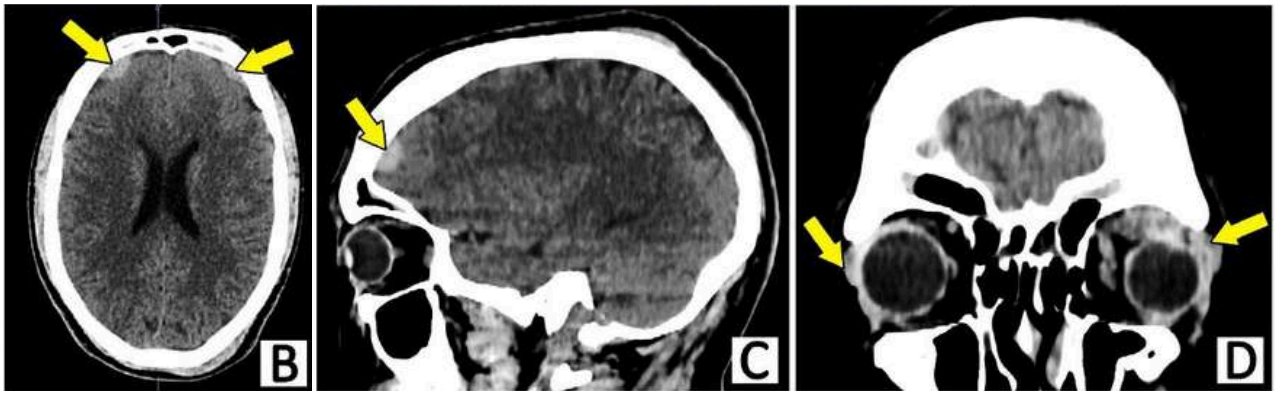

Figure 2 - **Panel B:** axial computed tomography of brain showing subdural soft tissue masses (arrow) adjacent to bilateral frontal lobes; **Panel C:** sagittal computed tomography of brain showing subdural soft tissue mass (arrow) adjacent to frontal lobe; **Panel D:** coronal computed tomography of head showing bilateral orbital masses (arrow) predominantly involving the left side.

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[1]Teaching Hospital Jaffna, Sri Lanka

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Severe mucositis as a rare manifestation of *Mycoplasma pneumoniae* infection

Kajananan S[1], Jithusman S[1], Nalayani J[1], Perananthara jah T[1]

A 15-year-old boy presented with a febrile illness accompanied by a productive cough with whitish sputum for three days. On the second day of the illness, he developed red eyes and oral ulcers involving the lips, tongue, and oral cavity mucosa. This inflammation of the oral mucosa caused pain and discomfort, particularly during eating and drinking. Subsequently, these ulcers worsened, becoming severe enough to cause bleeding, leading the patient to seek medical attention. He appeared ill and was febrile, but there was no respiratory distress, and his SpO_2 was 98% on room air. There were a few crepitations on auscultation of lungs. He had conjunctivitis with discharge in the physical examination of both eyes (figure 1-A). Examination of the mouth showed inflamed swollen lips with haemorrhagic exudate (figure 1-B), and severe mucosal inflammation with ulcers over the buccal mucosa, soft and hard palate, and tongue (figure 1-C). He did not have any skin rashes. His chest X-ray revealed bilateral inflammatory infiltrates predominantly in the left upper lobe (figure 2-D). The serum antibody to Mycoplasma pneumoniae titre was significantly positive, 1: 10,240 (reference level <1:40). The clinical presentation and investigations were consistent with Mycoplasma pneumoniae-induced mucositis. He was treated with azithromycin 500 mg daily with supportive care for mucositis including antiseptic mouthwash and eye drops. Follow up visit after two weeks showed complete resolution of the mucositis. Mycoplasma pneumoniae-induced mucositis typically affects younger patients and has limited cutaneous findings,and a more favourable prognosis compared to Stevens-Johnson syndrome / toxic epidermal necrolysis.(1)

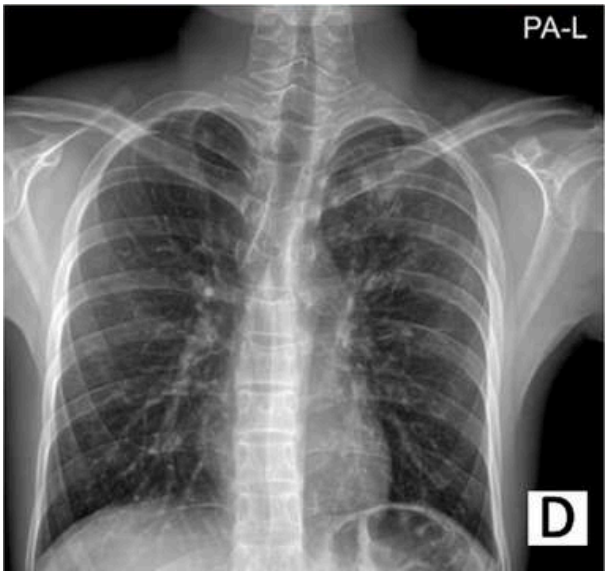

Figure 2 - **Panel D:** chest X-ray revealed bilateral inflammatory infiltrates predominantly in the left upper lobe

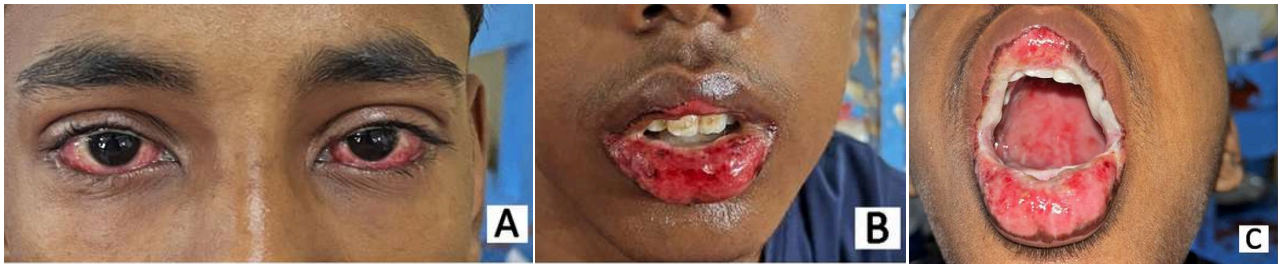

Figure 1 - **Panel A:** conjunctivitis with eye discharge from both eyes; **Panel B:** mucositis involving the lips leading to haemorrhagic exudative; **Panel C:** severe mucosal inflammation with ulcers over the palate

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CASE REPORT

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Fipronil poisoning presenting as seizures and rhabdomyolysis - an unusual presentation

Basnayake BRCM[1]*, Yathukulan S[1], Mayurathan P [1,2]

Abstract

Fipronil is a common N-phenylpyrazole group pesticide used in Sri Lanka. Literature on the effects of fipronil poisoning effects in humans are limited. Most are gastrointestinal and neurological effects which are short lasting; about three days. We report a case of fipronil poisoning presenting with convulsions. It was complicated with rhabdomyolysis, pigment induced acute kidney injury and altered liver profile.

Keywords: fipronil, seizures, rhabdomyolysis, acute kidney injury

Introduction

Globally, deliberate self-poisoning with insecticides is a very common problem accounting for 300,000 deaths in the year 1985.(1) Two new classes of insecticides; organophosphorus and organochlorine compounds, developed in the last two decades, had the highest mortality if accidentally ingested.(1) Among them fipronil is considered a less toxic pesticide to human beings.

Fipronil is a broad-spectrum N-phenyl pyrazole insecticide with a trifluoromethylsulfonyl moiety (figure 1) that inhibits gamma aminobutyric acid A (GABA A) gated chloride channels. It has lower animal toxicity than other insecticides due to its high affinity for insects compared to mammalian GABA receptors. Fipronil can cause neurological and dermatological manifestations along with hepatic dysfunction and acute kidney injury in humans after acute exposure. To date Sri Lanka has reported 7 cases of fipronil poisoning, but none of those patients had rhabdomyolysis as a complication.(2) However, Yadla et al in 2017 reported a 45-year-old woman with fipronil poisoning, admitted on day 10, who had developed acute kidney injury (AKI) with a high CPK level of 1119 mcg/L.(3) Here, we describe a case of severe fipronil poisoning complicated with rhabdomyolysis, AKI and altered liver profile.

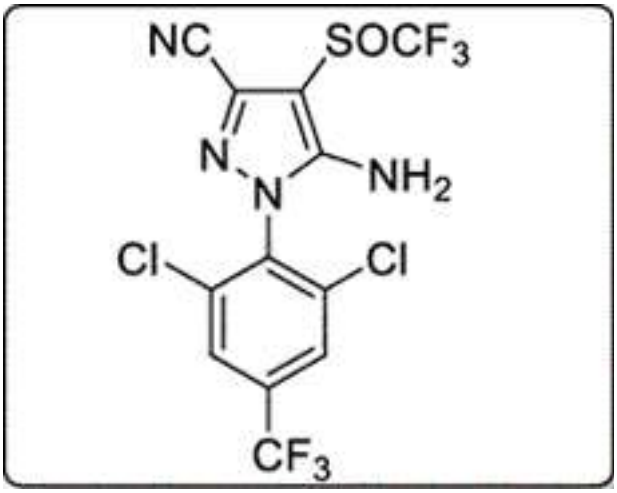

Figure 1 - chemical structure of fipronil

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Case presentation

A 38-year-old previously healthy man was admitted to the acute medical unit with a history of consumption of 50 mL of fipronil 6 hours prior to admission. He denied the consumption of any other possible poisons. He had 3 episodes of genralised tonic clonic (GTC) convulsions within the 1st 6 hours of presentation, each episode lasting for 3-4 minutes and resolving spontaneously. On admission GCS was 15, pulse rate was 102, blood pressure was 166/96 mmHg, pupils were reactive and the diameter was 2 mm. He had a tongue haematoma but other systemic examinations were unremarkable. Table 1 shows his investigation results on admission.

After 24 hours, he developed reduced urine output, <0.5 mL/kg/hour despite adequate fluid resuscitation. His serum creatinine rose to 293 from 149 umol/L. His repeat investigations showed; AST- 1176 U/L, ALT-134 U/L, serum phosphate - 1.5 (1.12-1.45 mmol/l), serum potassium 5.0 mmol/L (3.5-5.1 mmol/L), and serum calcium 2 mmol/L (2.12-2.55 mmol/l) after 24 hours. The 1st haemodialysis was performed after 48 hours of fipronil ingestion as he became anuric. Intravenous (IV) NAC 150 mg/kg bolus followed by a 6.25 mg/kg/hour infusion was started on day 2 as a liver protective measure because fipronil is known to cause liver damage. The infusion was stopped on day 4 as the INR was normal and liver functions were improving. CPK was done because of high serum creatinine.

Table 2 shows his clinical and biochemical parameters over the period of hospital admission.

Table 1 - Investigation results on admission

Investigation	Result	Reference range
Full blood count		
Haemoglobin (g/dL)	14.8	11.0 - 15.0
WBC (x10^3/uL)	23	4 - 11
Platelets (x10^3/uL)	453	150 - 450
Urine full report	Normal	
Serum electrolytes		
Serum sodium (mmol/L)	142	136 - 145
Serum potassium (mmol/L)	4.7	3.5 - 5.1
Liver function test		
Total bilirubin (mg/dL)	0.8	0.2 - 0.8
Serum albumin (g/dL)	3.7	3.5 - 5.5
Serum calcium (mmol/L)	2.3	2.12 - 2.55
Serum phosphate (mmol/L)	1.1	1.12 - 1.45
Arterial blood gas analysis		
pH	7.44	
pO2	45	
pCO2	88	
HCO3	21	
INR	1.01	(0.9 – 1.1)

Table 2 - Clinical and biochemical parameters over the period of hospital admission

Investigation	Reference range	Day									
		1	2	3	4	5	6	7	8	9	10
Blood urea (mmol/L)	2.1 -8.5	9.3	12.1	14.1	13.4	18.5	11.5	14.3	19.9	22.7	20.1
Serum creatinine (umol/L)	62-114	371	532	685	781	1017	745	709	811	838	671
AST (U/L)	12-78	1176	1738	2110	1308	672	279	198	118	89	54
ALT (U/L)	15-37	134	195	263	244	216	158	146	148	122	102
CPK (U/L)	55-170		87586	169086	109580	19176	5980	1385	1078		233
Urine output (mL)		50	100	145	305	520	550	828	770		

He was subjected to 3 cycles of haemodialysis during the hospital stay and discharged on day 14. At the end of four weeks, his renal functions and liver enzymes had normalised.

Discussion

Fipronil causes neuronal hyperexcitability by its cyclodiene and cycloalkane organochlorine components which act on GABA gated chloride channels and inhibits the passage of chloride ions.(4,5) Fipronil acts through an inhibitory neurotransmitter receptor called GABA A receptor.(6,7) The transmembrane hetero oligomeric glycoprotein GABA A receptor has five subunits from seven families.(8,9) In vitro, fipronil can act on either the beta 3 homooligomeric receptor or the native insect receptor with high affinity.(5,6)

Fipronil has 150-2000 times more selectivity and highest specificity towards insect GABA receptors over native mammalian receptors.(5,9) It binds to native human and mouse GABA receptors with around 6-fold higher avidity after being metabolised in mammals to a sulfone compound.(10)

Acute toxicity due to fipronil causes neurological symptoms at a dose >50 mg/kg (11,12) in laboratory rodents. The basic compound and active sulfone compound have the same toxicity.(12) However, the sulfone compound has the strongest binding ability to native human and animal GABA receptors. Rapid absorption of fipronil correlates with the clinical toxicity which peaks in the 1st few hours. Fipronil disappears rapidly from blood over the 1st 15-20 hours.(2) The gastric emptying procedures are not useful in fipronil poisoning due to comparatively low toxicity.(13)

In fipronil poisoning cases reported so far, patients presented with seizures but not rhabdomyolysis. This is the first case report where a patient presented with rhabdomyolysis due to fipronil poisoning.

A CPK value of more than 12 000 U/L is identified to have 64% sensitivity and 56% specificity for developing AKI.(14) So we monitored with CPK without assessing myoglobin levels since it was not available.

Conclusion

Fipronil can cause neurological and dermatological manifestations along with hepatic dysfunction and AKI in humans after acute exposure. Further prospective data are required to describe more fully, the natural history and characteristics of fipronil poisoning in humans. GTC convulsions following fipronil poisoning can be complicated with rhabdomyolysis and AKI. So, monitoring CPK and renal function are crucial within the 1st 48 hours. Seizure management should follow standard practice with administration of benzodiazepines as 1st line therapy together with oxygen and protection of the airway, followed by phenobarbital infusion as required for status epilepticus.(15) AKI may need

haemodialysis and if performed timely, the patient may recover as in this case. The timely assessment of serum biochemical parameters and prompt initiation of haemodialysis may result in better outcome. We hope this article helps primary care providers to understand the clinical manifestations and management of fipronil poisoning in humans, especially considering the rise in use of fipronil in the agricultural sector.

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest

Ethical Approval
Not applicable

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[2]Faculty of Healthcare Sciences, Eastern University Sri Lanka

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CASE REPORT

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Pulsating neck mass in a patient with transient ischaemic attack - an unusual case

Perera HMUAS[1]*, Premasiri DGAL[1], Rathnasiri KADV[1], Senadheera Y[1]

Abstract

The high-riding brachiocephalic trunk is a rare variation of the neck vessels that is often asymptomatic. It is usually discovered incidentally during neck surgeries and can sometimes result in life-threatening bleeding if not identified. Patients may have a pulsating mass in the front of the neck and may experience compressive symptoms such as difficulty in swallowing and stridor. We discuss a 71-year-old woman who presented with a pulsating anterior neck mass and also experienced a transient ischaemic attack. A computed tomography angiography of the neck vessels revealed normal carotid arteries and a high-riding variant of the brachiocephalic trunk along with atheromatous plaques. There were no signs of an aneurysm. Cerebrovascular accidents have been reported in patients with vascular anomalies of the neck vessels. However, the association of a high-riding variant of the brachiocephalic trunk with cerebrovascular accidents has not been discussed in current literature.

Keywords: high riding brachiocephalic trunk, pulsating neck mass, vascular anomalies, variations in neck vessels

Introduction

The brachiocephalic trunk, the first branch of the aortic arch, arises in the midline and travels upwards to the right, crossing the trachea. It then bifurcates posterior to the right sternoclavicular joint into the right subclavian and right common carotid arteries. While there are several anatomical variations of the neck vessels, a high-riding brachiocephalic trunk is a rare variant.(1)

Despite being mostly asymptomatic, it can be incidentally detected during neck surgeries, with patients potentially presenting with symptoms such as a pulsating anterior neck mass, stridor, or dysphagia due to tracheal and esophageal compression.

This variant is clinically significant, as it can lead to intraoperative complications like life-threatening bleeding during tracheostomy and thyroid surgeries, as well as late complications such as fistula formation.(2,3)

Although neck vessel anomalies are associated with the development of cerebrovascular accidents, the implications of the high-riding variant of the brachiocephalic trunk in the development of cerebrovascular accidents are poorly understood, and the available literature is limited.

Case presentation

A 71-year-old woman presented to the medical unit with complaints of weakness in the right upper and lower limbs and slurred speech which lasted for one hour. She had no history of diabetes mellitus, hypertension, or dyslipidaemia. The patient was on thyroxine following a total thyroidectomy performed 35 years ago for a multinodular goiter. No anatomical

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variants of neck vessels were noted during the surgery.

Upon examination, the patient was conscious, rational, and exhibited no weakness or sensory impairment in the upper or lower limbs. There were no cranial nerve palsies or cerebellar signs. The cardiovascular examination revealed no murmurs or irregular pulse. During the physical examination, a well-circumscribed, non-tender, and pulsatile anterior neck mass without a bruit was observed.

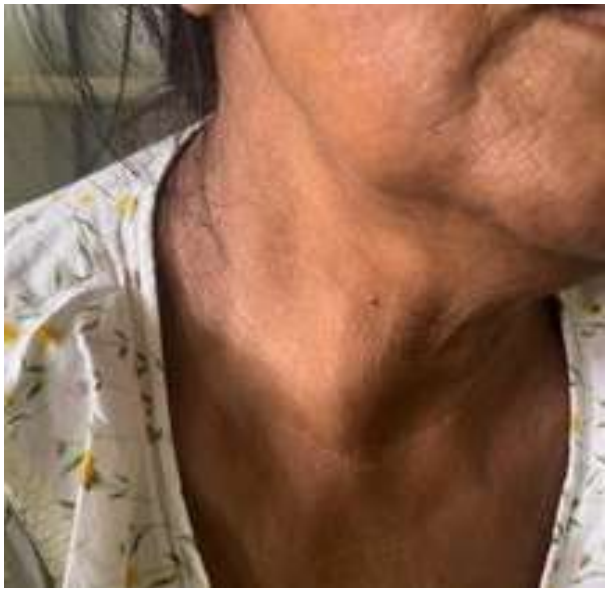

Figure 1 - Pulsating anterior neck mass

The NCCT brain showed no ischaemic changes or haemorrhages. There were no valvular lesions, intracardiac thrombi or vegetations on 2D echocardiogram. Ultrasonography of the neck showed focal dilatation of the bifurcation of the right brachiocephalic trunk with a degree of stenosis <50%, peak systolic velocity of the Internal carotid artery was <125 cm/sec, and the plaque estimate was <50%. Computed tomography angiography (CTA) of the neck vessels revealed normal carotid arteries, a high-riding variant of the brachiocephalic trunk, and two areas of atherosclerotic plaques without significant luminal narrowing or evidence of an aneurysm.

She received treatment for a transient ischaemic attack and was prescribed dual antiplatelet therapy and statins for the secondary prevention of ischaemic strokes. Screening for other vascular risk factors was conducted, revealing a HbA1c level of 5.4% with normal fasting blood sugar levels and a normal lipid profile. Her blood pressure remained within normal levels during the admission and subsequent follow-ups.

She was referred to the vascular surgery team for an assessment of the need for any surgical intervention for a high-riding brachiocephalic trunk. Since there was no aneurysmal dilatation in the CTA and considering the patient's age, no acute vascular surgical interventions were recommended. Instead, interval ultrasonographic screening for possible aneurysmal dilatation was suggested.

Discussion

The high-riding brachiocephalic trunk is a rare anatomical variant of neck vessels. In this variation, the brachiocephalic trunk is located between the 1st and 6th tracheal rings, as opposed to its normal position between the 6th and 13th tracheal rings.(4) This anomaly can complicate thyroid surgeries, tracheostomy, and may lead to life-threatening bleeding during surgery. Patients with this variant may experience symptoms such as dysphagia, stridor, and hoarseness of voice due to its proximity to the trachea and esophagus.(5)

Anatomical variants of neck vessels, particularly those involving aortic arch branches, can lead to increased pressure and altered branching patterns. This can result in high shear stress, endothelial damage, atheromatous plaque formation, luminal narrowing, and aneurysm formation. The altered hemodynamics can also lead to cardioembolic phenomena and predispose individuals to cerebrovascular events.(6,7)

In literature, it has been noted that variations in neck vessels are linked to cerebrovascular events. One particular variant, the bovine aortic arch, in which the brachiocephalic trunk and the left common carotid artery share a common origin, is more prevalent among patients who have experienced embolic strokes.(8)

Our patient, a 71-year-old woman, presented with a transient ischaemic attack. The CTA of the neck vessels revealed a high-riding variant of the brachiocephalic trunk with atheromatous plaques, without significant luminal narrowing and no evidence of aneurysm.

Although there is limited literature on the association between the high-riding variant of the brachiocephalic trunk and cerebrovascular accidents, it is possible that the mechanism of high shear stress leading to endothelial damage and altered haemodynamics in altered branched vessels may apply here as well.

Conclusion

In stroke patients, carotid and vertebral artery doppler studies are conducted as part of the routine stroke workup. Due to limited literature on anatomical variants of neck vessels and their association with cerebrovascular accidents, it is crucial to identify these variants in routine doppler studies. In cases of doubt, CT scans of the neck vessels are recommended. Proper documentation of these variants is essential when detected, as it can help prevent intraoperative complications.

Declarations

Author contributions
History taking, examination, necessary investigations arrangement, management under supervision, daily monitoring of the patient, and writing of the manuscript were done by Perera HMUAS. All authors contributed to writing the manuscript, read and approved the final manuscript.

Conflicts of interest
The authors declare that they have no conflicts of interest

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CASE REPORT

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Parathyroid adenoma causing severe hypercalcaemia presenting as acute psychosis; not to be overlooked

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Abstract

Neuropsychiatric manifestations due to hypercalcaemia is a known entity and rarely it can be the first manifestation of the disease. It can be challenging to diagnose acute psychotic symptoms associated with hypercalcaemia in individuals with existing psychological disorders particularly if organic causes are not properly evaluated. Therefore, it's important to consider hypercalcaemia as a potential cause in these patients. Mild cases may manifest as depression and cognitive changes, while severe cases can result in confusion, agitation, delusions, hallucinations and even coma.We present a case of a 68-year-old man with a previous history of diabetes mellitus, hypertension, dyslipidaemia and recently diagnosed moderate depression who presented to psychiatry services with psychomotor agitation, loss of short-term memory, disorientation, auditory hallucinations and delusions with a history of severe constipation. The patient showed poor response to psychotic medications and during the evaluation for organic causes, the patient was found to have severe hypercalcaemia with high parathyroid hormone levels. Ultrasound scan of the neck showed a heterogeneous hyperechoic lesion adjacent to the thyroid isthmus and 4D CT (parathyroid protocol) showed parathyroid adenoma in the right tracheoesophageal groove. Hypercalcaemia was initially managed with hydration and intravenous zoledronic acid. The patient's symptoms rapidly improved following the correction of hypercalcaemia and successful surgical resection of parathyroid adenoma without any post-surgical complications.

Keywords: hypercalcaemia, psychosis, parathyroid adenoma, primary hyperparathyroidism

Introduction

Primary hyperparathyroidism (PHPT) is the third most common endocrine disease, which can cause hypercalcaemia secondary to excessive parathyroid hormone secretion. In rare cases, it can initially present as acute psychosis. It is imperative to rule out organic causes before labeling it as primarily psychological. In patients with underlying psychiatric history, this is a diagnostic challenge.(13) Most patients are clinically asymptomatic but may experience signs or symptoms related to hypercalcaemia including polyuria, polydipsia, weakness, irritability, abdominal discomfort and nausea, skeletal complications/overt bone disease, nephrolithiasis, and occasionally acute pancreatitis. It is also known to cause neuropsychiatric manifestations including mood and cognitive changes. Rarely it also causes acute psychosis with aggression, delusions and hallucinations.(1-3)

Ultrasonography and Tc 99m-sestamibi scan and parathyroid four-dimensional CT are standard modalities for imaging parathyroid lesions. In overtly hypercalcaemic hyperparathyroidism, the decision to treat with parathyroidectomy is straightforward. Neuropsychiatric symptoms seen in patients with primary hyperparathyroidism often improve after parathyroidectomy.(4)

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Case presentation

A 68-year-old man with a previous history of diabetes mellitus, hypertension, dyslipidaemia and recently diagnosed moderate depression presented to psychiatry services with confusion, psychomotor agitation, loss of short-term memory, irritability, hallucinations and delusions for a week. He also had a history of severe constipation, depression and generalised weakness for 3 months. He had been evaluated by a psychiatrist previously and started on psychotherapy which had proven ineffective.

He was afebrile. Examination revealed a blood pressure of 130/70 mmHg and tachycardia at 92 beats per minute with clear lung fields. No organomegaly and focal neurological signs were observed. Psychiatric evaluation revealed psychomotor restlessness, lack of orientation in time and place, second person auditory hallucinations, paranoid delusions, and his mini-mental state score was 18.

Baseline investigations including full blood count, inflammatory markers, renal and liver function tests were initially normal with a calcium level of > 3.5 mmol/L. ECG showed a short QT interval. Myeloma screening was negative (table 1).

Skeletal survey showed features of hypercalcaemia including salt and pepper appearance on the skull X-ray and subperiosteal bone resorption along the radial aspects of the phalanges (figure 1). Supine X-ray abdomen showed impacted stools without air-fluid levels, which supported hypercalcaemia (figure 2).

Table 1 - Laboratory investigations of the patient

Investigation	Reference Range	Day 1	Day 3	Day 6
WBC (/udL)	4 -10	8.7	7.7	7.84
CBS (mg/dL)		185.3	154.2	126
ESR (mm/1st hour)	15 - 20	15		18
CRP (mg/L)	0 - 5	< 0.5	1.6	< 0.5
Serum creatinine (umol/L)	70 - 115	107.8	118.4	112.3
Serum sodium (mmol/L)	137 - 145	139	143	140
Serum potassium (mmol/L)	3.5 - 5.1	4.2	3.8	4.1
Serum calcium (mmol/L)	2.15 - 2.5	> 3.5	3.1	2.5
Serum magnesium (mmol/L)	0.7 - 0.9	0.5	0.3	0.5
Serum phosphate (mmol/L)	0.8 - 1.45	0.7	0.7	0.5
AST (U/L)	0 - 35	27	24	22
ALT (U/L)	0 - 40	24	21	28
PTH (pg/mL)	10 - 65		670.4	
TSH (mIU/L)	0.46 - 4.68		2.43	
UFR		Negative		
Urine calcium (mmol/L)	>0.6		6.4	3.6
Urine creatinine			5492	2510
Vit D level (ng/dL)	30 - 50		31	

WBC: white blood cells, CBS: capillary blood sugar, CRP: C reactive protein, ESR: erythrocyte sedimentation rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PTH: Parathyroid hormone, TSH: Thyroid stimulating hormone, UFR: urine full report

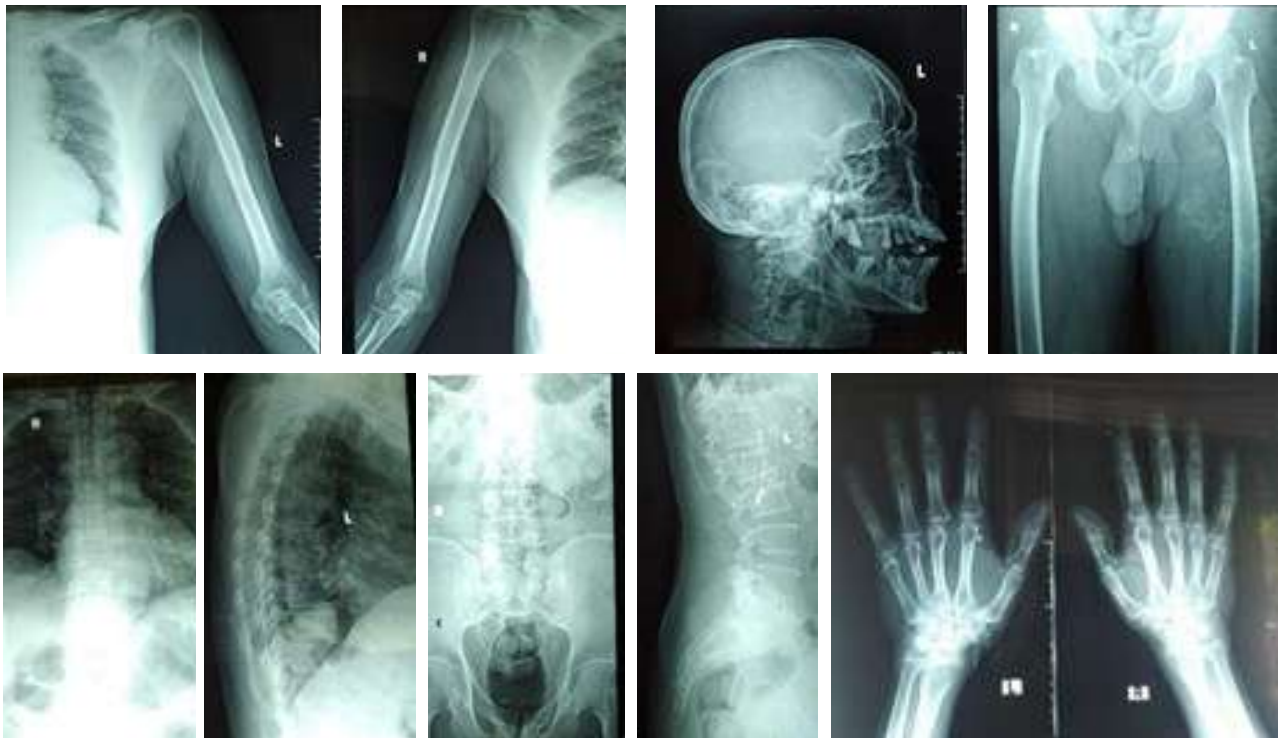

Figure 1 - The skeletal survey showed features of hypercalcaemia including a salt and pepper appearance on X-ray skull and subperiosteal bone resorption along the radial aspects of the phalanges

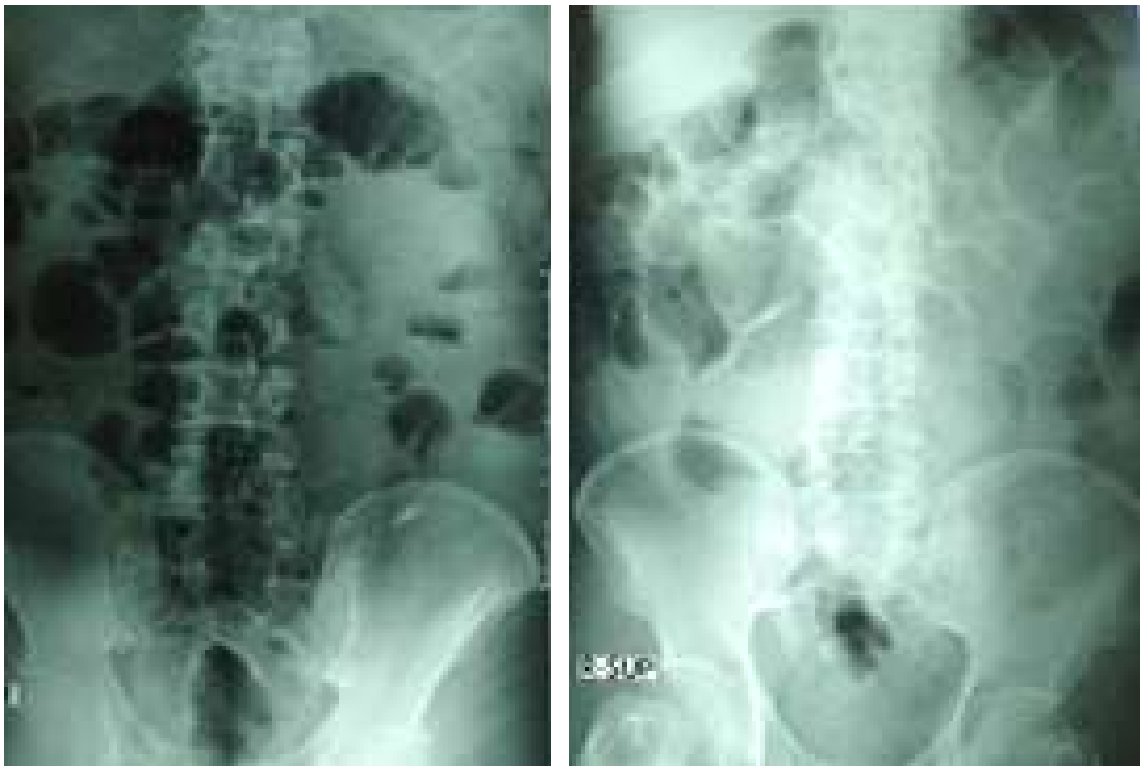

Figure 2 - Supine X-ray of the abdomen showing impacted stools without air-fluid levels supportive of hypercalcaemia

On the fourth day of admission, the intact parathyroid hormone level (PTH) was 670 pg/mL (10 – 65), thus confirming the clinical suspicion of primary hyperparathyroidism (pHPT). An ultrasound scan of the neck and abdomen revealed a well-circumscribed, rounded, hypoechogenic nodule of 0.9 x1.6 cm^2 in size adjacent to the thyroid isthmus, most likely a parathyroid adenoma with a left-side thyroid nodule, but no adrenal tumours were present.

4D CT parathyroid revealed a right trachea-oesophageal groove lesion suggestive of parathyroid adenoma.

The NCCT brain was normal and the MRI brain showed no haemorrhages/ infarctions or space-occupying lesions. There was no evidence to suggest vascular dementia. Neurological causes for changes in behaviour were excluded.

Primary hyperparathyroidism was considered the cause of severe hypercalcaemia and the reason for neuropsychiatric symptoms. Psychotropic medications were discontinued. The patient was hydrated with a continuous infusion of normal saline (4.5 L/day), and intravenous furosemide (80 mg/day).

Over the next 3 days, conservative therapy for the hypercalcaemia was continued with a mild decrease in calcium levels to 3.1 mmol/L. Daily Kleen enemas and laxatives were given for constipation. On day 3 of admission, according to the endocrine opinion, the patient was started on IV zoledronic acid 4 mg stat along with vitamin D3+ K2 supplementation.

On day 6, although the patient showed a good biochemical response to medical therapy, he had persistent lethargy, loss of short-term memory and disorientation. A surgical opinion was taken and the patient underwent right parathyroidectomy (figure 3). The histological diagnosis of the surgical sample was chief cell adenoma of the right parathyroid gland.

After removal of the parathyroid tumour, the serum calcium level dropped rapidly, returning to the normal range. Psychiatric symptoms improved with the disappearance of mental confusion and disorientation without any post-surgical complications.

Acute paranoid psychosis is not a frequent feature of primary hyperparathyroidism. It therefore requires early recognition to avoid unnecessary treatment with psychotropic drugs. Psychiatric symptoms often arise after a prolonged period of subclinical hypercalcaemia. However, their severity is poorly related to the degree of hypercalcaemia.

Our patient had gastrointestinal, skeletal, and neuropsychiatric manifestations of hypercalcaemia with acute psychosis which improved remarkably following combined medical and surgical treatment. One month later on follow-up, the patient remains in general good health, free of psychotic symptoms.

Discussion

The four parathyroid glands, located posterior to the thyroid gland, produce parathyroid hormone (PTH) which is an important regulator of calcium metabolism. Parathyroid adenomas, typically

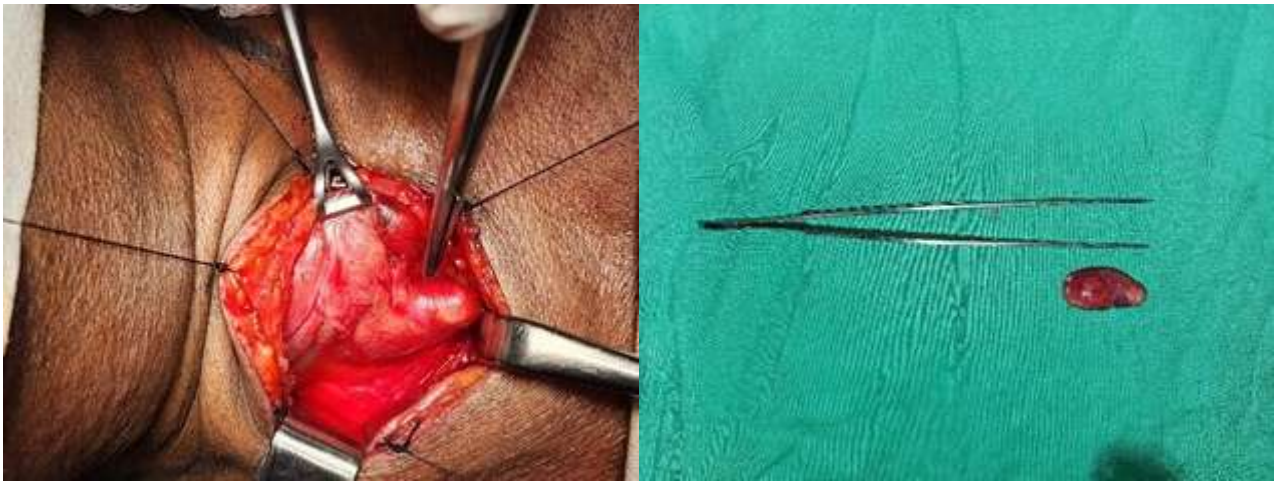

Figure 3 - Surgically resected right parathyroid adenoma

weighing less than 1g are the primary cause of hyperparathyroidism and hypercalcaemia, occurring at a rate of 20 - 22 per 100 000. About 80- 90% of cases are due to single parathyroid adenoma with other causes including hyperplasia of the gland (6%), double adenoma (4%) and parathyroid carcinoma (<1%). It can be a part of hereditary syndromes such as multiple endocrine neoplasia types 1 and 2A. Parathyroid adenoma, usually sporadic and benign, is more common in women than men (3:1) and can occur at any age, although it predominantly affects individuals between 50 - 60 years of age.(1-8)

Giant parathyroid adenomas weigh more than 3.5 g and have a diameter of >2cm. It is a distinct entity with clinical and biochemical features different from regular pituitary adenomas since these are usually clinically symptomatic and have many features overlapping with parathyroid carcinomas.(1 -2, 9)

The main pathophysiology of hyperparathyroidism is the excessive secretion of parathyroid hormone, which results in the release of calcium from bone cells through the inhibition of osteoblasts and promotion of osteoclast activity. PTH stimulates calcium resorption and inhibits the reabsorption of phosphate in the kidneys. Additionally, PTH enhances the absorption of calcium from the gut through active vitamin D by promoting the conversion of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D.(10)

Hypercalcaemia is a known organic cause that can result in neuropsychiatric manifestations. In mild cases, patients may exhibit anxiety, depression and cognitive changes, while altered mental status, psychosis, confusion and coma are hallmarks of severe hypercalcaemia. Sudden alteration in mental status accompanied by auditory hallucinations, paranoia and persecutory delusions are rare manifestations with an incidence of about 4.2%. Although the exact mechanism underlying hypercalcaemia-induced psychosis is yet unknown, alterations in monoamine levels in the central nervous system and glutamate-mediated excitotoxicity may provide some insight. The severity of symptoms correlates with the weight of the adenoma and PTH level.(1, 2, 10)

High calcium levels can be a catalyst for neuronal demise, possibly as a result of glutaminergic excitotoxicity as well as dysfunction in the dopaminergic and serotonergic systems. Reduced levels of dopamine, serotonin and norepinephrine levels have been found in cerebrospinal fluid in hypercalcaemia-induced psychosis caused by parathyroid adenoma. Restoration of normal calcium levels or removal of the parathyroid adenoma has been shown to rapidly resolve neuropsychiatric symptoms.(3)

Ultrasonography and Tc 99m-sestamibi scan, parathyroid four-dimensional CT are standard modalities for imaging parathyroid lesions. Management includes hydration with intravenous fluids and reducing calcium levels using bisphosphonates (zoledronic acid, pamidronate). Definitive management with surgical resection of the adenoma usually correlates with clinical improvement, particularly affective symptoms.(3,8)

Conclusion

Before initiating treatment with psychotropic drugs, it is crucial to first rule out potential reversible organic factors such as hypercalcaemia in a patient presenting with acute paranoid psychosis. This case emphasises the significance of excluding correctable organic causes before beginning psychotropic drug therapy.

Primary hyperparathyroidism due to parathyroid adenoma is the commonest cause of hypercalcaemia and prompt correction of hypercalcaemia with intravenous fluids and bisphosphonates is the effective therapy. It may require surgical resection of adenoma as well.

Declarations

Author contributions
History taking, examination, necessary investigations arrangement, management under supervision, daily monitoring of the patient, and writing of the manuscript were done by Premasiri DGAL under the supervision of Senadeera Y, Perera NM. Surgical management of the patient was carried out by Pinto D, Hapuarachchi E, Professorial surgical unit, CNTH.

Conflicts of interest
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CASE REPORT

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Tuberculous spondylitis mimicking acute inflammatory demyelinating polyneuropathy: a rare presentation

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Abstract

Cervical spine is an uncommon site for tuberculous spondylitis. Clinically spinal tuberculosis (TB) can be a great mimicker due to non-specific presentations and variable progression. Hence it is important to be highly vigilant about the differential diagnoses of TB in endemic settings such as Sri Lanka as untreated disease can lead to devastating paraplegia. This case report describes a patient who presented with acute history of symptoms leading to early onset quadriplegia with areflexia mimicking an acute inflammatory demyelinating polyneuropathy supported by the nerve conduction studies, eventually diagnosed with tuberculous spondylitis during the course of the illness.

Keywords: quadriplegia, tuberculous spondylitis, acute inflammatory demyelinating polyneuropathy

Introduction

Tuberculosis (TB) is one of the leading infectious diseases, exerting significant influence on mortality rates and imposing substantial financial and socioeconomic burdens on both individuals and nations. According to the Global Tuberculosis Report of World Health Organization (WHO) 2023, 10.6 million people worldwide have been infected with TB with the highest number of reported cases being from the south-East Asian region.(1) The incidence of TB in Sri Lanka was 65 per 100 000 population in 2015 according to WHO data. Skeletal TB accounts for 10% of extra pulmonary TB (EPTB) and spine is involved in 50%.(2)

M. tuberculosis enters the body through the respiratory tract and reaches the spine via anterior or posterior spinal arteries or Baston's paravertebral venous plexus. The rich vasculature and the venous plexus surrounding the vertebral column lead to spread of the infection to contiguous as well as non-contiguous vertebrae.(2)

Spinal TB affects the vertebral bodies starting from the anterior inferior portion and spreads to the central part of the body. Involvement of the disc becomes less prominent as the vascularity of the disc reduces with age.(2) Vertebral body involvement can result in collapse of the vertebrae and anterior angulation leading to 'gibbus' formation. Mechanical compression of the cord from para vertebral collections can result in neurological deficits.

The commonest sites affected by spinal TB are lower thoracic and lumbar spine followed by middle thoracic spine and cervical region.(2) Involvement of cervical spine is considered to be less common. Some studies report 66% of patients with lumbar spine involvement, 47% with thoracic spine involvement and 12% with cervical spine involvement.

We report a case of a Sri Lankan man who presented with cervical spine TB mimicking Guillain Barré syndrome (GBS) which led to a diagnostic dilemma and delay in diagnosis.

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The Official Journal of Sri Lanka College of Internal Medicine

Case presentation

A 55-year-old man, a paddy field farmer by profession, with a background history of diabetes mellitus and hypertension presented with high grade intermittent fever for 6 days, associated with arthralgia, myalgia without any identifiable focus for an infection except for a non- specific neck pain without radiation or worsening on neck movements which developed with the febrile illness.

On day 3 of illness he developed gradual onset bilateral upper limb weakness which was initially limited to difficulty in holding objects and later progressed to lifting both arms above the head. By day 4 of illness weakness progressed to bilateral lower limbs. No sensory or bladder involvement was noted. He denied any fluctuation of the weakness nor features of bulbar involvement. He denied any recent diarrhoeal illness, snake bite or canned food consumption.

On examination, he was averagely built, pale, icteric and febrile. There was no neck stiffness or tenderness over the posterior aspect of the neck. There were no muscle tenderness, rashes or contaminated wounds.

The neurological examination revealed flaccid bilateral upper limbs and lower limbs with proximal and distal power of 0/5. Global areflexia was noted. Sensations to touch, pain and vibration were intact in all four limbs and the face, with intact proprioception sensation in upper and lower limbs. Plantar responses were equivocal and anal tone was normal. Cranial nerve and cerebellar examination and other system examination were unremarkable.

Due to the presence of global areflexia with acute quadriplegia of descending nature, an atypical variant of GBS was suspected. Nerve conduction study (NCS) revealed reduced motor amplitudes with absent F waves in right tibial and ulnar nerves suggestive of a GBS variant. Intravenous immunoglobulin (IVIG) 4g/kg daily was started. 4D CT parathyroid revealed a right tracheoesophageal groove lesion suggestive of parathyroid adenoma.

Intravenous broad-spectrum antibiotics were commenced for suspected ongoing infection with an unclear focus for sepsis, evidenced by fever, CRP 120 mg/dL and ESR 112 mm/ 1st hour.

Despite 5 days of antibiotics and IVIG he continued to have a fever. The neck pain was persistent and on day 9 of illness the patient developed acute urinary retention leading to catheterisation.

In the presence of fever at the onset and bladder involvement which developed during the course of the illness which are not typical of GBS, a pathology at cord level was considered to explain the neurological signs. MRI Pan spine was done, which revealed an enhancing long pre, para and posterior vertebral collection with subligamentous spread from C2 level down to D2 level with significant spinal cord compression by a para vertebral collection suggestive of TB spondylitis (figure 1).

His chest radiograph did not show any features of active or past TB and Mantoux test was negative. With the MRI findings suggestive of cervical spine TB spondylitis, empirically anti-TB drugs were started according to local guidelines. Computed tomography (CT) guided aspiration from the collection was performed and decompressive laminectomy was planned. While awaiting surgery, unfortunately, the patient succumbed to death following a hospital acquired pneumonia.

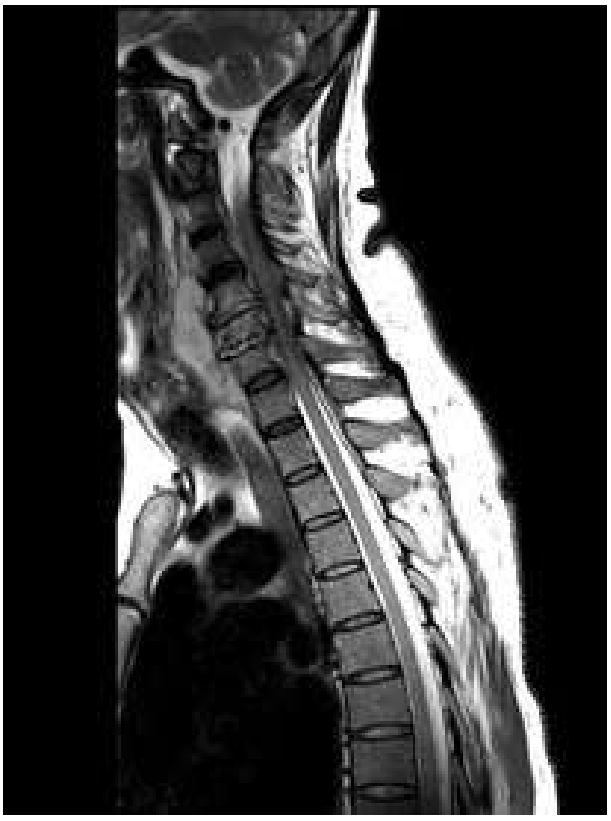

Figure 1 - MRI spine showing contrast enhancing long pre vertebral collection with subligamentous spread from C2 level down to D2 level. Contrast enhancement and high signals are seen in C5, C6 and C7 vertebral bodies with evidence of discitis.

Discussion

Spinal TB has an insidious onset. The time taken to diagnose TB from onset of symptoms could range from 1 week to 3 years with a median of 4 months.(3) This delay is due to the slow progression of the disease and the presence of vague symptoms, which persist until overt cord compression leads to neurological signs. Constitutional symptoms are present only in 20 – 30% osteoarticular tuberculosis. (2) Neck pain, restricted neck movements, neck stiffness are the commonest symptoms in patients with cervical TB.(4)

Many conditions can mimic GBS such as infectious or toxin mediated acute peripheral neuropathy, neuromuscular junction disorders like botulism, critical illness myopathy or neuropathy, infections targeting anterior horn cells like poliomyelitis or acute spinal cord compression(5). In our patient, progressive bilateral upper and lower limb weakness with global areflexia with relative symmetry of symptoms and the NCS favorable of GBS led to the initial diagnosis of GBS and commencing on IVIG therapy. However, our patient also had features casting doubt on the diagnosis of GBS such as fever at the onset of illness and involvement of bladder during the course of the illness. According to the diagnostic criteria for GBS developed by the National Institute of Neurological Disorders and Stroke (NINDS) presence of fever at onset, bladder bowel dysfunction at onset or during the course of illness, marked asymmetry of weakness, severe respiratory dysfunction, hyperreflexia and extensor plantar responses lower the possibility of GBS.(6)

NCS aid in identifying atypical presentations of GBS. (6) Absence or prolonged F waves, prolonged distal motor latency or conduction slowing or blocks mostly represent GBS.(7)

A less known fact is that F waves can be modulated by central nervous system factors such as radiculopathies mimicking GBS variants.(8) Other than Pott's disease, Spinal TB can manifest with neurological signs due to tuberculomas within the spinal cord causing a leptomeningeal reaction resulting in root demyelination, TB radiculitis and secondary axonal injury.(9) We believe that absence of F waves in ulnar and tibial nerves were as a result of co-existing TB radiculitis, hence it is important to relate these findings to the clinical context.

In literature, a similar case presentation was noted where a spontaneous epidural hematoma presented mimicking GBS.(10) Similarly case reports are available where GBS mimicked cord pathologies with a sensory level.(11) Hence careful clinical assessment is vital to differentiate GBS from a cord pathology when presenting with confounding symptoms.

Conclusion

Spinal TB can involve the cervical spine rarely. Symptoms and presentation could be vague. A febrile illness with neck pain should raise the suspicion of a paravertebral abscess. It should also help to identify spinal TB promptly and start treatment early as neurological involvement of the cervical spine can lead to quadriparesis causing devastating effects on a person's quality of life. Spinal TB also could mimic GBS, specially when presenting without a spinal sensory level in the acute spinal shock setting. Hence, it is important to carefully evaluate the symptoms for and against GBS and NCS results need to be clinically correlated before embarking on diagnosis and treatment.

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest

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CASE REPORT

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Concomitant arterial and venous thrombosis in a patient with adenocarcinoma of the ascending colon: a rare presentation

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Abstract

Colorectal cancer is the third most diagnosed cancer worldwide and it may not show typical symptoms at early stages. Patients with malignancies have an increased risk of, both venous and arterial thrombosis, and sometimes thrombotic events may be the only manifestation. We present a 61-year-old woman with diabetes mellitus and hypertension who developed a sudden onset right-sided headache and blurred vision of her right eye and was diagnosed with cavernous sinus and ophthalmic vein thrombosis. She later experienced an acute myocardial infarction. Further evaluation revealed adenocarcinoma of the ascending colon. Thrombophilia screening was negative. Anticoagulation was initiated with heparin and later switched to warfarin, while she awaited a right hemicolectomy.

Keywords: cavernous sinus thrombosis, arterial thrombosis, venous thrombosis, adenocarcinoma of the colon

Introduction

Colorectal cancer is the third most commonly diagnosed cancer worldwide and the second leading cause of cancer-related deaths.(1) It is the third most prevalent cancer among males and females in Sri Lanka, with an age-standardised rate of 10.2 per 100 000 population in 2019 (2).

Most colorectal cancers do not show symptoms in their early stages, often leading to delayed diagnosis (3). Persistent abdominal discomfort, changes in bowel habits, blood or mucus in the stool, unexplained anaemia, or weight loss should prompt suspicion of colorectal pathology.

Patients with malignancy are at an increased risk of both venous and arterial thrombosis. Venous thromboembolism is more common among cancer patients and is one of the leading causes of mortality and morbidity. In some cases, thrombotic events can be the first indication of an underlying malignancy (4). The concomitant occurrence of both venous and arterial thrombosis is rare. Here, we present a case of concomitant cavernous sinus thrombosis and acute anterior myocardial infarction with an underlying adenocarcinoma of the ascending colon.

Case presentation

A 61-year-old woman, a known patient with diabetes mellitus and hypertension presented with a sudden onset right-sided temporal headache for one day. It was associated with vomiting and blurred vision of the right eye.

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On physical examination, she had proptosis and chemosis of the right eye, along with complete ophthalmoplegia. Fundoscopy revealed papilloedema in the right eye while the rest of the neurological examination was normal. Cardiovascular and respiratory system examinations were unremarkable, and the abdominal examination revealed mild tenderness in the right iliac fossa.

Urgent non-contrast computed tomography of the brain showed no abnormalities. Magnetic resonance imaging and venography of the brain (MRI and MRV) revealed thrombosis of the right cavernous sinus and ophthalmic vein. Anticoagulation was initiated with heparin and later switched to warfarin.

During the hospital stay, the patient developed central chest pain. The ECG showed anterior ST elevation myocardial infarction, with a high-sensitivity cardiac troponin I value of >30000 ng/L. Primary PCI facilities were not available at the time and anticoagulation with heparin was continued. A coronary angiogram revealed complete occlusion of the right coronary artery and left anterior descending artery.

The patient was anaemic, (Hb - 9.8 g/dL, MCV - 78 fL), but other basic biochemical investigations were normal. Thrombophilia screening was negative. Cerebrospinal fluid studies, along with hepatitis B, tuberculosis, and retroviral screening were also negative. Her septic screening was negative, with no features suggestive of sinusitis, facial or dental infections and orbital cellulitis. There was no history of facial trauma or history of hormonal contraceptive use.

She had right-sided iliac fossa tenderness and on further inquiry, was found to have experienced intermittent abdominal pain and altered bowel habits for approximately one year. An ultrasound scan of the abdomen revealed a thickened bowel loop and an irregular fluid collection in the right iliac fossa. Colonoscopy revealed a malignant-looking growth in the ascending colon and a biopsy confirmed poorly differentiated adenocarcinoma. CECT of the abdomen and pelvis showed no local invasion or distant metastasis.

With the opinion of an oncological surgeon the patient was scheduled for a right hemicolectomy. Currently, she is awaiting a coronary artery bypass graft which was offered considering her high cardiac risk.

Discussion

Patients with malignancy have an increased risk of thrombosis, both venous and arterial. Sometimes the thrombotic event can be the first manifestation of an

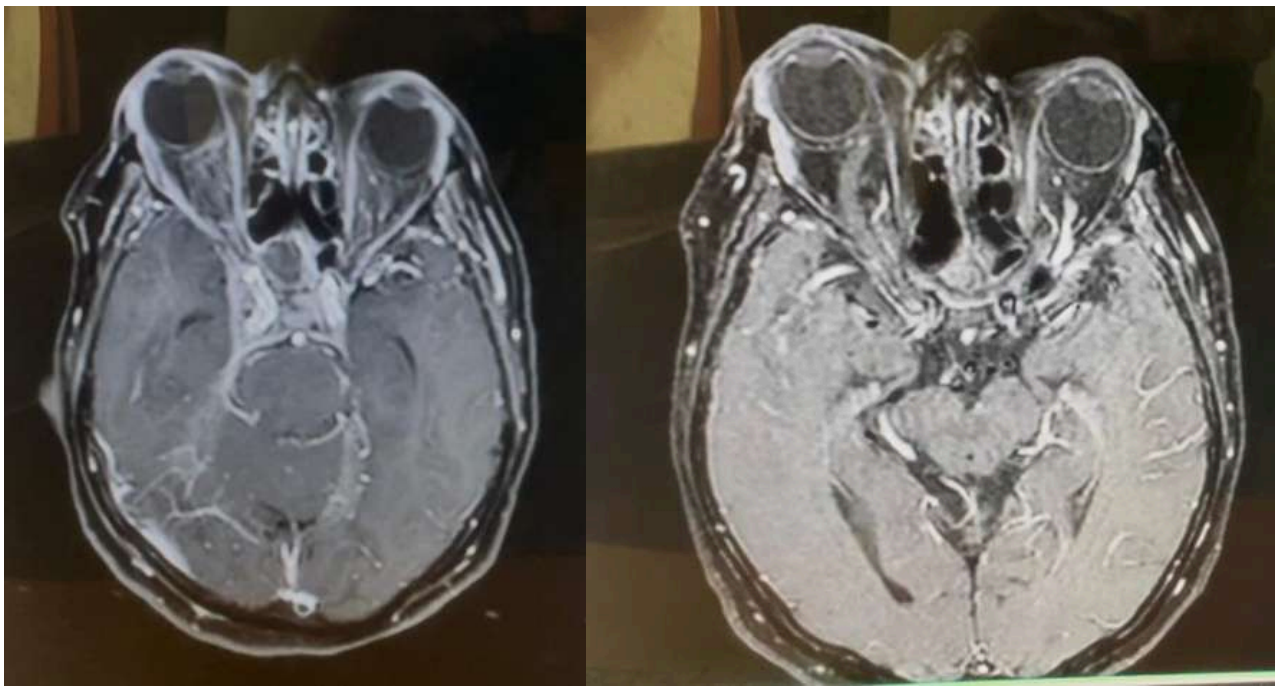

Figure 1 - Magnetic resonance imaging showing right side proptosis with enlarged superior ophthalmic vein

occult malignancy.

Blom et al. described the association between malignancy and venous thrombosis, where they showed a seven-fold increased risk of venous thrombosis in patients with malignancy. Patients with haematological malignancies had the highest risk of venous thrombosis followed by lung cancer and gastrointestinal cancer. The risk of venous thrombosis was highest in the first few months after the diagnosis and patients with distant metastases had a higher risk.(5)

Navi et al. described the association between malignancy and arterial thrombosis in a large retrospective study where the six-month incidence of myocardial infarction was 2% in cancer patients compared to 0.7% in the control group. The incidence of ischaemic stroke was 3% compared to 1.6% for the control group. Excess risk varied by cancer type and the highest risk was associated with lung carcinoma. (6)

Case reports on isolated venous and arterial thrombosis have been documented in the literature. However, the occurrence of concurrent arterial and venous thrombosis in patients with malignancy, as described in our patient, is a rare yet clinically significant occurrence.

Park et al. described a case of A 92-year-old woman with breast cancer presenting with left-sided weakness revealing a non-occlusive thrombus in the axillary artery, occlusive thrombus in the brachial artery, bilateral pulmonary embolism, and deep vein thrombosis in the right lower extremity.(7)

Alsamman et al described a case of an 87-year-old woman with a history of breast cancer in remission who presented with left arm weakness revealing an aortic thrombus extending into the left subclavian artery and bilateral pulmonary emboli with deep venous thrombosis in the left leg.(8)

The above two case reports detail instances of arterial and venous thrombosis in patients who had already been diagnosed with cancer. In contrast, our patient presented with a rare situation, experiencing arterial and venous thrombosis as the initial manifestation of an underlying malignancy.

There are several pathophysiological mechanisms which can describe malignancy associated-thrombosis. Malignant cells produce substances like tissue factor which activates the coagulation cascade leading to formation of factor Xa. Some cancer cells produce procoagulants which directly act on factor Xa. In addition to that venous stasis due to the compressive effect on blood vessels by the tumour, and prolonged immobility in critically ill patients produce a procoagulant state. Also chemotherapeutic agents like methotrexate, cyclophosphamide, cisplatin, doxorubicin, 5-fluorouracil, and lenalidomide are known to increase the risk of venous thrombosis.(9)

Liu et al. described the efficacy and safety of thromboprophylaxis in cancer patients where thromboprophylaxis decreased the incidence of venous thromboembolism in cancer patients undergoing chemotherapy or surgery with no increase in the incidence of significant bleeding.(10) Low molecular weight heparin is the preferred anticoagulation for the management of cancer-associated thrombosis. The dose recommendation is 1 mg/kg every 12 hours, and 1 mg/kg once daily for patients with creatinine clearance less than 30 mL/minute. Other options include warfarin and direct oral anticoagulants like apixaban and rivaroxaban. (11)

Direct oral anticoagulants (DOACs) have recently become a viable option for the treatment of venous thromboembolism in the general population, although data on their efficacy in patients with cancer is still limited. Nevertheless, DOACs can be an effective choice for cancer patients suffering from acute venous thromboembolism. It is important to exercise caution in individuals at a higher risk of bleeding, particularly in cases involving specific tumour types, such as gastrointestinal tumours, where the bleeding risk is notably increased.(12)

In a challenging therapeutic encounter, our patient was diagnosed with acute myocardial infarction in the context of cerebral venous thrombosis. A multidisciplinary team, comprising both a cardiologist and a neurologist, carefully assessed the risks and benefits of thrombolysis. Considering the potential for bleeding complications, the team concluded that the patient should be managed with anticoagulation using heparin.

Conclusion

Patients with malignancy are at a significantly increased risk of both venous and arterial thrombosis, with various cancer types showing differing levels of risk. The occurrence of concurrent arterial and venous thrombosis as the first manifestation of malignancy, as seen in our patient, remains a rare yet important clinical challenge.

The use of low molecular weight heparin has shown efficacy in managing cancer-associated thrombosis. Although DOACs are emerging as potential alternatives, some caution is advised in certain patient populations.

Declarations

Author contributions

History taking, examination, arrangement of necessary investigations, management under supervision, daily monitoring of the patient, and writing of the manuscript were done by Perera HMUAS. All authors contributed to write the manuscript, read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest

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CASE REPORT

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Concurrent infarctions in the territories of internal carotid artery and posterior cerebral artery in the background of foetal type variant of posterior cerebral artery

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Abstract

A 46-year-old woman admitted with a headache and syncopal episode to the hospital, was found to have an upper-motor-neuron type weakness on the left side of the body on waking up the following day. Simultaneous right-sided infarctions of middle and posterior cerebral artery (MCA and PCA) territories were seen in magnetic-resonance-imaging (MRI) of the brain along with a left-sided foetal-posterior-cerebral-artery (fPCA). The concurrent PCA and MCA infarctions could be postulated due to, either a left-sided fPCA supplying the contralateral cerebrum or an invisible thrombosed right-sided fPCA supplying the ipsilateral cerebrum. This emphasises the importance of identifying the relationship between fPCA and the risk of large territorial stroke.

Keywords: paradoxical large territorial infarction, foetal posterior cerebral artery, secondary stroke

Introduction

The internal carotid artery (ICA) originates from the cranial extension of the aorta while the basilar artery (BA) develops from the neural arteries. The ICA is connected to the vertebral artery by the posterior-cerebral-artery (PCA) which later joins a P1 segment from BA to maintain the connection between the anterior and posterior circulation. When the P1 segment grows in calibre than the PCA the normal anatomy of the circle of Willis is said to be complete. However, when the P1 is hypoplastic or absent the foetal posterior circulation is said to be retained (foetal-posterior-cerebral-artery – fPCA). The partial fPCA is when the P1 segment is hypoplastic while the complete fPCA is when the P1 segment is absent (figure1).(1)

The fPCA becomes clinically significant when an occlusion of the ICA results in a paradoxical infarction of PCA territory along with that of the ipsilateral ICA. Thus, there is a high risk of stroke in patients with an fPCA and the genuine necessity for prevention of stroke in people with an fPCA is eminent. This case report aims to highlight the importance of recommending an MRI brain in the background of concurrent dual territory infarctions.

Case presentation

A 46-year-old woman with a background history of type 2 diabetes mellitus and hypertension presented with a generalised headache associated with relentless vomiting for one day. There was also a witnessed syncopal episode lasting for one minute in the absence of tonic clonic movements or head injury. The patient denied fever, chest pain, shortness of breath and palpitations. She did not have any disability on admission.

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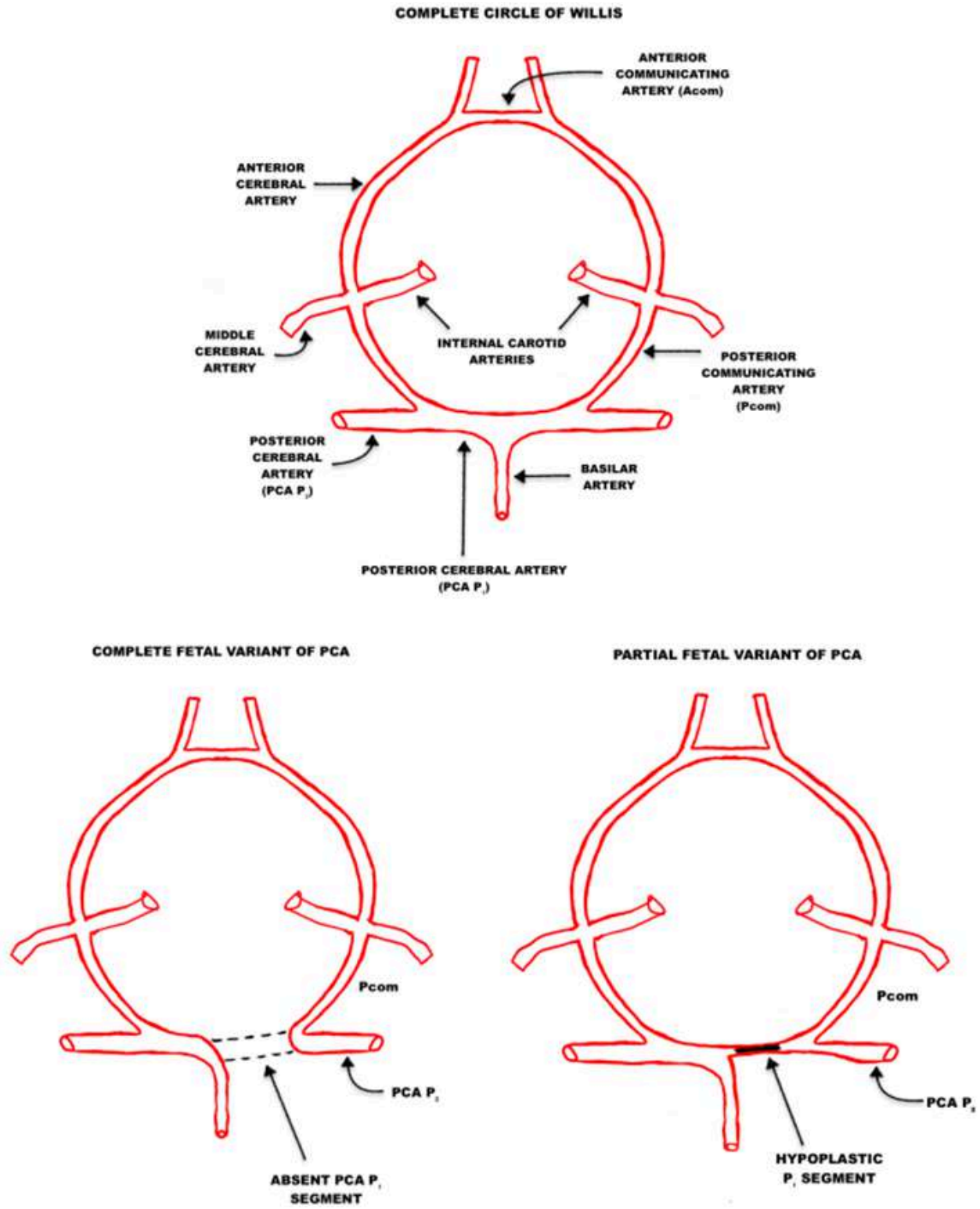

Figure 1 - Circle of Willis and the foetal variants of posterior cerebral artery

On examination, she was afebrile and was well-oriented to place, person and time. The blood pressure was 165/107 mmHg with a regular pulse rate of 85 beats/min. There were no murmurs or carotid bruits. The oxygen saturation was 100% on room air. The rest of the abdominal and respiratory examinations were unremarkable. She did not have neck stiffness and the fundi were normal. There were no cranial nerve deficits and both the upper and lower limb tone, power and reflexes were normal with bilateral down-going plantars. Her capillary blood sugar was 196 mg/dL and the electrocardiogram did not demonstrate arrhythmias or ischaemic changes (table 1).

The patient developed a left-sided weakness of the body with intact speech and swallowing, upon waking up from sleep the next day. The right-side power was normal while the left-side upper and lower limb power were 3/5 and 4/5 respectively. The left-sided reflexes were exaggerated while the left-side Babinski sign was positive. She was conscious and rational with pupils 2 mm in diameter and they were equally reactive to light.

A computed tomography scan (CT) and a magnetic resonance imaging (MRI) scan of the brain revealed a right-sided infarction in the middle cerebral artery (MCA) and PCA territories with cerebral oedema (figures 2 and 3). Subsequent magnetic resonance imaging angiography (MRA) of the brain revealed a co-existing left-fPCA (figure 2). Her 2-D echocardiography showed no cardiac source of thromboembolism. Her neurological weakness remained non-progressive and she was treated medically with the commencement of single antiplatelet therapy along with a statin. Physiotherapy was initiated early and she was managed at a dedicated rehabilitation centre. She made a good recovery at 6 months with a residual neurological deficit resulting in a Barthel index of 65. She was followed up at the medical clinic for the control of risk factors and showed good progress.

Discussion

Contralateral fPCA and paradoxical involvement of both MCA and PCA territories, in this case, could either be explained by the presence of two fPCAs with an occluded right-fPCA or an aberrant supply of right-PCA territory by left-fPCA.(2) This unilateral or bilateral fPCA variant is found to be prevalent in up to 30% of the population.(2) Arjal et al. in a descriptive study of fPCA revealed a mean age of presentation to be 51.83 years with the most common presentation being dizziness/vertigo followed by headache and focal neurological deficits.(3) Our patient's initial symptom was headache followed by transient loss of consciousness and focal neurological deficits. However, an MRI brain was done only after the

Table 1 - Laboratory investigations of the patient

Investigation	Patient's value	Reference range
WBC (10^9/L)	9.67	4.00-10.00
Haemoglobin (g/dL)	12.5	11.0-16.0
Platelet (10^9/L)	378	150-450
AST (U/L)	21.7	<50
ALT (U/L)	14.5	<50
CRP (mg/L)	30.6	0-5
Creatinine (µmol/L)	57.9	50.4-98.1
Sodium (mmol/L)	134.8	136-146
Potassium (mmol/L)	3.6	3.5-5.1
ESR (mm in the 1st hour)	25	
PT(s) /INR	12/ 1.0	11- 13/ 0.8-1.2
APTT (s)	28	25-33
ANA	Negative	
Thrombophilia screening after 3 months	Negative for acquired and inherited thrombophilia	

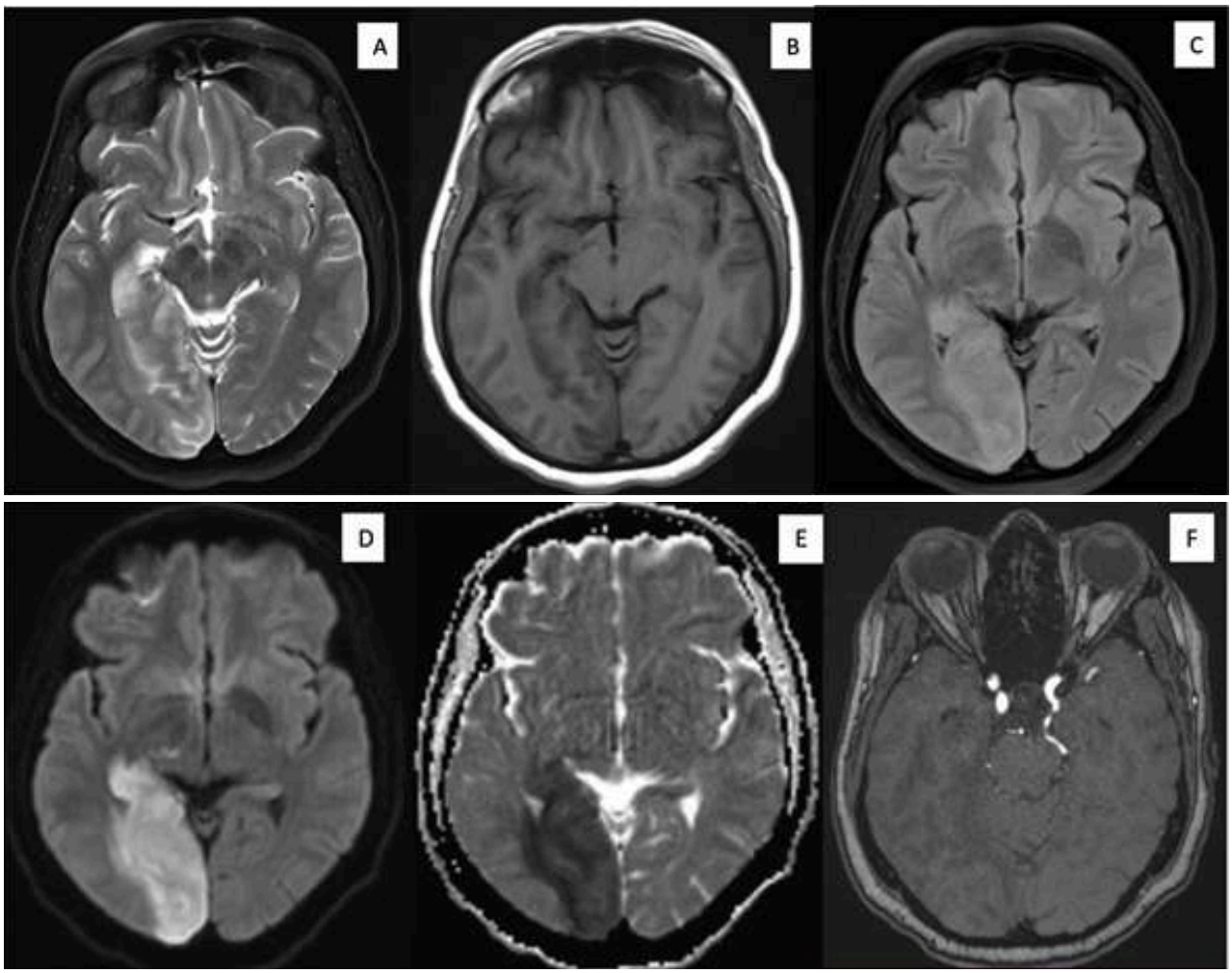

Figure 2 - Magnetic resonance imaging scans of the patient. **(A)** T2 axial image shows high signal intensity in R/temporo-occipital region **(B)** T1 axial image shows low signal intensity in R/temporo-occipital region **(C)** T2 FLAIR image shows high signal intensity in R/temporo-occipital region **(D)** & **(E)** DWI (diffusion-weighted magnetic resonance imaging) image and ADC (apparent diffusion coefficient) images show diffusion restriction in R/temporo-occipital region **(F)** MRA study shows left-sided foetal circulation

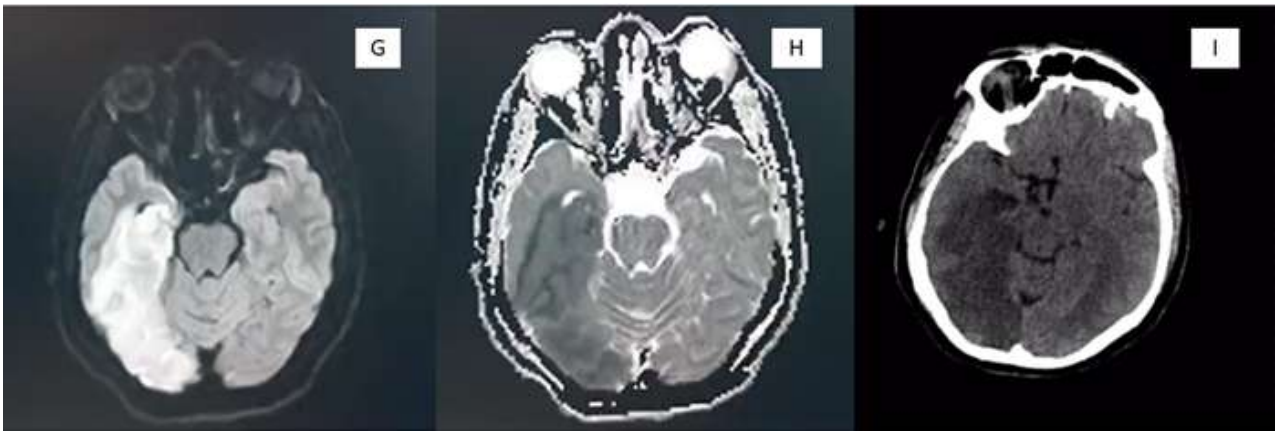

Figure 3 - **(G)** and **(H)** DWI image and ADC image show diffusion restriction extending from territory of PCA to MCA, **(I)** non-contrast brain image shows infarction involving PCA and MCA territories

development of the stroke which revealed a contralateral fPCA. It therefore raises the question whether early imaging would have led to identification of risk factors allowing a primary prevention or referral to other therapeutic options like endovascular treatment resulting in a better positive outcome.(4)

Shaban et al. analysed the influence of fPCA on stroke outcome and associated demographical data and found patients with complete fPCA to be older and predominantly female.(5) However, our patient was a middle-aged woman without any history of previous strokes or a family history of significant cerebrovascular accidents. Furthermore, it was found that the prevalence of ipsilateral or contralateral foetal circulation in association with a stroke is similar to the statistics of stroke prevalence in the normal population. However, this study was limited by the small number of patients to compare significant stroke outcomes among patients without fPCA and with partial or complete fPCA.

Lambert et al. presented 2 cases, out of which one showed an fPCA contralateral to the infarcted hemisphere. They postulated that the stroke was due to paradoxical cardio-embolisation via PCA resulting in concomitant occlusion of ICA to PCA in the background of an atrial fibrillation and had a previous CT showing the presence of a classic right-PCA.(4) Our patient had no previous CT done and neither had any cardiac source of thromboembolism nor atrial fibrillation to suggest paradoxical cardio-embolisation as such.

Several studies have been done to analyse the clinical significance of the fPCA as it is postulated to be a causative factor in increased risk of stroke. The postulations are based on some of the following: absent leptomeningeal collateral circulation between anterior and posterior cerebral circulation in a complete fPCA due to the tentorium acting as a physical barrier and steal phenomenon of diversion of blood from anterior circulation to posterior in fPCA. However, there are arguments for and against the relationship between such an increase in stroke risk and the presence of foetal posterior circulation. (3,5) Nevertheless there was another series of studies which demonstrated an association among fPCA, increased atherosclerotic plaque formation and positive vascular remodelling of MCA thus showing the value behind the early recognition of fPCA for the prevention of negative consequences such as stroke. (6)

Precautions to reduce the incidence of stroke in patients with fPCA are undeniably supported by case studies especially those with atrial fibrillation, carotid artery stenosis and risk factors for atherosclerosis. The importance of prior knowledge of such an anomaly in the anatomy is valuable in planning surgeries such as endarterectomy or stenting.(7,8) This case report draws clinical attention to the need for more large-scale studies to assess the relationship between stroke and fPCA, and the likelihood of benefit from primary prevention and endovascular treatments since the severity of outcomes in concurrent infarctions of major territories of cerebral arteries is sinister.

Conclusion

Multiple infarcts involving territories of MCA and PCA raise the suspicion of a possible existence of a foetal posterior circulation. Computed tomography angiogram or magnetic resonance imaging is recommended in confirming the presence or absence of a fPCA. Debilitating clinical outcomes in fPCA calls the need for a large-scale study to establish a relationship between its prevalence in Sri Lanka and incidence of stroke to establish a vigorous and more established approach to prevent stroke in that p

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest

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CASE REPORT

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Erythema nodosum leprosum presenting as fever of unknown origin

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Abstract

Erythema nodosum leprosum (ENL) is an immune-mediated sequela of multibacillary leprosy that usually occurs after the initiation of treatment. We report a rare case of ENL in a 40-year-old man , with a two-year history of bilateral lower limb numbness, who presented with intermittent fever, bilateral painful shins, painful nodular rash on extremities, inguinal lymphadenopathy and oligo-arthritis over 3 weeks. Investigations revealed neutrophilic leukocytosis with high inflammatory markers. Slit skin smear revealed presence of *Mycobacterium leprae* with a 4+ bacillary index confirming the diagnosis. Early treatment with multidrug therapy and steroids resulted in a rapid improvement in our patient.

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Keywords: fever of unknown origin, ENL, type 2 lepra reaction, multibacillary leprosy

Introduction

Leprosy is a chronic granulomatous infectious disease caused by *Mycobacterium leprae* that can present with various clinical manifestations. This disease remains a significant challenge, especially for developing and underdeveloped countries, as it can result in significant morbidity and thereby impact the quality of life of affected individuals.(1) Erythema nodosum leprosum (ENL) is an immune mediated reaction of multibacillary leprosy that presents with evanescent, tender erythematous nodules accompanied by fever, arthralgia, malaise and organ-specific manifestations such as acute painful peripheral nerve damage, iridocyclitis, orchitis, lymphadenitis and arthritis. Hepatosplenomegaly and renal impairment are also detected in rare instances. (2,3) It usually presents following the initiation of treatment for leprosy but may rarely precede the diagnosis and treatment. Here, we present a rare case of ENL presenting as fever of unknown origin (FUO).

Case presentation

A 40-year-old man, a carpet vendor, with a history of progressively worsening bilateral lower limb numbness over 2 years was admitted with severe bilateral shin pain for 3 days. It was associated with an intermittent, low-grade fever lasting for 3 weeks and a painful nodular rash over the extensor aspects of the bilateral lower and upper limbs which later progressed to blisters. One week into the illness, the patient developed left side knee pain and swelling with significant restriction of movement and later developed bilateral ankle joint swelling as well. There was a significant loss of appetite and lethargy during the acute illness, but the rest of the systemic inquiry was unremarkable.

On examination, the patient was febrile and there was a tender erythematous nodular rash over extensor aspects of both upper and lower limbs, sparing the trunk, face, and scalp (figure 1).

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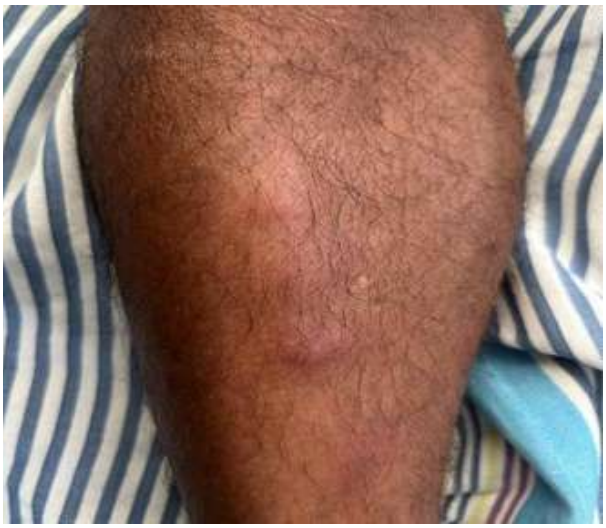

Figure 1 - Tender, nodular, erythematous rash over the shin

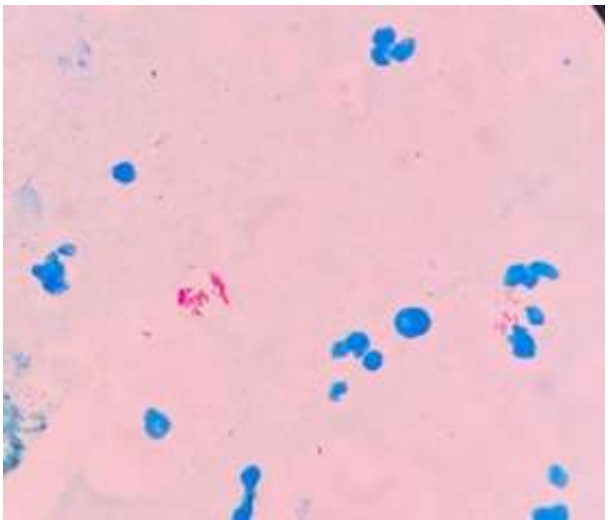

Figure 2 - *Mycobacterium leprae* in slit skin smear test

There was bilateral tender inguinal lymphadenopathy and lower limb large joint oligo-arthritis involving the left knee and bilateral ankles. Neurological examination revealed evidence of bilateral lower limb symmetrical sensory polyneuropathy up to the level of the ankles. Rest of the systemic examination was unremarkable.

At the presentation, full blood count revealed: haemoglobin of 14.1 g/dL, white blood cell count of 18.9×10^9/L (neutrophils-80.4%, lymphocytes-16.4%, eosinophils-1.5%), and a platelet count of 189×10^9/L. A peripheral blood smear examination showed features of bacterial infection. ESR and CRP tests were 57 mm/1st hour and 127 mg/L respectively. The procalcitonin level was 0.28 (<0.05 ng/mL). Renal function tests and the liver profile including ALT, AST and bilirubin were within the normal range. The serum ferritin was 1261 ng/dL (20-400). The left knee joint fluid aspirate analysis showed evidence of inflammatory type arthritis. There was bilateral symmetrical axonal type sensory polyneuropathy in the nerve conduction study. The skin biopsy showed evidence of granulomatous inflammation. The slit skin smear test (figure 2) revealed the presence of *Mycobacterium leprae* with a 4+ bacillary index, leading to a diagnosis of ENL.

Upon diagnosis, he was started on anti-leprosy treatment for multibacillary leprosy and steroids were initiated concurrently for the management of type 2 lepra reaction. The patient showed a dramatic clinical response over the next week and further follow-up was arranged at a dermatology clinic.

Discussion

Leprosy reactions are a significant cause of morbidity in the leprosy population. Erythema nodosum leprosum (ENL) is an immunological reaction affecting approximately 50% of patients with lepromatous leprosy (LL) and 10% of borderline lepromatous (BL) leprosy.(4) The pathogenesis of ENL is mainly driven by the release of bacillary antigens and the subsequent deposition of immune complexes, leading to an intense inflammatory response. The histology of ENL lesions shows an intense perivascular infiltrate of neutrophils throughout the dermis and subcutis.(5) It can be triggered by factors such as stress, concurrent infections or the initiation or modification of leprosy treatment, resulting in generalised clinical manifestations leading to a diagnostic challenge.(6) ENL mostly occurs during the first 6 months of treatment with multi drug therapy or after the completion of the treatment but its presentation as fever of unknown origin prior to the diagnosis of leprosy adds important consideration to clinical practice.

The extreme rarity of the ENL presenting as FUO preceding the diagnosis of leprosy adds significant complexity to the diagnostic process. Since the symptoms are not specific for the disease, it may easily be misdiagnosed as a common illness. In our case, common infections that present with fever and erythema nodosum, such as *Streptococcus* and *Staphylococcus* infections and atypical infections such as *Mycoplasma* and Lyme disease were considered

higher up on the list. In addition, sarcoidosis, cutaneous lymphoma and cutaneous and systemic vasculitis were among the differential diagnoses. This complexity resulted in a significant delay in the diagnosis of the index case. Reghukumar et al. reported a case of a similar nature; a 63-year-old woman who presented with polyarthralgia, multiple tender and erythematous nodules over her face, elbows, back, and legs, and a continuous fever for 2 months, later diagnosed with ENL after extensive evaluation. (7)

The delayed diagnosis of leprosy and ENL can lead to prolonged patient suffering and increased risk of complications.(8) Progressive sensory and motor neuropathy leading to significant functional impairment, disfiguration, severe necrotising ENL, deforming arthritis, and secondary bacterial infections are well known severe complications of ENL.(9,10) Additionally, due to the prolonged hospital stay, there will be financial and psychological burden for the patients as well as their families. In our case, there was a delay of 3 weeks in the diagnosis due to the diagnostic dilemma and delay in investigations such as slit skin smear and skin biopsy. There was a substantial psychological burden on the patient, leading to several attempts to leave against medical advice which was managed successfully with counselling sessions.

The management of our patient was done through a multidisciplinary team approach with the help of the physician, microbiologist, dermatologist, pathologist, psychiatrist, physiotherapist, and supportive staff. With the initiation of multidrug therapy with concurrent steroids, the patient was closely observed for clinical improvement as well as for drug related adverse events. The patient was educated on the importance of adherence to treatment, identification of recurrence of ENL and drug related side effects. Additionally, the patient and the family members were counselled on the possible psychosocial issues that can arise with the illness and how to deal with the social stigma of leprosy. It is of utmost importance to notify the disease to the relevant teams and to screen the close contacts for leprosy.

Conclusion

This case shows the complexities involved in diagnosing ENL, especially when it presents as a febrile illness prior to the diagnosis of leprosy. The integration of clinical, laboratory and histopathological findings was crucial in reaching the correct diagnosis. Prompt initiation of appropriate treatment for both leprosy and ENL led to significant improvement in the patient's condition. This case emphasises the importance of considering leprosy and its complications in the differential diagnosis of systemic febrile illnesses and highlights the necessity for timely and comprehensive management to prevent long-term complications.

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest

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CASE REPORT

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Chronic non-cirrhotic portal vein thrombosis with mild protein C deficiency and splenomegaly: an uncommon aetiology underlying long standing thrombocytopenia

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Abstract

Chronic portal vein thrombosis (PVT) is a rare and diagnostically challenging cause of thrombocytopenia in young individuals. This case report describes a young woman with a history of unexplained thrombocytopenia for more than five years. She was initially managed for primary immune thrombocytopenic purpura. She later presented with frank haematemesis and was found to have splenomegaly, oesophago-gastric varices, and chronic non-cirrhotic PVT, likely due to an underlying Protein C deficiency. This case highlights the challenges faced in establishing an accurate aetiological diagnosis for thrombocytopenia in young patients, and emphasises the importance of continuous monitoring, as well as comprehensive and multidisciplinary evaluation.

Keywords: thrombocytopenia, protein C deficiency, portal vein thrombosis

Introduction

Portal vein thrombosis (PVT) occurs acutely or chronically in the context of cirrhosis, prothrombotic states, and hepatobiliary neoplasms.(1) It is a rare entity, with an annual global incidence of 2 to 4 cases per 100,000 individuals.(2) Acute PVT that remains unresolved with or without treatment results in chronic PVT, which is characterised by the development of collateral cavernous veins, or portal cavernoma, that can be demonstrated radiologically. Protein C (PC) deficiency is an autosomal dominant thrombophilia, with over 160 different mutations identified in chromosome 2q13-14.(3) This is also rare, with the prevalence of heterozygotes being 0.14% to 5.6% in a healthy population, much higher than that of protein S or antithrombin III deficiency. (4,5) This report details a young woman with long standing thrombocytopenia, initially diagnosed with primary immune thrombocytopenic purpura (ITP), and later found to have chronic non-cirrhotic PVT, likely secondary to protein C deficiency.

Case presentation

This is a case of a female patient who was apparently well until 11 years of age. From 11 to 17 years, she had five hospitalisations with mild fever, sometimes accompanied by epistaxis and skin petechiae. Her platelet count fluctuated between 60 and 100 x 10^3/µL (150 – 450) during and between the hospitalisations. Blood collected in citrated tubes also showed thrombocytopenia. At 17 years, she presented to our unit with intermittent fever, upper respiratory tract symptoms, and mild splenomegaly. At that point, her investigations showed a white cell

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count of 4.1 x 10^3/µL (4 – 11) with normal differentials, haemoglobin of 11.1 g/dL (11 – 13) , mean corpuscular volume of 75.4 fL (83 – 99), and a platelet count ranging from 66 to 98 x 10^3/µL. A blood smear showed normocytic normochromic cells, hypochromic microcytic cells, and elliptocytosis, suggesting an underlying iron deficiency. There was no platelet clump formation. Serum electrolytes and the liver profile were within normal limits for her age. IgM and IgG antibodies against HIV1, HIV2, EBV, CMV, SARS-Cov2 and Dengue virus were negative. VDRL was non-reactive. Antinuclear antibody titre was <1:80. Ultrasonography confirmed a spleen of 11.5 cm, with no other abdominal abnormalities. A bone marrow biopsy indicated a normocellular marrow and normal megakaryopoiesis, without any dysplastic or neoplastic process. Blood lactate dehydrogenase and indirect bilirubin were within normal limits, excluding concomitant haemolysis. Despite the presence of mild splenomegaly, a possible diagnosis of primary ITP was considered by the hematology team. A tapering course of oral prednisolone starting from 40 mg daily along with bone protective measures was initiated. After three months, steroids were withheld as her platelet count improved up to 146 x 10^3/µL.

She defaulted clinic visits during the COVID-19 pandemic, and was readmitted at 21 years of age, with acute hematemesis and left upper abdominal ache. She was hemodynamically stable and moderate splenomegaly was noted. There were no signs of decompensated chronic liver disease, lymphomatous malignancy, autoimmune pathology, or chronic infections such as tuberculosis. Platelet count was 110 x 10^3/µL. The other investigations performed are summarised in table 1.

Abdominal ultrasound identified moderate splenomegaly and cavernous transformation of the portal vein (figure 1). Abdominal computed tomography confirmed the splenomegaly (measuring 13 x 5 x 9.5 cm^3), as well as a chronically thrombosed portal vein (figure 2). There were multiple collaterals at the porta hepatis that were apparently compressing the hepatic bile duct, causing intrahepatic bile ducts to dilate. The liver and the extrahepatic biliary system were radiologically normal. A liver biopsy showed an architecturally normal liver with no steatosis, cholestasis, viral cytoplasmic effects, granuloma, or fibrosis. Although few plasma cells were reported to be present along the portal tracts, the absence of interface hepatitis and necro-inflammatory lesions, made autoimmune hepatitis unlikely. The patient was referred to a gastroenterologist, and no specific aetiology for chronic hepatitis was found (table 1). Endoscopy revealed Grade 1 gastroesophageal varices and early post-hypertensive gastropathy. A final diagnosis of non-cirrhotic, chronic portal vein thrombosis with splenomegaly and portal hypertension was made. Oral carvedilol 3.125 mg daily was commenced. Her long-standing thrombocytopenia was attributed to splenomegaly-related consumptive thrombocytopenia.

She was referred to the haematologist. She had no family members with thrombotic disorders, or prior history of thrombosis at other sites. Extensive investigations for underlying thrombophilia revealed low PC levels (table 1). Genetic testing was not performed due to unaffordability. Anticoagulation was not initiated as the patient had chronic portal vein thrombosis with good collateral flow. Currently she is under surveillance for varices and new thrombotic events by the haematology and gastroenterology teams. She has been advised about the importance of anticoagulation during high-risk prothrombotic situations such as pregnancy or perioperative states.

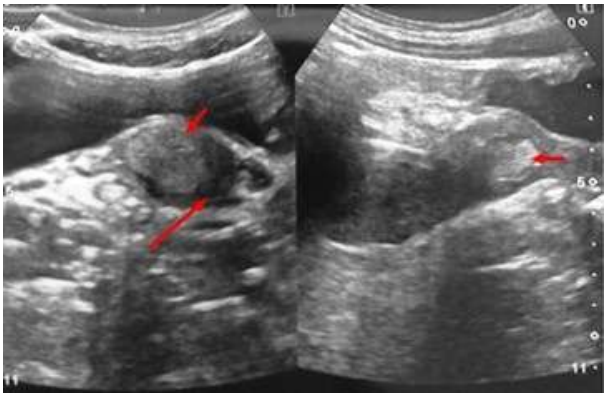

Figure 1 - Ultrasound showing cavernous transformation of portal vein (long arrow), and chronic thrombus (short arrow)

Discussion

Most patients of chronic PVT are asymptomatic at early stages and are incidentally diagnosed during abdominal imaging. Over time, symptoms related to complications of the disease appear. Serious complications of chronic PVT include portal hypertension, portal cholangiopathy, and intestinal ischaemia if the thrombus extends to the mesenteric veins. Mortality rate from these complications is less than 10%.(6) Gastrointestinal (GI) bleeding from

Table 1 - Summary of investigations

Investigation	Patient's value	Reference range
White blood cell count (x10^3/uL)	4.3	4.0 – 11.0
Haemoglobin (g/dL)	11.5	12.0 – 15.0
Mean corpuscular volume (fL)	81.3	83.0 – 99.0
Platelet count (x10^3/uL)	85	150 - 450
ESR (mm/h)	13	< 15
CRP (mg/L)	2.2	0.1 – 5.0
PT/INR	1.10	0.07 – 1.13
APTT (sec)	27	
Alanine transaminase (U/L)	24.9	5 - 39
Aspartate transaminase (U/L)	26.6	13 - 31
Total bilirubin (umol/L)	7.0	3 - 21
Direct bilirubin (umol/L)	0.5	1 - 7
Alkaline phosphatase (U/L)	188.8	98.0 – 258.0
Gamma GlutamylGlutaryl Transferase (U/L)	31.9	0.1 – 32.0
Albumin (g/dL)	46.7	35.0 – 50.0
Globulin (g/dL)	32.7	25.0 – 33.0
Amylase (U/L)	80.3	28.0 – 100.0
Serum creatinine (umol/L)	53	60 - 120
Serum sodium (mmol/L)	145	135 -145
Serum potassium (mmol/L)	4.1	3.5 – 4.5
Serum ceruloplasmin (mg/dL)	18	16 – 45
24 – hour urine copper excretion (umol/L)	0.84	0.22 – 0.90
Immunoglobulin G (mg/dL)	1878	650 - 1600
Anti-nuclear antibody titre	1:160	<1:80
Anti-smooth muscle antibody	negative	
Anti-double stranded DNA	negative	
Hepatitis B surface antigen (ELISA)	negative	
Hepatitis C antigen and antibody (ELISA)	negative	
Dilute Russel's viper venom test for lupus anticoagulant	negative	
Anti-beta 2 glycoprotein	negative	
Serum homocysteine	negative	
Protein C (PC) assay (automated chromogenic assay on ACL ELITE PRO Coagulation system)	59.3% (first value) 58.9 % (repeat value)	70 – 140 %
Protein S assay (automated latex ligand immune assay on ACL ELITE PRO Coagulation system)	94.8%	57.6 – 112.5%

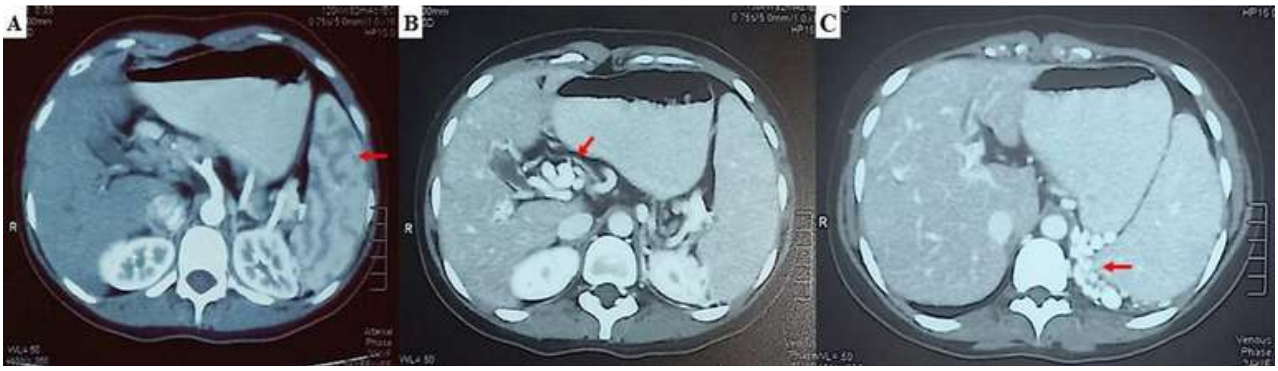

Figure 2 - Axial contrast computed tomographic scan – panel **A**: arterial phase showing congestive splenomegaly (arrow), panel **B**: venous phase showing portal vein cavernoma (arrow), panel **C**: venous phase showing peri splenic varices.

portal hypertension is the commonest clinical presentation of symptomatic chronic PVT.(1) A retrospective study of 48 patients with non-cirrhotic, non-malignant chronic PVT, showed that, oesophageal varices, gastric varices, portal hypertensive gastropathy and gastrointestinal bleeding were seen in 52%, 42%, 44% and 21% respectively at the time of diagnosis.(7) Consequently, endoscopic surveillance for varices is recommended for all patients with chronic PVT, irrespective of symptoms.

In our patient, splenomegaly was detected many years preceding the gastrointestinal bleeding. Splenomegaly, reported in 25 to 100% of patients with chronic PVT, is secondary to portal hypertension and increased venous congestion.(8) The chronic thrombocytopenia observed in this patient was eventually attributed to hypersplenism, after excluding other potential causes such as dysmegakaryopoiesis, peripheral destruction, and spurious causes.

Small-volume ascites can be seen in 10 to 20% of cases of non-cirrhotic PVT patients, typically accompanying massive fluid resuscitation for GI bleeding.(8) A subclinical encephalopathy may also occur in over 50% on non-cirrhotic PVT cases, though overt encephalopathy is rare.(8) These manifestations were not observed in our patient.

In non-cirrhotic PVT, the full liver profile is often normal, although elevated alkaline phosphatase and bilirubin may indicate portal cholangiopathy. Magnetic resonance angiography is the preferred imaging modality due to its higher sensitivity (100%), specificity (around 99%), non-invasive nature, and ability to detect serosal, submucosal, and peri-oesophageal collaterals.(9) Malignancy related PVT is suggested by endoluminal enhancement of the portal vein with a diameter exceeding 23mm.(10) A hypercoagulability workup is warranted in all patients with acute and chronic PVT, regardless of the hepatic status.(1)

Nonselective beta blockers or endoscopic therapy help to reduce the risk of variceal bleeding, and a trans-jugular intrahepatic portosystemic shunt (TIPS) is considered in severe portal hypertension that is refractory to treatment.(1) Severe portal cholangiopathy and cholangitis require endoscopic or open surgical biliary decompression.(1)

The role of anticoagulation in patients with chronic PVT is still debated. The primary goals of anticoagulation are to prevent recurrent thrombosis, prevent thrombus extension, and promote recanalisation.(1) Decisions regarding anticoagulation should be individualised, with consideration given to patients with lower bleeding risk and an underlying prothrombotic state. For patients not requiring anticoagulation, observation and follow-up may be appropriate.(1)

Unfractionated heparin, enoxaparin, and warfarin targeting an INR of 2-3 have traditionally been used but are increasingly being replaced with direct oral anticoagulants, supported by recent observational studies.(1) Anticoagulant therapy is typically recommended for three to six months and may be continued until recanalisation or lifelong if the patient has an irreversible procoagulant condition or mesenteric vein thrombosis. A retrospective cohort study of 136 nonmalignant, noncirrhotic PVT patients (of whom 76% had chronic PVT, and 84% received anticoagulation), showed that anticoagulation significantly reduced the risk of thrombosis without significantly increasing the risk of bleeding.(11)

Protein C deficiency can be either type I or type II, depending on quantity or quality affected, respectively. The chromogenic functional assay utilising "Protac" snake venom as a PC activator, as used in our patient, is preferred over the clot-based functional assays because it is not affected by non-warfarin-based anticoagulants.(12) This test should ideally be repeated or confirmed by another quantitative or qualitative method, as a single positive result is insufficient for diagnosis. Gene identification is confirmatory but remains expensive.

Patients with confirmed PC deficiency are recommended to be anticoagulated during prothrombotic circumstances or long-term, following an unprovoked thrombotic event.(3) Special caution is needed when using warfarin, as it can exacerbate thrombosis or cause purpura fulminans in patients with PC deficiency due to its effect on PC, a vitamin K-dependent anticoagulant with a short half-life.(13)

Conclusion

This case underscores the delayed and complex process involved in diagnosing the aetiology for a young individual's chronic thrombocytopenia, and the challenges in diagnosing and managing chronic portal vein thrombosis and protein C deficiency. The potential underlying cause for the thrombocytopenia needs to be explored in all, as certain conditions can be treated successfully to minimise complications.

Declarations

Conflicts of interest
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CASE REPORT

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"Hashitoxicosis" and possible acquired Gitelman syndrome: dual pathology leading to a catastrophic hypokalemic periodic paralysis

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Abstract

Thyrotoxic periodic paralysis (TPP) is more commonly seen in Graves' disease. But TPP can occur in any condition leading to a hyperthyroid state. It's important to identify the underlying aetiology of the thyrotoxic state as the management differs with the aetiology in the long run. Here we present a case of Hashimoto thyroiditis presenting with hypokalemic periodic paralysis as the first manifestation of the disease along with possible coexisting Gitelman syndrome (GS) aggravating the hypokalemic status leading to a catastrophic periodic paralysis.

Keywords: Hashimoto thyroiditis, hyperkalemic periodic paralysis, thyrotoxic periodic paralysis

Introduction

Hashimoto thyroiditis is a chronic autoimmune disease that causes gradual thyroid failure.(1) Hashitoxicosis is simply the hyperthyroid phase of the Hashimoto disease. It's characterised by the release of preformed thyroid hormones into the serum. Hashitoxicosis is differentiated from Graves' disease due to the reduced uptake in technetium uptake scans. Anti thyroid peroxidase (TPO antibodies are 90% of the time positive in Hashimoto's disease.(2) It's important to identify the exact aetiology of thyrotoxic periodic paralysis when a patient presents with paralysis to provide a tailor made management plan for the patient. Management of thyrotoxic state in Hashimoto thyroiditis is watchful waiting, without active interventions.(3) However, in scenarios where a patient becomes debilitated or remarkably symptomatic during the thyrotoxic phase, active treatment is warranted. Acquired Gitelman syndrome (GS) is seen in patients with autoimmune disease including autoimmune thyroid diseases(AITD) and Sjogren's syndrome.(4) In our patient GS further contributed to debilitating symptoms with severe hypokalemia. This case report highlights the importance of working out the exact underlying aetiology of the thyrotoxic state and the importance of active lookout for association of additional autoimmune or acquired potassium lowering conditions.

Case presentation

Here we discuss a 29-year-old man who presented with a history of inability to get up from the bed in the morning due to the weakness of bilateral upper and lower limbs. The weakness involved proximal muscles of both upper and lower limbs. He could talk and move his neck. The patient had experienced a similar episode while working abroad. Though the

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patient described having received intravenous drug therapy as treatment, medical records were not available. He had no past history of any chronic disease. Neurological examination confirmed proximal weakness in all four extremities, predominantly in lower limbs. Reflexes were absent in both upper and lower limbs. Neck muscle power was normal. His consciousness was preserved and he had no respiratory compromise. Serum potassium level was 1.1 mEq/L and the patient was given an intravenous KCL infusion, 40 mmol in 400 mL of normal saline over 2 hours with close cardiac monitoring. His potassium rose to 4 mmol/L with repeated potassium corrections and he gradually regained functionality over 2 days. The patient's CPK, TSH and T4 were 557 U/L, <0.015 uIU/ml and 6.54 ng/dlL respectively. Initially Graves' thyrotoxicosis was suspected. The ultrasound scan (USS) of the thyroid showed diffuse enlargement of the thyroid gland with coarse echogenicity suggestive of thyroiditis in the absence of any nodules, suspicious lymph nodes or increased vascularity. The urinary electrolytes during this presentation showed marginally elevated urine potassium (28 mmol/L) and ABG showed a mild degree of metabolic alkalosis with a pH of 7.38. Since the thyroid functions were highly suggestive of thyrotoxicosis, a renal loss of potassium was not entertained.

Anti TPO antibodies were more than 1000 IU/mL. Thyroid receptor antibodies (TRAb) were planned but not carried out as it was unaffordable. Later the patient was subjected to a technetium 99 uptake scan which showed reduced uptake bilaterally (right-0.1%, left-0.3%) suggestive of thyroiditis (figure 1).

The diagnosis of "Hashitoxicosis" was made based on highly positive anti TPO antibodies, absence of clinical features suggestive of Grave's disease and reduced uptake in technetium scan. Even though watchful waiting is the usual management for Hashitoxicosis, considering the patient's life threatening presentation he was initiated on treatment. He was initiated on carbimazole 10 mg three times a day and propranolol 20 mg three times a day. While on treatment with good compliance he was readmitted after 2 months with severe hypokalemia (1.8mmol). The initial arterial blood gas analysis showed a metabolic alkalosis with a pH of 7.465. Urine potassium level was 40 mmol/L (normal range <20 mmol/L), serum calcium was normal with low serum magnesium levels and Gitelman syndrome was suspected. Urine calcium creatinine ratio was 0.01(normal range for males 0.04-0.45) with urine calcium level of 0.84 mg/dL, which tallied with the diagnosis of Gitelman syndrome. Genetic studies for the SLCA123 gene could not be carried out. The other causes of hypokalemia such as primary hyperaldosteronism was unlikely as the patient was normotensive throughout and had normal aldosterone /renin ratio (ARR). Patient did not have any symptoms to suggest a gastrointestinal loss of potassium. Furthermore, he had not used any medications that could cause renal loss of potassium/ any drugs that lead to transcellular shift of potassium. Subsequently our patient was initiated on KCL tablets, magnesium salts and spironolactone 50 mg mane. The patient remained asymptomatic with no further attacks of periodic paralysis and he became euthyroid with normal TSH and normal T4 levels highlighting the quick conversion of "transient" thyrotoxic state to euthyroidism in hashimoto thyroiditis. After 3 months the patient became hypothyroid with a TSH of 5 uIU/mL and normal T4 level (1.5 ng/dL) suggesting the development of hypothyroid phase of Hashimoto thyroiditis. However the patient did not have clinical features suggestive of hypothyroidism.

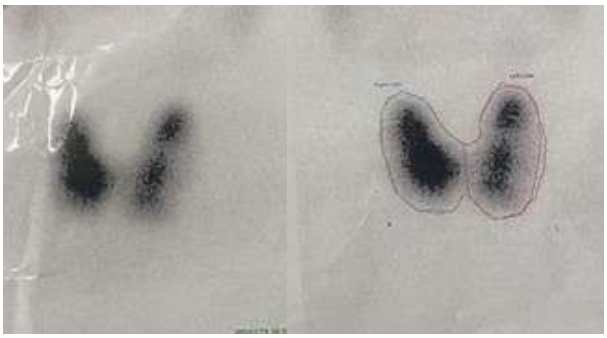

Figure 1 - technetium 99 uptake scan of thyroid showing reduced uptake bilaterally

Discussion

There are numerous causes for hypokalemic periodic paralysis(HPP).(5,6) Grave's disease (GD) accounts for most of the TPP. But our case highlights a patient with Hashimoto's thyroiditis, in transient hashitoxicosis phase presenting with HPP. Though GD presenting with TPP is widely reported,only a handful of cases report HPP associated with Hashimoto's thyroiditis. It's worthwhile to know that thyrotoxicosis of any origin can give rise to HPP. In literature, TPP has been reported in patients with thyroiditis, toxic adenoma, ingestion of T4 or T3, De Quervain's thyroiditis, amiodarone therapy, radiation induced thyroiditis. Since our patient didn't have neck pain, fever, painful goitre or flu like symptoms, De Quervain's thyroiditis was deemed unlikely.

Hashimoto thyroiditis is an autoimmune condition which leads to gradual destruction of the thyroid gland and release of preformed thyroxine into the bloodstream from the inflamed thyroid gland. Rarely, a patient has signs and symptoms of hyperthyroidism and this hyperthyroid state resolves over weeks to months. In HPP an excessive amount of thyroxine causes shift of potassium into the cells due to increased permeability. Our patient's low TSH and high free T4 values, positive anti TPO antibodies with low uptake in the technetium scan and USS thyroid findings highly suggested that we were dealing with a case of Hashimoto thyroiditis. The management of hashitoxicosis is typically observation and most will revert back to euthyroid state without any treatment. But in rare instances, similar to ours, patients can present with muscle failure, congestive heart failure and more debilitating features during the Hashitoxic phase. It is important to prevent further attacks until euthyroid state is achieved and therefore treatment with thianomide and beta blockers is justified.

"Hashitoxicosis – Three Cases and a Review of the Literature" by Alexander et al. highlights cases of hashitoxicosis in which treatments were warranted with carbimazole.(7) Another case report published by Oh et al. in 2012 highlights a case of thyrotoxic periodic paralysis associated with transient thyrotoxicosis due to painless thyroiditis, which is similar to our case.(8)

In our patient, both thyrotoxic state and renal potassium wasting due to GS, contributed to severe hypokalemia. GS is characterised by the presence of antibodies to the sodium chloride channel transporter. GS is an autosomal recessive, salt-losing tubulopathy characterised by renal potassium wasting, hypokalemia, metabolic alkalosis, hypocalciuria and hypomagnesemia. Hypomagnesemia in GS is due to reduced TRPM6 channels. Downregulation of these channels in the distal tubule result in urinary magnesium wasting. Acquired GS is associated with many autoimmune conditions such as Sjogren's syndrome and autoimmune thyroid disease.(9) Literature suggests the prevalence rates of both autoimmune thyroid disease (AITD) and GS among East Asian populations are higher than those among European populations. (4) Autoimmune thyroid diseases (AITDs) are complex genetic diseases. Gitelman disease is due to a defect in the SLC12A3 gene. A case published by Zhou reports a 45 year old male with GD complicated with TPP for 12 years, ultimately revealing the mutation in SLC12A3. The above proves that GS is associated more commonly with AITD and the incidence could be higher than expected. However there is no definite evidence to show a solid association between the SLC12A3 gene and the pathogenesis of autoimmune thyroid disease though many case reports have shown the prevalence of both GS and AITD in the same patient.(10) Our case has a significance since the number of cases of TPP associated with transient thyrotoxic states of thyroiditis are few. It highlights the importance of finding causes other than Graves' disease for thyrotoxic paralysis. It's important that clinicians consider the possibility that some patients may present with life threatening complications that warrant treatment. GS combined with AITDs can cause hypokalemic periodic paralysis indicating that the possibility of GS should be considered in clinical cases with hyperthyroidism and persistent hypokalemia.

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest

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CASE REPORT

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Hypereosinophilic syndrome with cardiac and neurological involvement in the setting of FIP1L1-PDGFRA-gene rearrangement

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Abstract

We describe a case of a 62-year-old man with two episodes of ischaemic strokes who was diagnosed to have hypereosinophilic syndrome(HES) with cardiac and neurological involvement. Further workup for causes of hypereosinophilia ruled out secondary(reactive) causes while bone marrow aspiration and trephine biopsy raised the suspicion of clonal eosinophilia which was confirmed by the detection of FIPILI-PDGFRA gene rearrangement in peripheral blood for FISH analysis. He was started on low-dose imatinib for which he showed a good haematological response with normalisation of eosinophil counts.

Keywords: hypereosinophilic syndrome, clonal eosinophilia, FIP1L1-PDGFRA gene rearrangement, imatinib

Introduction

Eosinophilia is associated with a wide variety of allergic, rheumatological, infectious, neoplastic and rare idiopathic disorders. Clinical manifestations range from benign asymptomatic presentations to life-threatening complications including myocardial fibrosis and thromboembolism.(1) In the presence of significant organ dysfunction emergency treatment is required while evaluating for possible aetiology. After excluding possible reactive eosinophilia, investigating for clonal eosinophilia including FIP1L1-PDGFRA positive myeloid neoplasm is an important aspect of the targeted therapy with imatinib in management.

Case presentation

A 62-year-old man presented with a left-side face, arm and leg weakness for 1 day. He had a similar episode 3 months back which resolved spontaneously suggestive of a transient ischaemic attack. On admission, CT brain was done which showed a left side old infarct without haemorrhage. He had not been previously evaluated for risk factors of stroke such as hypertension, diabetes mellitus or dyslipidaemia. He was a heavy smoker for 30 years with a history of frequent consumption of alcohol twice a week. Basic evaluation with FBC revealed WBC of 18.52x10^9/L with an absolute eosinophil count of 10.67 x10^9/L (57.6% of WBC), haemoglobin of 8.2 g/dL, platelet count of 127x10^9/L. Further inquiry for severe eosinophilia was made and a previous record done one month back in a base hospital revealed severe eosinophilia in FBC. He has no history of chronic cough, allergies, skin disorders, exposure to drugs, gastrointestinal symptoms, joint pain with rashes etc. But he complained of recent loss of appetite with loss of weight over 2 months. On examination, he had bilateral lower limb oedema, pan systolic murmur best heard in the apex with loud

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pulmonary second heart sound, palpable tip of the spleen, left side upper motor 7th nerve palsy with grade 4 out of 5 weakness of left upper and lower limbs compatible with right side middle cerebral artery infarction.

His initial liver function tests were normal. Serum creatinine was 126 µmol/L while CRP was 13.3 mg/dL, ESR 25 mm/1st hour and LDH 326 mg/dL. Ultrasound scan of the abdomen showed mild splenomegaly (14.4cm) with evidence of early liver parenchymal changes. Chest x-ray was normal. The stool sample for parasites, amoeba, and ova cysts was negative. Serum cortisol level was normal. End organ assessment was done with ECG, troponin I and 2D Echocardiogram which revealed elevated high-sensitivity troponin I of 0.0528 ng/mL, The echocardiogram appearance showing thickened endocardium around the apex with moderate mitral regurgitation and moderate pulmonary hypertension was suggestive of eosinophilic cardiomyopathy.

Blood picture showed leukocytosis with marked eosinophilia, many bilobated and few hypo and hyper-lobated forms, and occasional eosinophilic myelocytes without any blasts. Bone marrow aspiration revealed moderately hypercellular marrow fragments, and moderately hypercellular granulopoiesis with markedly increased eosinophils and eosinophil precursors. Some eosinophil myelocytes contained dark basophilic-staining abnormal granules with mild basophilia. Erythropoiesis and megakaryopoiesis were normocellular with few dysplastic megakaryocytes. Bone marrow trephine biopsy showed markedly hypercellular granulopoiesis with markedly elevated eosinophils and eosinophil precursors. Some marrow spaces showed markedly increased fibrosis with fibroblast proliferation and reduced normal haemopoiesis. Reticulin stain showed grade 3 fibrosis according to WHO classification. Findings raised the possibility of clonal eosinophilia with fibrosis (figures 1,2,3,4 and 5).

Just after bone marrow aspiration the patient was started on oral prednisolone 1mg/kg considering hyper-eosinophilic syndrome. Along with steroids, he was started on mebendazole 100 mg twice daily for 3 days followed by a diethylcarbamazine course of 100 mg thrice daily for 21 days. He was strongly advised on cessation of smoking while continuing aspirin and statin. The patient was reviewed 2 weeks after steroids and his eosinophilic count did not show any response . Steroids were tailed off.

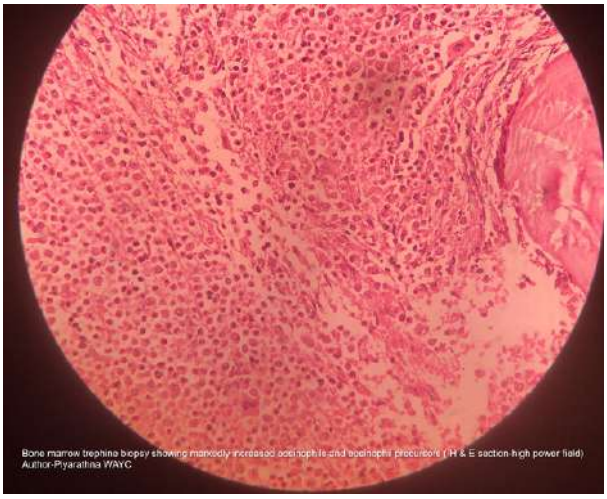

Figure 1 - Bone marrow trephine biopsy showing markedly increased eosinophils and eosinophil precursors (H&E section-high power field

After excluding possible reactive causes, such as clonal eosinophilia, peripheral blood for FIPILI-PDGFRA with FISH analysis was done. It revealed positive evidence of a deletion of the CHIC2 locus, resulting in the fusion of FIPILI with PDGFRA in 85% of the cells. The patient was initiated on imatinib 100 mg daily. After one month of treatment, his FBC revealed a WBC of $4.70x10^9$ /L with an absolute eosinophil count of $0.17x10^9$ /L (3.7% of WBC), a normal count. Currently, he is maintaining a normal eosinophil count on imatinib 100 mg daily.

Discussion

Hyper-eosinophilic syndrome (HES) will be defined in the broadest sense as hypereosinophilia (HE; a peripheral eosinophil count >1.5x109/L documented on at least 2 occasions) or marked tissue eosinophilia and clinical manifestations directly attributed to the eosinophilia or presumed to be due to eosinophilia and for which no alternative cause can be identified. (1) Causes of hypereosinophilia can be classified into three groups: (A) secondary (reactive), which is caused by infections, allergic disorders, medications, autoimmune disorders, and endocrinopathies, (B) primary (clonal/neoplastic), which includes acute leukemias, chronic myeloid disorders, and myeloproliferative syndromes where eosinophils form part of the neoplastic clone; (C) idiopathic HES, in which no underlying disease or syndrome is apparent.(2)

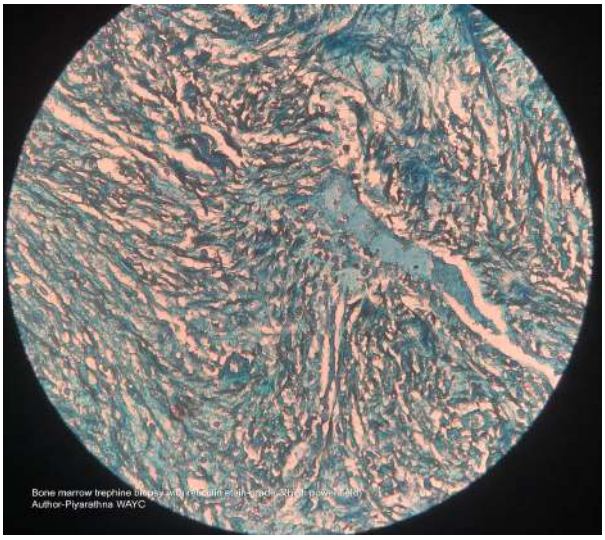

Figure 2 - Bone marrow trephine biopsy with reticulin stain-grade 3 (high power field)

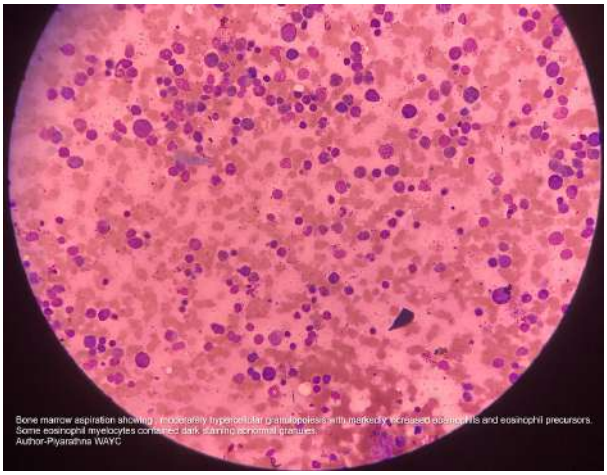

Figure 4 - Bone marrow aspiration showing moderately hypercellular granulopoiesis with markedly increased eosinophils and eosinophil precursors. Some eosinophil myelocytes contain dark staining abnormal granules

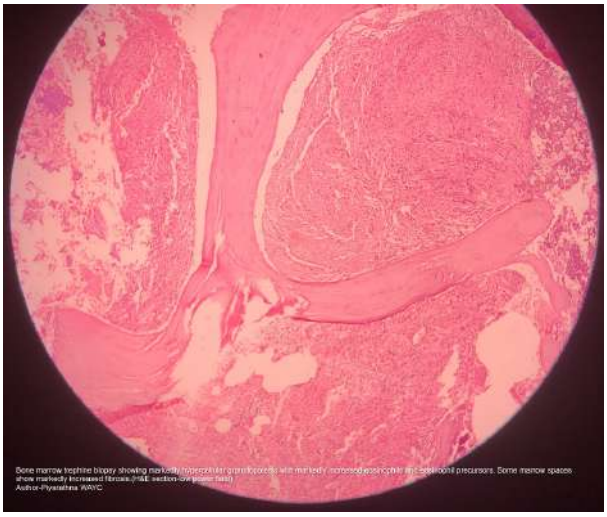

Figure 3 - Bone marrow trephine biopsy showing markedly hypercellular granulopoiesis with markedly increased eosinophils and eosinophil precursors. Some marrow spaces show markedly increased fibrosis (H&E section-low power field

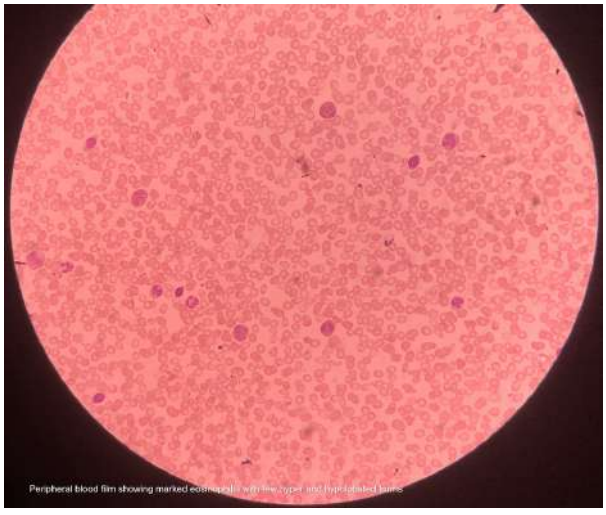

Figure 5 - Peripheral blood film showing marked eosinophilia with few hyper and hypolobated forms

Eosinophils can accumulate in multiple organs, including the heart, skin, nervous system, and lungs, causing end-organ damage in patients with HES. The basic pathology of HES is the sequestration of eosinophils in organ tissues or systems. Eosinophil-derived neurotoxin, eosinophil cationic protein and major basic protein are enzymes released by eosinophils that cause endothelial damage and promote fibrosis, thrombosis and infarction.(3-7)

HES can present with neurological manifestations, including stroke, encephalopathy, and sensory polyneuropathy. The possible mechanisms of cerebral infarction include hyper-eosinophilic cardiac thromboembolism from endomyocardial fibrosis, local thromboses due to eosinophil-induced endothelial dysfunction of cerebral vessels, and hypereosinophilic coagulopathy.(3,8)

Cardiac HES is characterised by progressive sub-endocardial fibrosis due to the toxicity of the eosinophilic basic protein released by eosinophilic granulocytes, causing local destruction of the endocardium, valve leaflets with subjacent fibrosis of the myocardium, leading to the formation of intracardiac thrombi. These proteins play an important role in platelet activation and thrombus formation by inhibiting thrombomodulin.

Fibrosis due to cardiac HES could result in restrictive dysfunction of the left ventricle causing cardioembolic stroke. Most cases of stroke with HES were not associated with large thromboemboli. Rather there were multiple infarcts in the watershed area. The proposed pathophysiological mechanisms include microembolism from endomyocardial fibrosis or local thromboses due to eosinophil-induced endothelial dysfunction of the cerebral vessels. In addition, blood hyperviscosity can deteriorate the microcirculation and lower the clearance of the microemboli, and eosinophilia can result in elevated blood viscosity. Moreover, eosinophil-derived substances can lead to hypercoagulability through other mechanisms. These reasons can explain why HES-associated cerebral infarctions are typically multiple, especially in watershed areas.(3)

In our patient, involvement of the middle cerebral artery territory was more suggestive than a watershed infarct with the clinical manifestation of face, arm, and leg weakness. Eosinophils are activated in the setting of atherosclerosis, and they help plaque development. In the background history of chronic smoking, eosinophilia may have precipitated atherosclerotic plaque formation.

In the presence of significant organ dysfunction emergency treatment is required. Corticosteroids were initially the mainstay of HES treatment and are currently recommended as first-line therapy. Symptomatic patients should be treated with steroid therapy; prednisolone at a dose of 1 mg/kg/day until clinical improvement occurs, after which the dose should be tapered gradually.(2) In our patient steroids were started just after taking samples for bone marrow assessment with the aim to reduce the absolute eosinophil count, reduce tissue infiltration and eosinophil-mediated tissue damage. Our patient describes a steroid unresponsive case which did not show any response after 1 month of steroid therapy.

The treatment of eosinophilia should be directed at the underlying cause. Secondary (reactive) causes should be excluded at an early stage. Morphological assessment of the marrow is vital for the exclusion of haematological and non-haematological malignancies. It is a bit challenging to differentiate clonal eosinophilia from reactive eosinophilia only with the morphological assessment as both conditions can have similar morphology except for the blasts, mast cell proliferation or lymphoid infiltrations. Causes of clonal eosinophilia include haematological neoplasms where the eosinophils form part of the neoplastic clone such as(2);

- Myeloid and lymphoid neoplasms with rearrangement of *PDGFRA, PDGFRB* or *FGFR1* or with *PCM1-JAK2, ETV6-JAK2* or *BCR-JAK2*
- Chronic eosinophilic leukaemia, not otherwise specified (CEL, NOS) including cases with *ETV6-ABL1*, *ETV6-FLT3* or other tyrosine kinase fusion genes
- Atypical chronic myeloid leukaemia with eosinophilia (aCML-Eo)
- Chronic myelomonocytic leukaemia with eosinophilia (CMML-Eo)
- Chronic myeloid leukaemia in accelerated phase or transformation (occasional cases)
- Other myeloproliferative neoplasm in transformation (occasional cases)
- Acute myeloid leukaemia with eosinophilia, particularly with t(8;21)(q22;q22.1) or inv(16)(p13.1q22) (occasional cases only) (AML-Eo)
- Acute lymphoblastic leukaemia, only if eosinophils are demonstrated to be part of the neoplastic clone
- Systemic mastocytosis

According to the 2022 WHO classification of tumours of haematopoietic and lymphoid tissues, Myeloid/lymphoid neoplasms with eosinophilia and

tyrosine kinase gene fusions(MLN-TK) is a different entity of myeloid or lymphoid neoplasms. It is driven by rearrangements involving genes encoding specific tyrosine kinases. The majority of MLN-TK cases are associated with PDGFRA rearrangements. FIP1-like-1-platelet-derived growth factor receptor-alpha (FIP1L1-PDGFRA) results in a constitutively active tyrosine kinase which induces uncontrolled cell proliferation and primary HES. FIP1L1-PDGFRA positive myeloid neoplasm with eosinophilia is reported to account for up to 10% of all patients with HES.(9). These patients are highly sensitive to imatinib at a starting dose of 100 mg daily.(2) Imatinib mesylate is a specific tyrosine kinase inhibitor with potent inhibiting activity against the ABL and BCR-ABL protein kinase activity as well as c-kit and PDGFR.(10)

Conclusion

Our case illustrates an uncommon association of ischaemic stroke, hypereosinophilic syndrome with cardiac and neurological involvement and the importance of genetic analysis in targeting the therapy, especially in steroid-resistant hyper-eosinophilic cases.

Declarations

Conflicts of interest
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CASE REPORT

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Gabapentin-induced DRESS syndrome

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Abstract

DRESS syndrome (drug rash with eosinophilia and systemic symptoms) is a severe multiorgan hypersensitivity drug reaction, which includes a maculopapular rash, fever, lymphadenopathy, hepatitis, and hematological abnormalities including eosinophilia/atypical lymphocytosis with a mortality rate of 10%. It is mostly associated with anticonvulsants, antibacterial and anti-inflammatory drugs.

We present a case of Gabapentin-induced DRESS syndrome in a 66-year-old man, a diagnosed patient with diabetes mellitus and hypertension who presented with a generalized maculopapular rash mainly on the face and extremities associated with fever and lymphadenopathy. Before the hospital admission, he had been treated for Ramsay Hunt syndrome followed by herpes zoster neuralgia with gabapentin for four weeks. He had deranged liver enzymes and leukocytosis with eosinophilia on the full blood count. Physical examination and laboratory findings aided in supporting the diagnosis of Gabapentin-induced DRESS syndrome. The causative drug was discontinued immediately and he was treated with topical and oral steroids with marked clinical and biochemical response.

Keywords: DRESS Syndrome, eosinophilia, gabapentin

Introduction

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a severe, potentially life-threatening adverse drug reaction that includes urticarial, exfoliative skin eruption, fever, lymphadenopathy, hematological abnormalities including eosinophilia, atypical lymphocytes and internal organ involvement [liver, kidney, lungs, heart or pancreas]. It is typically characterized by a long latency period [2-6 weeks to 3 months] from drug exposure. The estimated incidence of DRESS syndrome ranges from 1 in 1000 to 1 in 10,000 drug exposures and it has a mortality rate of about 10%.(1-3)

It is most commonly induced by aromatic anticonvulsants like phenytoin, phenobarbitol, carbamazepine, and antibiotics [amoxicillin, ampicillin, azithromycin, levofloxacin, sulfasalazine, vancomycin, minocycline]. Non aromatic anticonvulsants such as topiramate,ethosuximide, gabapentin and valproic acid are rarely encountered.Gabapentin is a non aromatic anticonvulsant structurally related to the neurotransmitter GABA. It is currently indicated for use in partial seizures, postherpetic neuralgia, postoperative pain, fibromyalgia, and hemodialysis-associated pruritus. Various adverse effects are recorded for gabapentin and common adverse effects are nausea, oedema, nystagmus, fever, ataxia, and fatigue whereas serious effects are Stevens-Johnson syndrome, hypoglycemia, anaphylaxis and DRESS syndrome.(1,4)

DRESS syndrome has no age-sex predilection. Facial oedema due to the involvement of the vascular endothelial growth factor pathway, which can be found in 76% of patients, is the hallmark feature of the DRESS syndrome.(5,4) It is an immune-mediated idiosyncratic reaction where the exact pathogenesis remains unknown. But, known associations are;

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deficiency of hydroxylase enzyme that detoxifies the metabolites, sequential reactivation of herpesvirus family and predisposition with human leukocyte antigen (HLA) alleles.

The diagnosis is confirmed by the presence of four of the following: development of a maculopapular rash > 3 weeks after initiating the culprit drug, lymphadenopathy >2 cm in diameter, leukocytosis /eosinophilia > 1500/mm3 or atypical lymphocytes, fever anhHepatitis/ interstitial nephritis.

Types of liver injury differ according to the liver enzyme levels. There are three types; cholestatic, hepatocellular and mixed. Among DRESS patients cholestatic type liver injury is the most prevalent.(5 -8)

Histopathological changes observed on skin biopsy in DRESS syndrome are infiltrations of inflammatory cells and evidence of vessel wall damage.

Prompt diagnosis of the syndrome and withdrawal of the offending drug are the most essential steps in the management. Systemic corticosteroids are the treatment of choice with or without topical steroid therapy.(6,9,10)

Case presentation

A 66-year-old man with a previous history of diabetes mellitus and hypertension, recently diagnosed with Ramsay Hunt syndrome with postherpetic neuralgia one month back was started on gabapentin for neuropathic pain. He had on and off fever and a maculopapular exfoliative itchy rash involving the face, trunk, and extremities associated with marked facial oedema, and cervical lymphadenopathy without organomegaly.

Baseline investigations including full blood count showed lymphocytosis with marked eosinophilia. The blood picture showed eosinophilia with few reactive atypical lymphocytes. His renal functions were normal whereas liver function tests showed cholestatic-type liver injury.

There was no organomegaly, gallbladder calculi or biliary duct dilatation on ultrasound scan abdomen. Laboratory investigations of the patient are summarised in table 1.

DRESS syndrome due to gabapentin was considered as the diagnosis with the clinical and biochemical criteria using the RegiSCAR scoring system along with dermatology opinion.

Gabapentin was withdrawn soon after the diagnosis and the patient was started on topical steroids along with oral prednisolone 1mg/kg/day initially which was gradually tapered off over 4-6 weeks. Oral antihistamines were initiated for pruritus and a skin biopsy was taken.

Over the next week, the patient showed a good clinical and biochemical response including resolution of facial oedema. Skin biopsy showed lymphocytic infiltration in the perivascular and papillary dermis confirming the diagnosis. He was

Figure 1 - Urticarial, exfoliative skin eruption with facial oedema

Table 1 - Laboratory investigations of the patient

Investigation	Day 1	Day 3	Day 6	Day 9	Reference Range
WBC (10^9/L)	16.83	25.63	19.58	14.09	4-10
Neutrophil (10^9/L)	8.43	10.39	9.1	8.69	2-7
Eosinophil (10^9/L)	3.63	5.54	4.52	2.47	0.02- 0.5
CRP (mg/L)	5.3	3.2	1.4	< 0.5	0-5
S. Cr (micg/L)	68.2	73.4	76.9	84.7	70-115
AST (U/L)	62	92	114	108	0-35
ALT (U/L)	136	185	125	112	0-40
ALP (U/L)	469	602	427	206	46-116
GGT (U/L)	293	340	270	114	0-50
Albumin (g/dL)	3.1	3.0	2.8	2.9	3.5-5.3
Globulin (g/dL)	2.8	2.7	2.5	2.5	2.5-3.5
T B(micmol/L)	47.1	52.3	33.4	23.7	5- 19
D B (micmol/L)	38.6	43.3	25.6	16.5	0-5
I B (micmol/L)	8.9	8.4	7.2	6.4	<1
LDH (U/L)		363.4	214		0- 240
TSH (mIU)			1.67		0.46- 4.6

WBC: white blood cells, CRP: C reactive protein, S. Cr: serum creatinine, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, T B: Total bilirubin, D B: Direct bilirubin, I B: Indirect bilirubin

clinically well with normalized liver functions after one month. He was discharged with strict advice to avoid gabapentin in the future.

Discussion

The acronym DRESS which stands for Drug Reaction with Eosinophilia and Systemic Symptoms is an uncommon potentially life-threatening adverse drug reaction with a 10% mortality. It was first recognized in 1950 and has an estimated prevalence of about one in 10,000 cases of exposure to culprit drugs. Features include severe exfoliative pruritic skin eruption with facial oedema, fever, lymphadenopathy, hematologic abnormalities [eosinophilia or atypical lymphocytes], and internal organ involvement, mainly liver and kidney. The presence of facial oedema is a characteristic presentation, which might be a predictor of disease. It has a usually delayed onset of 2-8 weeks post-initiation of the inciting drug and the symptoms may persist or aggravate despite its discontinuation. Pathogenesis involves a deficiency of hydroxylase enzyme that detoxifies the metabolites, sequential reactivation of the herpesvirus family, and predisposition with HLA alleles.

It is most commonly engendered by aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine).Non aromatic anticonvulsants like gabapentin are rarely encountered.

RegiSCAR scoring system is an accepted scoring system for DRESS syndrome and skin biopsy has a

Figure 2 - Resolved facial oedema and rash following steroid therapy

place. Spongiosis, interface dermatitis, vascular wall damage, and superficial perivascular infiltrations are histopathological findings of DRESS syndrome. (2-4, 7,11)

The mainstay of treatment is withdrawal of the offending drug, initiation of oral or topical corticosteroids, antihistamines, and maintenance of fluid and electrolyte balance. The starting daily dose of prednisolone is 0.5–1.0 mg/kg. It is gradually tapered off over 2–3 months. The outcome is better if corticosteroids are started at the acute stage. Intravenous immunoglobulin (IVIG) is another treatment option with limited data available. (1,5,6,10,12)

Conclusion

DRESS is a severe drug reaction with high morbidity and mortality. We should always think about the possibility of DRESS syndrome, when a patient presents with fever, maculopapular rash, and lymphadenopathy 4-6 weeks after starting a new drug, specially aromatase anticonvulsants.

Declarations

Author contributions
History taking, examination, necessary investigations arrangement, management under supervision, daily monitoring of the patient, and writing of the manuscript were done by Premasiri DGAL. All authors contributed to writing the manuscript, read and approved the final manuscript.

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Conflicts of interest
The authors declare that they have no conflicts of interest

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CASE REPORT

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Neurocysticercosis: a rare cause of new-onset seizures

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Abstract

Neurocysticercosis, a prevalent helminthic infection of the central nervous system, is primarily transmitted through the faeco-oral route via contaminated water or vegetables. The revised diagnostic criteria (2017) provide a standardized framework for categorizing cases based on diagnostic certainty and diagnostic criteria. Neuroimaging modalities, computed tomography (CT) and magnetic resonance imaging (MRI), are the gold standard for diagnosis. We report a case of an immunocompetent patient residing in an endemic region with minimal exposure to risk factors, who presented with new-onset seizures. Neurocysticercosis was diagnosed based on radiological evidence of a single enhancing lesion with the characteristic "hole-with-dot" appearance. The patient received anti-inflammatory, antiepileptic, and analgesic medications, followed by antiparasitic treatment. Clinical improvement was observed with resolution of perilesional edema and successful seizure control.

Keywords: neurocysticercosis, Taenia solium, parasitic diseases, new-onset seizure

Introduction

Neurocysticercosis is the most prevalent helminthic infection affecting the human central nervous system.(1) It is caused by the ingestion of embryonated eggs of the parasite Taenia solium.(2,3) The clinical manifestations of neurocysticercosis vary according to lesion location, parasite burden, and the host's immune response.(3) Neurocysticercosis is endemic in regions like Central and South America, sub-Saharan Africa, and parts of the Far East, reaching an incidence of 3.6% in some areas.(3) The prevalence of Taenia solium taeniasis, determined through microscopic examination, typically ranges around 1%.(4)

Case presentation

A 25-year-old man with no significant past medical history presented to the emergency department (ED) having experienced a seizure 15 minutes prior to arrival. A colleague had witnessed the patient experiencing tonic-clonic movements of the extremities lasting approximately 2 minutes, followed by a period of lethargy. The patient denied any associated symptoms including fever, headache, nausea, vomiting, visual disturbances, focal neurological deficits, facial asymmetry, speech or swallowing difficulties, or recent head trauma. There was no history of recent travel.The patient reported a history of undercooked food consumption and infrequent fresh vegetable intake.

Vital signs at presentation were within normal limits, with a temperature of 36.8°C, blood pressure of 110/80 mmHg, pulse rate of 100 beats per minute, and respiratory rate of 20 breaths per minute. There was no neck stiffness or focal neurological signs. Cardiovascular and pulmonary examinations were unremarkable. Abdominal examination and fundoscopic evaluation were normal.

Laboratory investigations are summarised in table 1.

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Table 1 - Laboratory investigations of the patient

Laboratory parameter/Investigation	Patient's result	Reference range
Haematology		
Total white cell count (x 10^3/uL)	12.5	4.0-11.0
Neutrophil count (%)	51	55-65
Lymphocyte count (%)	37	25-35
Hemoglobin level (g/dL)	13.6	12.0-16.0
Platelet count (x10^9/uL)	262	140-400
Biochemistry		
Serum sodium (mmol/L)	137	136-145
Serum potassium (mmol/L)	3.8	3.5-5.1
Serum calcium (mg/dL)	8.7	8.6-10.0
Serum magnesium (mg/dL)	2.0	1.6-2.6
Serum phosphate (mg/dL)	2.5	2.5-4.5
Serum creatinine (mg/dL)	1.10	0.67-1.17
Total protein (g/dL)	8.1	6.4-8.2
Serum albumin (g/dL)	4.0	3.4-5.0
Serum globulin (g/dL)	4.1	2.0-3.2
Aspartate transaminase (U/L)	25	15-37
Alanine transaminase (U/L)	27	16-63
Alkaline phosphatase (U/L)	89	46-116
Random blood sugar (mg/dL)	149	
CSF and body fluid		
Protein (g/L)	0.4	0.2-0.4
White blood cell (cell/mm^3)	2	0-8
Neutrophil (%)	Too low to differentiate	55-65
Lymphocytes (%)	Too low to differentiate	25-35
Red blood cells (cell/mm^3)	0	None reported
Sugar (mg/dL)	88	45-85
Indian ink	Not found encapsulated budding yeast	
CSF gene xpert	Not detected	
CSF culture	No growth	
CSF cytology	No atypical cells seen	
Microbiology		
Urine full report	Albumin nil, no cells or cast	
Urine culture	No growth	Urine culture
Blood culture	No growth	Blood culture

Table 1 - Laboratory investigations of the patient (continued...)

Laboratory parameter/Investigation	Patient's result	Reference range
RPR	Nonreactive	
Anti TP	Negative	
HIV antibodies	Negative	
Imaging		
Electroencephalogram	A 1.5 x 1.7 cm hypodense lesion with a peripheral hyperdense rim and internal calcification (3 mm) is noted in the left frontal lobe, surrounded by perilesional edema. Neurocysticercosis should be considered. Differential diagnoses include tuberculoma, brain abscess, or tumor. Please correlate with other investigations.	

A comprehensive infectious disease evaluation was performed. Cerebrospinal fluid, blood, and urine cultures were negative. Cerebrospinal fluid analysis revealed a white blood cell count below the clinically significant range, with normal protein and glucose levels. Serologic testing for HIV, syphilis (RPR - rapid plasma reagin), and anti-Treponema pallidum (anti-TP) antibodies were unremarkable. A complete blood count demonstrated leukocytosis with a neutrophilic predominance.

Given the concerning nature of the seizure, a computed tomography (CT) scan of the head was performed. The imaging study revealed a small enhancing cyst with an eccentric scolex, surrounded by mild oedema and minimal mass effect, suggestive of a granular nodular stage (figure 1).

A diagnosis of neurocysticercosis was entertained. Initial management focused on seizure control with a loading dose of phenytoin followed by oral maintenance therapy. To mitigate cerebral oedema, intravenous dexamethasone was administered at a dose of 8 mg once daily, with close monitoring. Antiparasitic treatment with albendazole 400 mg twice daily was initiated one day post-admission and continued for a 14 day course. Dexamethasone was gradually tapered. The patient demonstrated clinical improvement with resolution of perilesional oedema and seizure control, allowing for outpatient management.

Discussion

Neurocysticercosis is an emerging public health issue in developed countries due to increased migration from regions where the disease is endemic.(1,3) It remains a significant public health burden in low- and middle-income countries (LMICs), particularly in Latin America, Asia, and sub-Saharan Africa.(2,4) The life cycle of Taenia solium involves humans as definitive hosts and pigs as intermediate hosts.(5) Human infection occurs through faeco-oral transmission via contaminated water or vegetables contaminated with viable eggs from an infected individual.(5) Taenia solium infection can lead to the formation of cysticerci (larval stage) throughout the human body, with the most severe consequences occurring when they develop in the central nervous system.(6) In the present case, the patient exhibited no evidence of immunodeficiency but documented exposure to risk factors.

In many cases, the infection is asymptomatic as evidenced by population-based studies from regions endemic for the disease.(1) The incubation period is highly variable but typically ranges from 2-5 years.(7) A median incubation period of 3.5 years has been reported.(8) Neurocysticercosis is a highly variable disease whose clinical manifestations are primarily determined by parasite location.(2) Headaches, epilepsy, and hydrocephalus are common presentations. Epilepsy is the predominant symptom in parenchymal neurocysticercosis, affecting 60-90% of patients.(1-3,9) In extraparenchymal disease, intracranial hypertension is the most frequent finding, occurring in approximately 70% of patients.(2,3) First seizure is a common initial manifestation of the disease consistent with the presentation of our patient.

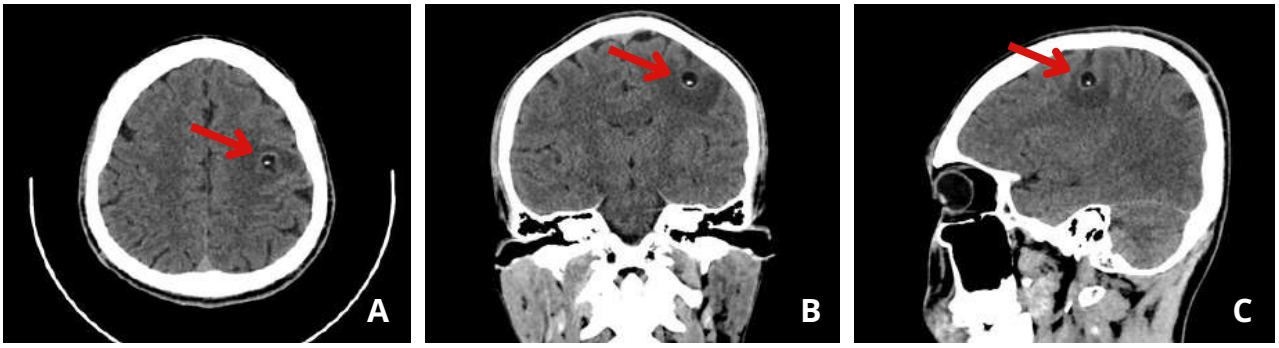

Figure 1 - **A:** Non contrast CT brain of the patient. (Left) Axial view, **B:** (Middle) Coronal view, **C:** (Right) Sagittal view, presented with A 1.5 x 1.7 cm hypodense lesion with a peripheral hyperdense rim and internal calcification (3 mm) is noted in the left frontal lobe, surrounded by perilesional edema.

Upon elicitation of the host's inflammatory response, cysticerci undergo distinct stages of involution. Initially, a colloidal stage ensues, characterized by a pericyst inflammatory reaction and a turbid, granular cyst interior. Subsequently, cysticerci calcify or resolve entirely.(1,2,11) The natural evolution of neurocysticercosis correlates closely with advanced imaging findings obtained via CT and MRI. This classification remains the predominant framework for contemporary neurocysticercosis imaging studies. (6,7,9,11) In the vesicular stage, imaging demonstrates a well-circumscribed cyst with a thin (2-4 mm) non-enhancing wall. The cyst fluid exhibits cerebrospinal fluid-like characteristics. A pathognomonic imaging feature of this stage is a discretely located scolex within the cyst.(11) During the colloidal vesicular stage, larval degeneration commences at the scolex, progressing to hyaline degeneration and size reduction. The cyst fluid acquires a turbid appearance due to proteinaceous content, while the cyst wall thickens in response to surrounding brain inflammation. Imaging reveals a thickened, irregular cyst wall with pronounced contrast enhancement, indicative of blood-brain barrier disruption. The cyst fluid demonstrates increased density compared to cerebrospinal fluid on CT.(11) As cysticercus degeneration advances in the granular nodular stage where the cyst diminishes in size, transforming into a smaller granulomatous nodular lesion. Imaging may depict a nodular or thick, annular enhancement. Surrounding oedema is less pronounced compared to the late colloidal vesicular stage and gradually subsides.(11) Interestingly our patient had an eccentric hyperdense nodule representing the scolex, “hole-with-dot” appearance, which is pathognomonic of neurocysticercosis.

Immunodiagnostic testing often yields inconclusive results. In such instances, specific serological assays become invaluable for diagnostic confirmation. Enzyme-linked immunoelectrotransfer blot (EITB) is the preferred method for antibody detection. Additionally, molecular techniques such as polymerase chain reaction (PCR) and deep genomic sequencing of CSF have been employed to detect neurocysticercosis DNA.(4,6,7) However, immunodiagnostic testing was not conducted in this case.

Despite advancements in neuroimaging and immunodiagnostic testing, establishing a definitive diagnosis of neurocysticercosis remains challenging. (1) Neuroimaging modalities, primarily CT scan and MRI, serve as the gold standard for diagnosis. The 2017 revised diagnostic criteria for neurocysticercosis introduced a standardized framework for categorizing cases based on diagnostic certainty (definitive or probable) and diagnostic criteria (absolute, neuroimaging, clinical/exposure).(10) Our patient fulfilled the criteria for a definitive diagnosis of neurocysticercosis, as evidenced by the absolute criterion of a conclusively demonstrated scolex within a cystic lesion on neuroimaging study.

The disease must be characterized by the location and number of cysticerci within the central nervous system, their viability, and the severity of the host's immune response. Treatment typically involves a combination of symptomatic and antiparasitic therapies.(1,2) Optimal management necessitates effective symptomatic control, including the administration of anti-inflammatory, antiepileptic, and analgesic medications, prior to initiating antiparasitic treatment. These agents address symptoms such as seizures, headaches, and intracranial hypertension. Antiparasitic drugs, such as albendazole and praziquantel, are indicated for the elimination of viable or degenerating cysticerci.

(1,2,4,6) The efficacy of antiparasitic drugs in the treatment of single enhancing lesions remains controversial, with some studies demonstrating no significant clinical benefit.(3,11) Surgical intervention, encompassing cyst resection or shunt placement, may be considered for intraventricular cysts but is less frequently required.(12) The primary objective of dead parasite treatment in our case is seizure management. Nevertheless, in contrast to the established consensus on the limited efficacy of antiparasitic drugs in this context, the patient demonstrated a favorable outcome.

Conclusion

This article highlights the importance of considering neurocysticercosis in the differential diagnoses of patients, especially in endemic areas, presenting with neurological symptoms. Early diagnosis and appropriate treatment can significantly improve outcomes and prevent long-term complications.

Declarations

Conflicts of interest
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CASE REPORT

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A case of severe systemic lupus erythematosus with elevated free light chains in a young man

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Abstract

A 36-year-old man presented with bilateral lower limb weakness for two weeks with absent reflexes and normal upper limbs. He developed oedema, psychosis, aphasia and became bedbound. Investigations revealed axonal polyneuropathy, multiple cerebral infarctions and nephrotic-range proteinuria with active sediments. ANA, anti-Smith and anti-U1RNP antibodies were positive with elevated kappa and lambda light chains. Renal biopsy revealed class 2 lupus nephritis with renal deposition of both light chains. Elevated free light chains have been postulated as a marker of systemic lupus erythematosus (SLE) disease activity. SLE with neuropsychiatric manifestations and lupus nephritis was diagnosed and treatment commenced. However, he remained significantly debilitated.

Keywords: systemic lupus erythematosus, elevated kappa and lambda light chains, lupus nephritis

Introduction

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease, with a female to male ratio of 9:1(1) and an estimated prevalence of 9.2 per 100 000 in men.(2) Studies have demonstrated that the presence of elevated free light chains in serum and urine reflect disease activity.(3) We report a rare case of a young man who developed rapidly evolving debilitating neuropsychiatric symptoms, proteinuria and peripheral neuropathy with elevated free light chains, culminating in a diagnosis of severe SLE with neuropsychiatric manifestations and lupus nephritis.

Case presentation

A 36-year-old previously healthy man presented to a tertiary care center in Sri Lanka with bilateral lower limb weakness and loss of appetite for two weeks, with no history of trauma, urine retention, fever or recent respiratory/ gastrointestinal illness. The weakness was of gradual onset involving both legs symmetrically with no upper limb weakness. On examination, he was conscious and rational. His pulse rate was 68 bpm, blood pressure was 130/80 mmHg and his cardiovascular, respiratory and abdominal examinations were unremarkable. He had reduced tone, power of 3/5 in all muscle groups with absent reflexes and equivocal plantar reflexes in bilateral lower limbs with normal sensation. Upper limbs and cranial nerves examinations were normal.

He was initially managed for Guillain Barre syndrome and treated for five days with intravenous immunoglobulin for which he had a poor response. His investigations during the hospital stay were as follows (table 1).

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Table 1 - Trend of investigations during the hospital stay

Investigation	Initial	Mid	Final	Normal range
White blood cell count (x 10^3/uL)	5.8	5.8	6.6	4.0-10.0
Haemoglobin (g/dL)	9.9	9.9	10.1	13-16.5
Platelet count (x 10^3/uL)	197	140	240	150-450
Serum creatinine (mg/dL)	0.8	2.0	0.7	<1.2
ESR (mm/1st hour)	79	129	80	0-15
C reactive protein (mg/L)	18	23	20	<6
Alanine transaminase (U/L)	18			0-55
Aspartate transaminase (U/L)	9			0-50
Total bilirubin (mg/dL)	0.4			0-0.5
Serum sodium (mmol/L)	129	127	129	135-145
Serum potassium (mmol/L)	3.5	4.1		3.5-5.5
Corrected calcium (mg/dL)		7.8		8.5-10
Serum magnesium (mg/dL)		1.7		1.7-2.2
Creatine phosphokinase (U/L)	126	100	45	39-308
Albumin (g/L)	3.6			3.5-5.0
Globulin (g/L)	5.0			2.5-3.5
APTT (s)	27.8			21-35
TSH (mIU/L)	2.4			0.5-5

The nerve conduction study revealed reduced motor amplitude with neurogenic changes in both lower limbs suggesting lumbosacral plexopathy/acute motor axonal neuropathy. MRI pan-spine was normal. He developed abnormal behavioural changes with psychotic symptoms and later developed complete aphasia. Within one month, he became bedbound. MRI brain revealed multiple acute infarcts in bilateral corona radiata, right posterior limb of the internal capsule and right temporal lobe. Magnetic resonance angiography (MRA) was normal.

He developed generalized body oedema and proteinuria (albumin +++) with active urinary sediments (red cells- 15-20/hpf) and a raised creatinine of 2 mg/dL. Urine protein: creatinine ratio was 4.8 mg/mmol. Contrast enhanced computed tomography of chest, abdomen and pelvis, 2-Dimensional echocardiogram and trans-oesophageal echocardiogram were normal. No changes were observed in electroencephalography (EEG). Further investigations are summarized in table 2.

Renal biopsy revealed mild mesangial proliferation without amyloid deposits. Immunofluorescence revealed 2+ granular staining for IgG and C3, 1+ for IgA and C1q and trace for IgM (full house staining pattern) with 2+ stain for both kappa and lambda in glomerular capillary walls and mesangium. With the positive ANA and the highly SLE specific anti-smith antibody,(4) a diagnosis of SLE with neuropsychiatric disease, class 2 lupus nephritis and peripheral neuropathy was made.

A bone marrow biopsy revealed 2% plasma cells and Congo-red staining was negative for amyloidosis. In the absence of clonal proliferation of plasma cells in the marrow, elevated light chains (both kappa and lambda)and nodular glomerulosclerosis on renal biopsy, light chain deposition disease was excluded. It was postulated that the increased light chains were secondary to SLE disease activity. The patient was started on intravenous methylprednisolone pulses, hydroxychloroquine and cyclophosphamide. However, he remained aphasic and recovery was poor.

Table 2 - Trend of investigations during the hospital stay

Test	Result
AntinuclearAnti-nuclear antibody (ANA)	Positive >1:80 (nuclear fine speckled pattern)
Anti-dsDNA	Negative
Anti-Smith	Positive
Anti- U1RNP	Positive
Anti-JO-1	Negative
Anti-Ro, Anti-La	Negative
c-ANCA, p-ANCA	Negative
HIV antibodies	Negative
Hepatitis B surface antigen	Negative
Hepatitis C IgM IgG	Negative
VDRL	Negative
Rheumatoid factor	Negative
C3 (mg/dL)	104 (80-178)
C4 (mg/dL)	40 (15-45)
Urine Bence Jones protein	Positive
Serum protein electrophoresis	Negative
Urine protein electrophoresis	Negative
Serum free Kappa light chains (mg/L)	71 (increased) (3.3-19)
Serum free Lambda light chains (mg/L)	41 (increased) (5.7-26.3)
Kappa/lambda ratio	1.7 (increased) (0.26-1.6)
Blood picture	Normocytic cells. Marked rouleaux formation
Ferritin (ng/mL)	1037 (22-322)
Mantoux	Negative
CSF protein (mg/dL)	95 --> 214 --> 185 (15-45)
CSF glucose (mg/dL)	35 --> 35 --> 28
Corresponding plasma glucose (mg/dL)	81 --> 78 --> 75
CSF neutrophils	Nil --> Nil --> Nil
CSF Lymphocytes	16 --> 25 --> Nil
CSF red cells	70 --> 10 --> 20
CSF tuberculosis PCR	Negative
CSF viral panel	Negative
CSF cryptococcal antigen	Negative
CSF culture	Negative
Serum osmolarity (mOsm/L)	262 (275-292)
Urine sodium (mmol/L)	75 (<20)
Urine osmolarity (mOsm/kg)	308 (50-1200)
Random cortisol (nmol/L)	462 (140-690)
Procalcitonin (ng/mL)	0.4 (<0.05)

Discussion

This case describes a previously healthy man who, in the presence of a positive ANA, neuropsychiatric disease, lupus nephritis along with anti-Smith antibody positivity, fulfilled the 2019 EULAR/ACR classification criteria of SLE.(5) The accelerated nature of disease progression in this patient over a period of one month was striking, along with the presence of elevated free light chains.

Elevated free light chains in SLE was first observed in 1966.(6) It has been reported that during periods of SLE activity, there are hyperactive polyclonal B cells which produce increasing number of immunoglobulins resulting in increased light chain production.(3) Several studies have reported elevated free light chains as a marker of disease activity in SLE.(7) Aggarwal et al., demonstrated that serum free light chain levels, along with C3, correlated with disease activity in SLE.(8) A study done to assess the correlation of urine free light chains and SLE disease activity found that the urine kappa and lambda light chain levels were highest in the severe disease group, followed by moderate, mild and stable groups.(3) Hopper et al., demonstrated the elevation of urine free light chains preceding SLE flares by 4-8 weeks.(9)

The classic hallmark of SLE on renal biopsy, the full-house immunofluorescence pattern encompasses all 5 major immunofluorescent stains on a renal biopsy (IgG, IgA, IgM, C3, and C1Q).(10) The presence of light chain deposition evidenced by kappa and lambda renal biopsy stains in SLE is less frequently described. A study involving 56 patients with biopsy proven lupus nephritis(LN) found that patients with proliferative LN had more frequent light chain deposition in glomeruli than those with non-proliferative lupus. This study highlighted the need for more studies to identify the potential prognostic significance of light chain deposition in SLE.(11)

However, it has also been reported that patients with stable SLE have higher free light chain levels compared to healthy subjects.(7) Furthermore, elevated free light chains have been reported with viral infections, other rheumatological conditions and conditions with immune system reactions such as multiple sclerosis and diabetes mellitus. Therefore, elevated free light chains in SLE should be interpreted with these caveats in mind.(12)

Conclusion

This case report highlights the diverse and severe manifestations of SLE in a young man and sheds light on the potential significance of elevated free light chains as a marker of disease activity in SLE.

Declarations

Author contributions
All authors contributed to the writing of the manuscript. The manuscript has been read and approved by all authors.

Conflicts of interest
The authors declare that they have no conflicts of interest

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CASE REPORT

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Pseudomembranous colitis: fatal clostridium difficile infection in pregnancy

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Abstract

Clostridium difficile infection (CDI) is a disease primarily affecting the large intestine, characterised by diarrhoea, abdominal pain and fever due to enterotoxins. The severe form of this infection, known as pseudomembranous colitis, carries a high mortality rate if not promptly recognised and treated. Its incidence is on the rise among pregnant women, posing significant risks to both the mother and foetus. Here, we report a fatal case of pseudomembranous colitis in a young pregnant woman. Maintaining a high index of clinical vigilance in pregnant individuals experiencing unexplained diarrhoea enables timely investigations and prompt treatment, averting adverse maternal and foetal outcomes.

Keywords: CDI in pregnancy, clostridium difficile, pseudomembranous colitis, morbidity in pregnancy

Introduction

Clostridium difficile infection (CDI) primarily affects the large intestine, causing inflammation of the mucosal lining due to enterotoxins. Well-known risk factors include recent antimicrobial therapy, prolonged antibiotic use, and multiple antibiotic usage. However, prolonged hospitalisation, chemotherapy and immunocompromised status also contribute to CDI.(1) Globally, the prevalence of CDI is increasing due to rising antibiotic usage and the emergence of hypervirulent strains.(2) Clinical symptoms range from mild, self-limiting diarrhoea and abdominal pain to severe, potentially fatal colitis and toxic megacolon.(3) Recent literature indicates a rise in CDI rates among pregnant women.(1) Pseudomembranous colitis remains poorly studied in Sri Lanka due to limited access to advanced diagnostic investigations in most of the health care centres.(4) Clostridium difficile infection remains a critical concern due to the health care infrastructure limitations as advanced diagnostic tests such as polymerase chain reaction to detect clostridium difficile toxin A and B are not widely available in most of the government hospitals in Sri Lanka, posing a significant diagnostic gap. Here we report a fatal case of Pseudomembranous colitis in a young pregnant woman, which posed challenges in clinical diagnosis and management.

Case presentation

A 28-year-old primigravida at her 21 weeks of gestation presented with symptoms of cold and tested positive for Influenza B. She was prescribed oseltamivir and discharged after three days as her symptoms improved. However, she returned the following day complaining of a watery diarrhoea. She denied using antibiotics or any other over-the-counter medications. On examination, she appeared pale but was hemodynamically stable, with a soft, non-tender abdomen. The rest of the systemic examinations were unremarkable. Considering her recent viral infection and laboratory parameters (WBC-13000, Neutrophil-81.4% and elevated C-reactive protein (CRP 136 mg/dL), she was started on parenteral ceftriaxone. Considering the neutrophil leucocytosis and rise in CRP, CDI was not considered early as the patient denied prior exposure to

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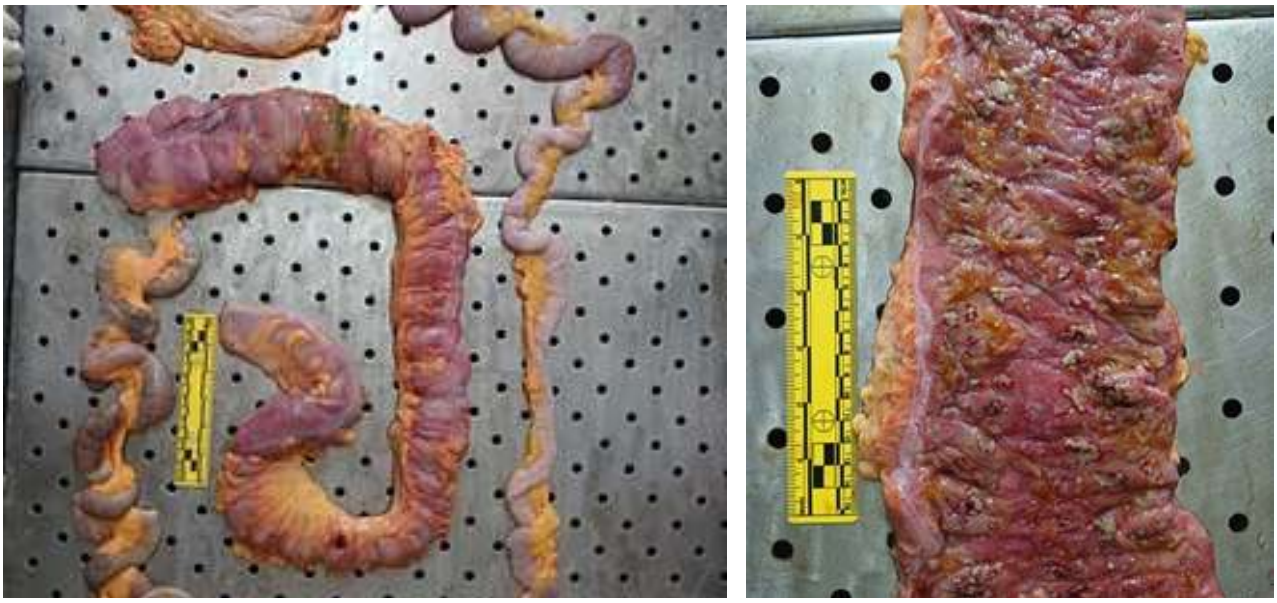
antibiotics. Stool microscopy and culture did not reveal any microorganisms. Performing confirmatory diagnostic tests for Clostridium difficile including PCR, toxin or glutamate dehydrogenase, are not readily available in many government health care centres in Sri Lanka.Considering the poor socioeconomic background of the patient, these tests were not done in the private sector.

On the third day of admission, she experienced abdominal cramps and delivered the foetus prematurely. Subsequently, she became hemodynamically unstable. Obstetric emergency care was provided with adequate fluid resuscitation, blood transfusion and the administration of inotropes. Parenteral metronidazole was commenced to alleviate potential obstetric infections, and she was transferred to an intensive care unit. An ultrasound scan revealed free fluid in the abdomen and pelvis, prompting an urgent contrast-enhanced computed tomography (CECT) scan of the abdomen and a mesenteric angiogram, which confirmed pancolitis with ascites. Despite prompt and aggressive resuscitation, her clinical condition further deteriorated. Flexible sigmoidoscopy confirmed the presence of fulminant colitis with evident mucosal oedema, suggesting pseudomembranous colitis. Intravenous Vancomycin preparation was administered rectally and via nasogastric tube due to unavailability of oral and rectal preparations. Despite all the efforts, she succumbed to the illness within 24 hours. Pathological postmortem reconfirmed the clinical diagnosis of fulminant pseudomembranous colitis, depicted in figure 1, 2 and 3.



Figures 1 & 2 - Autopsy findings: diffuse pseudomembranous colitis with yellow patches

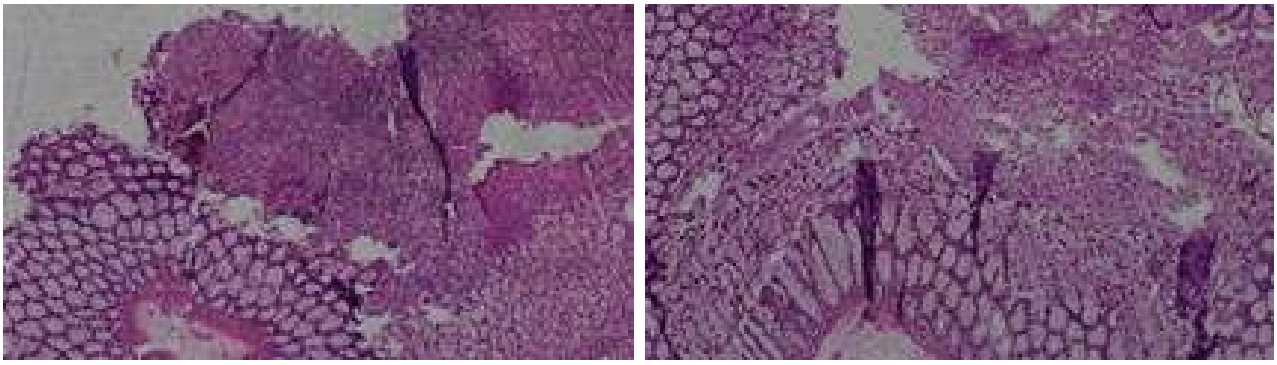


Figure 3 - Magnification into 40, pseudo membranous colitis- mucosal acute inflammation with volcano eruption like exudate(formed of neutrophils, fibrin, mucus and cellular debris), prominent sub mucosal oedema

Discussion

Clostridium difficile infection (CDI) poses significant challenges in diagnosis, particularly in vulnerable populations such as pregnant women. While antibiotic use remains a well-known risk factor, CDI can manifest in immunocompromised individuals even without prior antibiotic exposure.(5)Pregnant women, in particular, experience unique immunological changes that may predispose them to CDI and its devastating complications. Recent studies have shed light on the underlying mechanisms, including altered pro-inflammatory cytokine production, compromised cell-mediated immunity, and hormonal fluctuation during pregnancy, which exacerbate and contribute to the severity of CDI.

Our case highlights the importance of considering CDI as a differential diagnosis in pregnant women with diarrhoea, even in the absence of prior antibiotic use. The diagnostic challenges, include the unavailability of specific tests in all health care centres especially in poor resource settings to detect Clostridium difficile by polymerase chain reaction or its toxin reiterate the need for a high index of suspicion and prompt management. Rapid diagnostic methods (enzyme immunoassay (EIA) toxin assays, nucleic acid amplification testing) are widely available in high resource settings leading to early diagnosis of CDI and prompt initiation of treatment, reducing the progression of disease to fulminant colitis. Anaerobic culture is generally not performed due to the long turnaround time.(8) Bridging the gaps in health care infrastructure in resource poor settings like Sri Lanka is crucial for early diagnosis of CDI and to reduce the mortality related with delayed diagnosis leading to fulminant colitis.

The clinical spectrum of CDI is broad, ranging from mild self-limiting symptoms to fulminant colitis and toxic megacolon. Pseudomembranous colitis, characterized by the formation of pseudo membrane over the colonic mucosa, is a severe manifestation of CDI associated with significant morbidity and mortality. Despite advances in diagnostic modalities and treatment options, the prognosis of pseudomembranous colitis remains guarded, particularly in pregnant women.

The management of CDI during pregnancy indeed presents some challenges and controversies. Oral metronidazole or vancomycin is recommended treatment for Pseudomembranous colitis. Rifamycins and fidaxomicin are gaining attention due to the emergence of treatment failure with metronidazole and vancomycin.(8) Even though bacteriotherapy with faecal micro biota transplantation is effective than the conventional treatment with antibiotics, it still remains a limitation in resource poor settings.(9)

Striking a balance between the risks to maternal and foetal well-being requires careful consideration by a multidisciplinary team involving obstetricians, microbiologist, Infectious disease specialists, and Neonatologists. Maternal CDI can profoundly affect foetal health. Fulminant CDI during the peripartum period associated with adverse foetal outcomes, including foetal loss and the potential need for colectomy.(6) Understanding the pathophysiological mechanisms underlying foetal complications in maternal CDI is essential to inform clinical decision-making and improve perinatal outcomes.(7)

Conclusion

In conclusion, recognizing and managing CDI during pregnancy is a clinical challenge that necessitates a multidisciplinary approach and close monitoring. This case highlights the vital role of diagnostic accessibility and improving health care infrastructure particularly in resource poor settings. Maintaining a high index of suspicion, making diagnostic evaluation tools readily available, and promptly initiating treatment are crucial to mitigate adverse maternal and foetal outcomes. Further research is necessary to better understand the mechanisms underlying CDI pathogenesis in pregnancy, with the goal of improvising diagnostic and management strategies and ultimately enhancing maternal and foetal outcomes.

Declarations

Author contributions
All the authors contributed to data interpretation and writing the manuscript. All authors read and approved the final manuscript.

Conflicts of interest
The authors declare that they have no conflicts of interest

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CASE REPORT

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Imidacloprid poisoning causing delayed liver Injury

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Abstract

Imidacloprid (IC), a widely used nicotine-containing insecticide, is primarily metabolised in the liver by the cytochrome P450 enzyme. Case reports have highlighted respiratory and central nervous system complications as the most lethal outcomes in humans. Presented here is a case involving a previously healthy 29-year-old woman who presented after ingesting an IC-containing agrochemical. On the fifth day, she developed a delayed liver injury. This case underscores the potential for delayed hepatic dysfunction following IC ingestion, despite its rarity. It is imperative to clinically review patients and repeat liver enzyme tests within the first week to promptly address delayed liver toxicity.

Keywords: imidacloprid poisoning, liver injury

Introduction

Imidacloprid (IC) is a nicotine-based insecticide used globally. Human toxicity with the agrochemicals varies depending on the type of chemical and the amount of consumption leading to effects that can be immediate or delayed. Neonicotinoids are primarily metabolized in the liver cytochrome P450 enzyme, and its metabolites act as nicotinic acetylcholine receptor agonists leading to secondary liver toxicity. Literature on imidacloprid poisoning-induced liver injury is limited and the mechanisms behind the liver toxicity is not fully understood.

Animal studies have shown increased liver weight and increased aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels following high-dose exposure due to hepatocyte necrosis.(1) IC induced liver toxicity involves multiple pathways. Oxidative stress plays a significant role by increasing reactive oxygen species generation, causing oxidative damage and loss of antioxidants like glutathione. Furthermore mitochondrial dysfunction leads to reduction in ATP production due to disruption of the electron transport chain leading to hepatocyte injury. An Inflammatory response is triggered due to the activation of pro-inflammatory cytokines (e.g., TNF-α, IL-6) escalating liver damage. Moreover enzyme disruption impairs cytochrome P450 leading to toxic metabolite accumulation. IC also causes direct liver damage by binding directly to nicotinic acetylcholine receptors.(2,3) It is reported that the energy dependent anabolic processes like urea synthesis and gluconeogenesis are impaired due to IC induced oxidative suppression of phosphorylation.(4)

Case presentation

A 29-year-old previously healthy woman was admitted after ingesting 150 mL of an agrochemical containing IC 10% W/V. She experienced mild nausea and an episode of vomiting soon after the ingestion but remained haemodynamically stable. Her liver enzymes were within the normal limits on day one and she remained asymptomatic. She was discharged after two days of supportive care and counseling. The patient was readmitted five days after discharge with vomiting and severe abdominal pain. She was not icteric and showed no signs of bleeding whilst her vitals remained stable.

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On the fifth day following IC ingestion her AST and ALT levels rose up to 1704 U/L and 2393 U/L respectively. The INR was 2.24, CRP was 10.6 and amylase was.93 All the other haematological and biochemical parameters remained within normal limits. Her investigations are detailed in table 1. During this period the patient denied any re-exposure to IC, hepatotoxic medication or herbal product ingestion. Ultrasonography of the abdomen and viral hepatitis screening were negative.

Her management included an intravenous N-Acetylcysteine (NAC) bolus followed by a maintenance regime with close monitoring of liver function. Her liver functions were repeated daily. Notably, there was a significant reduction in liver enzyme levels with the treatment and NAC was continued for 48 hours. The patient remained clinically stable with no signs of hepatic failure and was subsequently discharged home after five days of hospital admission.

Discussion

IC disrupts normal nerve function, by acting as a competitive inhibitor at nicotinic acetylcholine receptor level. It binds more strongly to insect nerve receptors than to mammalian ones. Even though there have been few case reports of lethal injuries in humans, the most severe complications have involved respiratory and central nervous system effects.(8) Though hepatotoxicity is rare, it remains a significant concern.

Hepatic toxicity due to IC ingestion is rarely reported in humans and delayed hepatotoxicity is often unrecognized as most patients do not receive follow up liver function tests. The mechanism of delayed liver injury is unclear due to limited research. It can be due to the slow release of toxic agents. Further study with regard to the mechanism of liver toxicity is warranted to prevent and manage hepatic dysfunction.

Whilst animal studies deliver beneficial insights to the mechanism of IC induced liver toxicity, application of these findings to humans is quite demanding owing to differences in metabolism, receptor sensitivity and toxin elimination. Few case series have documented dose-related liver injury with patterns varying between hepatocellular, hepatotoxic, or mixed types. In our case, the pattern observed was hepatocellular pattern. Liver derangements have been reported to occur five days post exposure.(5-7) As in our case, delay in the onset of derangements of liver enzymes, highlights the importance of monitoring the liver enzymes even after apparent recovery following IC ingestion.

N-acetyl cysteine(NAC) acts as an antioxidant by replenishing the glutathione stores thereby reducing the oxidative stress that causes liver damage as in the mechanisms postulated for IC induced liver toxicity. It is known that NAC has anti-inflammatory effects like modulating inflammatory responses, which could prevent further liver damage. In this case it remains unclear whether the patient's recovery was spontaneous, or NAC contributed to the normalization of liver enzymes. However, it is logical to use NAC, given the mechanism of oxidative stress induced liver injury in few animal studies. Further controlled studies need to be undertaken to determine the therapeutic role of NAC in IC induced hepatotoxicity.

Table 1 - Summary of investigations

Investigations	Day 5	Day 6	Day 7
ALT (U/L)	2393	1804	1063
AST (U/L)	1704	922	600
Total Bilirubin (micromol/L)	15.4	15	14.8
Alkaline phosphatase (IU/L)	90	92	78
Sodium (mmol/L)	141	140	138
Potassium (mmol/L)	3.7	3.8	4
Serum creatinine (micromol/L)	43	58	60

A setback for our assessment was the inability to measure the blood levels of IC to establish dose related response relationship and to monitor efficacy of NAC.

Conclusion

It is evident that imidacloprid can cause delayed hepatic dysfunction. Though initial liver enzymes remain normal, it's essential to anticipate delayed liver toxicity. Hence, it is imperative to clinically review patients and repeat liver enzyme tests within the first week post-ingestion to anticipate and promptly address delayed liver toxicity.

Declarations

Author contributions
All authors contributed to data interpretation and writing the manuscript. All authors read and approved the final manuscript.

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CASE REPORT

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Acute B-cell lymphoblastic leukaemia presenting as acute hepatitis

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Abstract

Acute lymphoblastic leukaemia (ALL) typically presents with symptoms of bone marrow failure. Acute hepatitis is a rare and atypical presentation. We report the case of a 16-years old healthy boy, who presented with elevated liver enzymes and jaundice. His Initial investigations ruled out common infectious aetiology of hepatitis. Despite symptomatic management, the patient had persistent bicytopenia, prompting further evaluation with bone marrow biopsy which confirmed CD10-positive B-cell ALL. This case report illustrates the importance of a pragmatic approach to a non-resolving hepatitis.

Keywords: acute B-cell lymphoblastic leukaemia, acute hepatitis

Introduction

Acute lymphoblastic leukaemia (ALL) occurs commonly in children aged 2-10 years and is rarely seen in adults.(1) It usually presents with symptoms and signs of bone marrow failure and hematopoietic infiltration like fever, recurrent infections, and excessive bruising. Though ALL is generally thought to originate in the bone marrow, leukaemic blasts are often seen systemically and it involves the reticuloendothelial system including bone marrow, thymus, liver, spleen, lymph nodes, testes, and central nervous system.(2)

ALL could present with hepatitis , more specifically with hyperbilirubinaemia due to leukaemic infiltration of the liver which is an extremely rare manifestation. (1) In rare instances ALL can also present with fulminant hepatic failure.(3) However altered liver biochemistry is observed frequently during therapeutic interventions in ALL.

Here we report the case of a 16-year-old boy who initially presented with acute cholestatic hepatitis and was subsequently diagnosed with CD 10 positive acute B-cell lymphoblastic leukemia.

Case presentation

A 16-year-old previously healthy boy presented with a 4 day history of intermittent right hypochondriac pain, yellowish discoloration of eyes and palms, pale stool and dark urine. There was no history of fever or loss of weight but he reported loss of appetite. He denied any travel history, consumption of undercooked food or unfiltered water, diarrhoea, substance abuse, alcohol consumption, night sweats, history of blood transfusion, needle prick injury, and history of tattooing or high risk sexual behaviours. There was no history of bleeding manifestation or family history of liver disease or leukaemia.

On arrival, his vital signs were stable with a heart rate of 90 bpm and blood pressure of 100/60 mmHg. Further, his physical examination revealed deep icterus with hepatomegaly, whilst his other systemic examinations remained unremarkable. His initial blood investigations are summarized in table 1 below.

Ultrasound scan of the abdomen revealed features consistent with hepatitis including hepatomegaly and gallbladder wall congestion. The initial blood

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Table 1 - Initial investigations

Blood investigation	Result	Reference range
WBC (x10^9 g/L)	1.09	(4-10)
Haemoglobin (g/dL)	10.5	(13-17)
MCV (fL)	87.1	(80-100)
Platelets (x10^9 g/L)	130	(150-400)
Neutrophil (%)	0.9	(37-72)
Lymphocyte (%)	88.1	(20-50)
Monocyte (%)	10.1	(0-14)
AST (U/L)	383	(15-37)
ALT (U/L)	2281	(16-63)
Alkaline phosphatase (IU/L)	444	(34-104)
GGT (U/L)	135	5-37
Total protein (g/dL)	56	(64-82)
Albumin (g/dL)	33	(34-50)
Total Bilirubin (micromol/L)	222	(0-17.1)
Direct Bilirubin (micromol/L)	142	(0-6.8)
LDH (U/L)	220	(120-246)
Uric acid (micromol/L)	199	(208-506)
INR	1.09	(0.8-1.2)
Serum creatinine (micromol/L)	40	(62-115)

investigations revealed moderate thrombocytopaenia and neutropaenia raising suspicion of an infective aetiology.

Further evaluation done to exclude the other causes of liver injury, yielded negative results for hepatitis A,B,C,D,E , cytomegalovirus (CMV) and Epstein-Barr virus (EBV)panel. The antinuclear antibody levels and urine toxicology test were also negative.
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In the following days his liver enzymes continued to rise, reached a peak and gradually declined. Though he showed clinical improvement in jaundice, his full blood count continued to show pancytopaenia. Repeat blood film examination revealed pancytopaenia with large cells which prompted a bone marrow biopsy and flow cytometry leading to the diagnosis of CD 10 positive acute B-cell lymphoblastic leukaemia as shown in figures.1 and 2 Despite specialized onco-haematology care, the patient succumbed to severe neutropaenic sepsis.

Discussion

ALL is rarely seen in young adults and is associated with poor prognosis demonstrating survival rates ranging from 20%–40%.(1) The extramedullary form of this disease is rare, and it commonly involves the bones, followed by soft tissue, skin and lymph nodes. (4) Common symptoms of ALL include fever, night sweats, weight loss and fatigue. Lymphadenopathy, hepatomegaly and splenomegaly can occur due to extra medullary involvement in up to 20% of patients.

Though liver involvement in ALL can be a frequent phenomenon, hyperbilirubinemia is not frequently observed.(5) The pathophysiology of obstructive jaundice in patients with ALL includes mechanisms, ranging from obstruction of the biliary duct, formation of bile duct strictures, and infiltration of hepatic sinusoids by tumour cells.(6) Acute liver failure is extremely rare and has been reported predominantly in the paediatric population and less often in the adult population.(7)

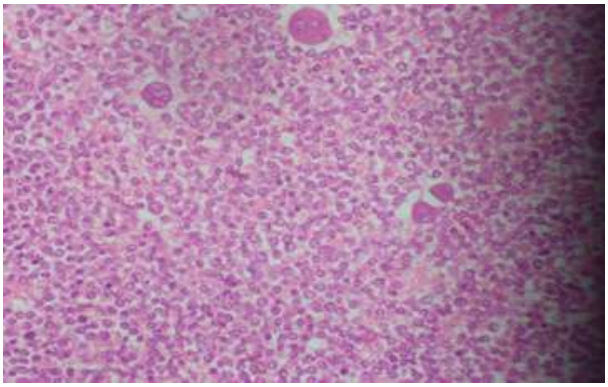

Figure 1 - Bone marrow trephine biopsy shows diffuse interstitial infiltration of blasts with suppression of normal haemopoiesis

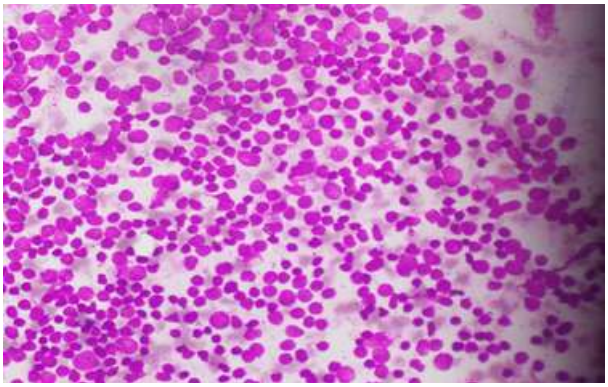

Figure 2 - Bone marrow aspirate shows more than 80% of marrow nucleated cells, medium sized blasts with high nuclear cytoplasmic ratio, diffuse nuclear chromatin pattern and indistinct nucleoli resembling lymphoblast

This case highlights an uncommon and challenging presentation where ALL manifested with features of acute cholestatic hepatitis, including elevated liver enzymes, jaundice, and hepatomegaly, leading to an initial suspicion of viral hepatitis, hindering the diagnosis of the underlying leukaemia. Neutropaenia, as seen in this patient, increases the suspicion of infective aetiology, including those that can involve the liver, but it is important to have a high index of suspicion of ALL. Although primary presentation with hepatitis is rare, we emphasize the need for considering haematologic malignancies in patients with unexplained cytopaenias and concurrent liver dysfunction.

Conclusion

Although acute lymphoblastic leukemia is more common in children than adults, this case illustrates the importance of clinical vigilance and thorough diagnostic evaluation in a young man presenting with hepatitis when the usual cases are ruled out. Acute lymphoblastic leukaemia, although primarily a hematological disorder, can present with atypical extramedullary signs, including acute cholestatic hepatitis. Early recognition and diagnosis are critical for prompt initiation of therapy and improving outcomes of such treatable potentially fatal conditions.

Declarations

Author contributions
All authors contributed to data interpretation and writing the manuscript. All authors read and approved the final manuscript.

Conflicts of interest
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CASE REPORT

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Massive haematemesis complicated with an acute ischaemic stroke due to internal carotid artery pseudoaneurysm

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Abstract

Haematemesis, commonly associated with upper gastrointestinal disorders, can rarely result from cranial vascular anomalies like internal carotid artery aneurysms (ICAAs). ICAA rupture may cause fatal nasopharyngeal epistaxis, with swallowed blood presenting as hematemesis, posing a diagnostic challenge. We report a 75-year-old woman with life-threatening haematemesis, epistaxis, and right hemiplegia. Despite negative findings from otolaryngological and gastrointestinal evaluations, CT angiography identified a left internal carotid pseudoaneurysm. This case emphasizes the importance of considering cranial vascular anomalies in patients with unexplained epistaxis and haematemesis. Endovascular stent embolisation is recommended for managing ICAAs while preserving arterial integrity.

Keywords: massive haematemesis, ischaemic stroke, internal carotid artery pseudoaneurisym

Introduction

Haematemesis is typically a manifestation of upper gastrointestinal tract bleeding.(1) Cranial vascular anomalies such as internal carotid artery aneurysm, can rarely present as epistaxis and haematemesis, due to their anatomical contiguity with the pharynx and esophagus.(2) Epistaxis is associated with 0.55% of cases, who presents with haematemesis. We present a case of a 75-year-old woman who experienced life-threatening massive haematemesis and epistaxis secondary to an extracranial internal carotid artery pseudoaneurysm rupture, leading to haemodynamic instability causing cerebral watershed infarctions.

Case presentation

A 75-year-old woman presented with reduced level of consciousness following massive haematemesis. She had experienced epistaxis for three days prior to this presentation. She is a known patient with type 2 diabetes mellitus and hypertension, both reasonably controlled. She denied any upper respiratory tract infections, head trauma or ENT surgeries prior to this event. She was drowsy with a Glasgow Coma Scale (GCS) score of 12/15, severely pale, and haemodynamically unstable upon presentation (BP 70/40 mmHg, HR 120 bpm with low volume). She required urgent resuscitation with fluids, multiple blood transfusions, and subsequent inotrope support. Neurological examination revealed right-sided hemiplegia with reduced tone, reflexes, and grade 3/5 motor weakness. Rest of the systemic examination was unremarkable.

Haematological investigation revealed a low hemoglobin level of 7.4 g/dL. Rest of the laboratory investigations were unremarkable as shown in table 1.

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Table 1 - Summary of laboratory investigations

Blood investigation	Result
Full blood count	WBC-16 x 10^9 /L Hb- 7.4 g/dL PLT- 314x 10^9 /L
Liver functions	AST- 45 U/L (15-43) ALT 56 U/L (11-63)
Renal functions	Serum Creatinine - 86 micomol/L (65-90)
Serum electrolytes	Na-136 mmol/L (136-145) K- 3.8mmol/L (3.5-5.1)
APTT	34 s (25-35 s)
PT/INR	PT- 12s (11-13 s) INR- 1.08
Upper GI endoscopy	Reflux esophagitis, no active bleeding or altered blood
NCCT brain	Left MCA-PCA and MCA-ACA watershed infarctions
CT angiography	PA of C3 segment of left ICA at foramen lacerum associated with bone remodeling. Small aneurysm at the junction of petrous and cervical segment of left ICA

WBC-white blood cell, PLT-platelets, HB-hemoglobin, ALT- alanine aminotransferase, AST- aspartate aminotransferase, PT- prothrombin time, INR- international normalized ratio, MCA- middle cerebral artery, PCA- posterior cerebral artery, ACA-anterior cerebral artery, PA- pseudoaneurysm, ICA- internal carotid artery

Upper gastrointestinal endoscopy (UGIE) and ultrasound abdomen were normal. Otolaryngology examination for the evaluation of epistaxis did not reveal any source of bleeding. Non-contrast computed tomography (NCCT) of the brain (figure-1) revealed watershed cerebral infarctions involving left anterior, middle and posterior cerebral artery territories. Massive haematemesis resulting in haemodynamic compromise and significant haemoglobin drop despite normal otolaryngeal and endoscopic examination, led us to consider the rare possibility of bleeding from cranial vascular anomalies. CT angiography of cranial vessels (figure-2) confirmed the presence of a pseudoaneurysm of the left internal carotid artery in the C3 (lacerum) segment and a small aneurysm in C2 (petrous) segment of ICA. Digital subtraction angiography (DSA) and endovascular coil embolization of the pseudoaneurysm were recommended but were not performed due to patient's and family's concerns.

She was discharged with a follow up plan to initiate antiplatelets for the management of the cerebral infarctions.Antiplatelet therapy was not started during this presentation due to the life-threatening massive bleeding. The patient and the family members were informed about the possibility of life-threatening re-bleeding and the prognosis if it occurs. They understood and accepted the clinical circumstance and opted for conservative management.

Discussion

Although haematemesis is typically a manifestation of upper GI disorders, it can also be a rare presentation of cranial vascular anomalies, such as ICAAs. The rupture of these aneurysms may cause bleeding into sphenoid sinus, resulting in fatal posterior nasopharyngeal epistaxis.(4) Blood from nasopharyngeal sources can be swallowed and manifest as haematemesis or malena. This clinical scenario is extremely rare and has been scarcely reported in the literature.(5)

ICAAs are a rare presentation commonly seen in females and the incidence would increase with advanced age.(6) They are mostly considered asymptomatic. However, some may develop compressive symptoms due to the increasing size of the aneurysm, which can compress adjacent cranial nerves. Others may cause thromboembolism or massive bleeding due to the rupture of these aneurysms.(7) These aneurysms can either be true aneurysms, involving all three layers of arterial wall, causing dilatation of intact arterial wall, or pseudoaneurysms, which have only a fibrous cap or a blood clot. True ICAAs occur at the carotid bifurcation or proximal ICA, while pseudoaneurysms can be seen near suture lines or traumatic areas. The skull base areas most commonly affected by ICAAs' are the ethmoid, sphenoid and frontal bones.(8)

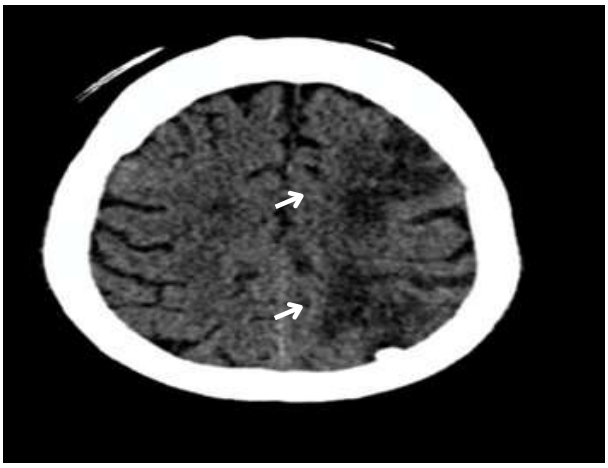

Figure 1 - NCCT brain showing left MCA-PCA and MCA-ACA watershed infarctions

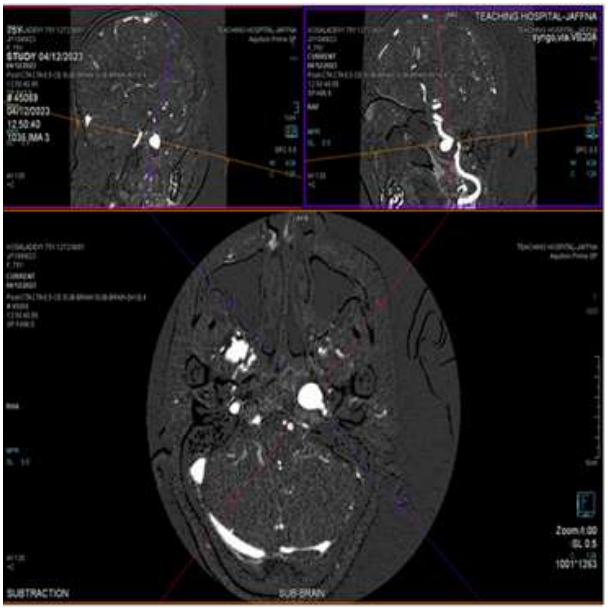

Figure 2 - CT angiogram showing left ICA pseudoaneurysm in C3 segment

The aetiologies of ICAA include head trauma, cranial surgeries, congenital factors, radiation therapy, and infections such as tuberculosis, chronic otitis media, skull base osteomyelitis, or invasive fungal sinusitis. (9) Non-traumatic aneurysms are extremely rare, and present a diagnostic challenge, especially in cases presenting with massive epistaxis or haematemesis as in our case.(10)

Bleeding into sphenoid sinus causing epistaxis following the rupture of an ICAA can be recurrent, with the severity of bleeding increasing with each occurrence, leading to a mortality rate of 30-50 % of cases. It typically takes about 3 days to 6 months from the formation of an ICAA until clinical symptoms manifest. However, the majority (50-80%) of patients will exhibit clinical symptoms within 3 weeks.(11) These minor symptoms at the initial presentation can cause a delay in seeking medical treatment, contributing to a higher mortality among patients with ICAAs. Lehmann et al.(12) has reviewed 36 cases of ICAA from 1950 to 2006 and reported a mortality rate of 22 %. When untreated, the mortality rate significantly rose to 71.4%. Unilateral blindness, orbital fracture and massive epistaxis form a clinical triad that is pathognomonic for ICAA. Digital Subtraction Angiography is considered the gold standard diagnostic test to confirm ICAA.(13)

Management of ICAA or pseudoaneurysms can be either surgical or endovascular. Endovascular therapy with detachable balloon or coil embolization is currently the preferred approach, as surgical ligation and clipping can be relatively difficult due to anatomical constraints and the fragility of the lesion. (14) Occlusion of the parent vessel, whether surgically or endovascularly, could result in severe cerebrovascular events such as strokes if there is an absence of collateral circulation in the circle of Willis. Therefore, it is essential to confirm the adequacy of collateral circulation by performing an occlusion test with a non-detachable balloon. If the occlusion test is successful, the parent vessel can be occluded; if the test is unsuccessful, a vascular bypass may be considered to address this issue. Nevertheless, 5-22% of cases with a successful occlusion test still develop major neurological deficits, such as strokes.(15) Endovascular stent-assisted embolization is considered the preferred approach, as it allows for proximal and distal occlusion of the pseudoaneurysm, leading to the complete exclusion of the lesion from the arterial circulation while preserving the patency of the ICA. A post-embolization DSA would be useful to demonstrate the occlusion of the pseudoaneurysm.(13)

Our patient's presentation can be explained by possible cerebral hypoperfusion secondary to massive bleeding from the left ICA pseudoaneurysm. As the otolaryngeal and upper gastro endoscopic examination did not locate the source of bleeding, the co-existing epistaxis and haematemesis suggested the possibility of vascular bleeding from an adjacent vascular focus. Therefore, cranial vessel CT angiography was performed, which confirmed the rare presentation of the left ICA pseudoaneurysm involving the C3 (lacerum) and a small aneurysm in

the C2 (petrous) segment of the ICA. We believe that the rupture of ICA pseudoaneurysm caused the posterior nasopharyngeal epistaxis, and the collected blood in the posterior pharynx manifested as massive haematemesis, causing haemodynamic instability and watershed cerebral infarctions.

She was discharged with a follow up plan to initiate antiplatelets for the management of the cerebral infarctions. Antiplatelet therapy was not started during this presentation due to the life-threatening massive bleeding. The patient and the family members were informed about the possibility of life-threatening re-bleeding and the prognosis if it occurs. They understood and accepted the clinical circumstance and opted for conservative management.

Conclusion

An ICA pseudoaneurysm can rarely cause life-threatening epistaxis or haematemesis due to rupture into the sphenoid sinus and posterior pharynx. Accurate clinical judgment and proper investigations are vital for diagnosing the source of bleeding and providing prompt treatment to reduce mortality and morbidity.

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest

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CASE REPORT

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Undiagnosed patent foramen ovale: a rare cause for acute pulmonary embolism and cryptogenic stroke

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Abstract

Patent foramen ovale (PFO) is a congenital cardiac anomaly found in 25-30% of the population. Though often asymptomatic, it may lead to paradoxical embolism and cryptogenic stroke. We present a case of a young man with simultaneous acute pulmonary embolism (PE), ischaemic stroke, and lower limb deep vein thrombosis (DVT), culminating in cardiopulmonary arrest. Transoesophageal echocardiography revealed an undiagnosed PFO, supporting the theory of a paradoxical shunt causing stroke. This case highlights the critical role of optimising anticoagulation in managing unprovoked DVT. PFO is a silent culprit and may result in adverse outcomes in patients with pulmonary embolism.

Keywords: acute pulmonary embolism, cryptogenic stroke, paradoxical embolism, patent foramen ovale

Introduction

Stroke remains the third leading cause of death and disability when considered together.(1) The overall incidence of stroke has significantly risen over the past decade to 85-94 per 100,000 people in a year, but it is recorded to be as high as 1151-1216 per 100,000 in a year, in people who are above 75-years.(2) The reported crude stroke prevalence rate for Sri Lanka is 10.4 per 1000 adults.(3)

Among stroke patients, 85% contribute to ischaemic strokes whereas the remainder accounts for haemorrhagic strokes. Important causes of ischaemic stroke could be categorised into atherosclerotic, cardio-embolic and lacunar infarctions. About 25-39% of ischaemic strokes do not have an identifiable cause on thorough evaluation, and are labeled cryptogenic strokes.(4)

Most cryptogenic strokes are predominantly seen in younger adults, in particular those who are less than 55-years of age.(5) It is considered to be embolic in origin when arising from proximal arterial sources, venous sources, or from the heart with right to left shunts, such as patent foramen ovale (PFO).(6) PFO is a connection between left and right atria that could allow blood or blood clots to pass paradoxically from right to left atria. PFO could be found in 20-25% of the general population. Mostly they are asymptomatic.(7) However, rarely it could lead to cryptogenic strokes by paradoxical embolisation. This accounts for 10-77% of cryptogenic strokes.(8)

Here we present a young man with concurrent acute pulmonary embolism (PE) and acute ischaemic stroke (AIS), leading to cardiac arrest.

Case presentation

A 32-year-old man was found to have severe dyspnoea and reduced level of consciousness and was rushed to the Emergency Department (ED) of

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Teaching Hospital Jaffna. Upon arrival at the ED, he was in asystole and was given cardiopulmonary resuscitation (CPR) for 15 minutes, after which he achieved haemodynamic stability.

He had a history of unprovoked deep vein thrombosis (DVT) in lower extremities in 2018. He had defaulted follow-up and treatment three months after the initiation of anticoagulation. He did not have a family history of vascular anomalies or coagulopathies. He is a non-smoker and claimed not to consume alcohol or illicit drugs.

His blood pressure was recorded as 100/60 mmHg, pulse rate was 130 bpm, oxygen saturation 92% on room air, and the Glasgow coma scale (GCS) was 14/15. The respiratory and abdominal examinations were unremarkable. On neurological examination, he was disoriented and confused. He had dysarthria with grade 4 motor weakness on the right upper and lower limbs.There were no sensory deficits, and reflexes were intact with absent Babinski sign. He was transferred to the intensive care unit for post resuscitation care.

An urgent 12 lead ECG revealed S1, Q3, T3 pattern (figure 1) and CT pulmonary angiogram demonstrated a thrombus involving bilateral main and descending pulmonary arteries (figure2). Non-contrast CT brain revealed an acute infarction involving posterior cerebral artery (PCA) territory on the left side (figure 3). As he had right-side lower limb swelling, a venous doppler study was requested, which confirmed DVT involving external iliac vein. A bedside 2D-echocardiogram showed right atrial and right ventricular dilation, a Tricuspid Pressure Gradient (TRPG) of 52 mmHg with a mild tricuspid regurgitation.

Basic biochemical work including renal and liver profiles were unremarkable. The coagulation profile is listed in table 1.His homocysteine levels were normal and bilateral carotid duplex scan did not show a significant stenosis. Due to the strong suspicion of a cardiac structural anomaly with right to left shunt, a transoesophageal echocardiography with agitated saline bubble study was arranged, which revealed the presence of a small PFO (<3 mm) with a right to left shunt (figure 4).

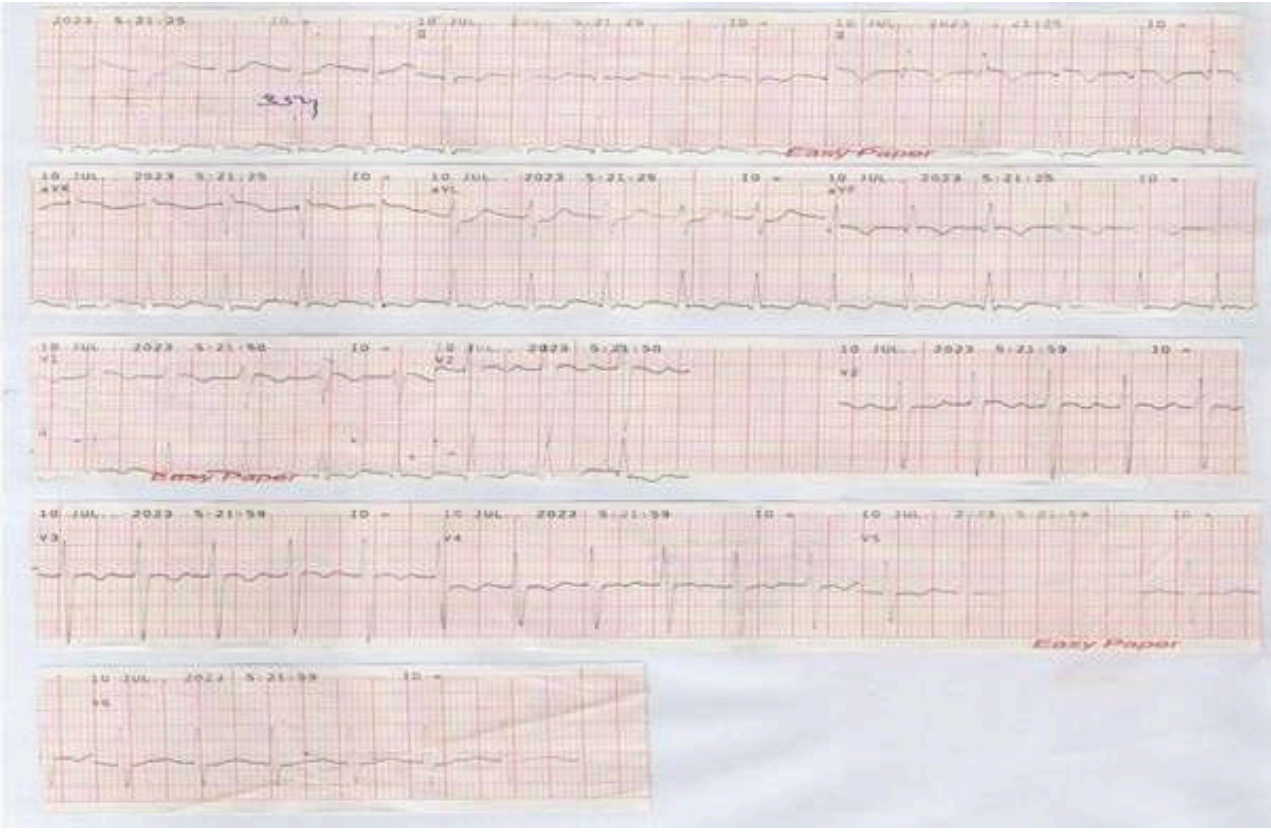

Figure 1 - Electrocardiogram showing sinus tachycardia and S1Q3T3 pattern

Since the patient recovered haemodynamically after prolonged CPR it was decided not to administer intravenous recombinant tissue plasminogen activator (IV rt-PA). Antiplatelet therapy was started with aspirin. Due to the presence of concurrent acute PE, anticoagulation was started with low molecular weight heparin 1 mg/kg subcutaneously together with warfarin 9 mg daily. Physiotherapy and logopedic rehabilitation were initiated and carried out to improve the strength deficit and dysarthria.

As the patient was clinically well and had achieved the therapeutic INR target with warfarin, he was discharged after arranging cardiology and medical clinic follow-up.

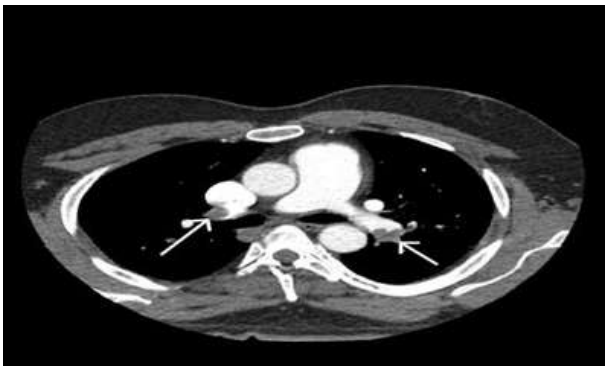

Figure 2 - CTPA showing bi-lateral pulmonary embolism

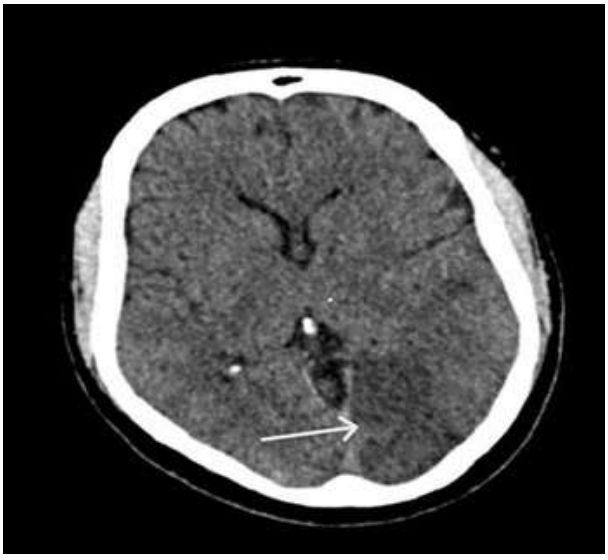

Figure 3 - NCCT brain showing left side PCA territory infarction.

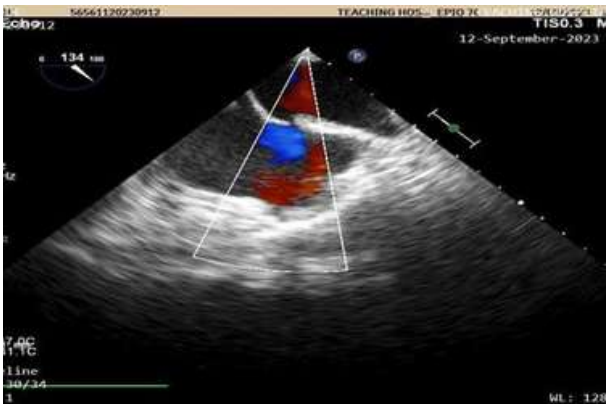

Figure 4 - Transesophageal echocardiogram showing patent foramen ovale

Discussion

Both PE and acute ischaemic stroke (AIS) carry very high morbidity and mortality. In a rare clinical scenario, they could co-exist in the presence of a lower limb DVT in a patient with PFO. In a retrospective study carried out using confirmed cases of stroke in 2021, out of 439 total confirmed cases only 2 cases had simultaneous AIS and PE.(9)

The risk of development of an AIS following a PE is approximately 1-10%. However, PE is the main cause of mortality in the first 2 to 4 weeks following an AIS. (10)

The treatment of these conditions simultaneously is complex due to the concurrent need of rapid administration of IV rt-PA for medical thrombolysis in AIS when they present within 4.5 hours and mechanical thrombectomy up to 24 hours of symptom onset.(11) On the other hand PE would require systemic anticoagulation in order to prevent clot progression and new clot formation which are well-known contraindications following medical thrombolysis owing to high bleeding risk. There are no specific management protocols formulated to guide the management whenever AIS and PE co-exist. Therefore, multidisciplinary approach should be sought to decide upon further management.(12,13)

Surgical closure of PFO is believed to be beneficial in secondary prevention of further strokes. However, presence of a PFO could serve to counteract the increased RA pressure and maintain cardiac output at the expense of low systemic saturation as described in this particular scenario.(14)

In our case a 32-year-old man, with a past history of venous thrombosis presented with sudden onset shortness of breath, hypotension and circulatory collapse leading to cardiac arrest suggestive of a massive PE. Later it was confirmed by CTPA. While evaluating for an acute confusion and right-side hemiparesis, NCCT-brain revealed an acute PCA territory infarction. The venous doppler confirmed the presence of DVT in the external iliac vein.

The triad of concomitant DVT, acute PE and arterial thrombosis with left side PCA territory infarction made us consider an intracardiac shunt leading to a paradoxical embolism. Massive PE results in severe pulmonary hypertension and elevated RA pressure, which in turn could open up an undiagnosed intracardiac right to left shunt causing a paradoxical embolus, which could have been the culprit of the stroke.

To confirm the sequence of clinical events, we requested a 2D-echocardiogram which revealed right atrial and right ventricular dilatation and moderate pulmonary hypertension. However, an intracardiac shunt was not demonstrable. Therefore, a transesophageal echocardiogram was requested, which revealed a small PFO with a right to left shunt.

Conclusion

The triad of DVT, PE, and AIS suggests a possible intracardiac defect with a right-to-left shunt, leading to paradoxical embolism. Cardiac shunts like PFO are common but often underdiagnosed. Physicians should remain vigilant to identify these rare associations for comprehensive care.

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest

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Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Table 1 - Coagulation profile

Investigation	Result
International normalize ratio (INR)	0.8 (0.8-1.1)
Prothrombin time	13 s (11-13 s)
International normalize ratio (INR)	0.8 (0.8-1.1)
Activated partial thromboplastin time (APTT)	32s (25-35 s)
Prothrombin gene mutation	negative
Factor V laden mutation	negative
Methylenetetrahydrofolate reductase (MTHFR) mutation	negative
Protein C deficiency	negative
Protein S deficiency	negative
Beta 2 glycoprotein antibody	negative
Lupus anticoagulant	negative
Anti cardiolipin antibody	negative

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CASE REPORT

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Ischaemic stroke and intracranial haemorrhage from an internal carotid artery aneurysm: a management dilemma

Fernando MSPK[1]*, Selvarathnam G[2], Pradeepan J[2], Sujanitha V[2], Rajendran N[3]

Abstract

Internal carotid artery aneurysms (ICAAs) are rare and predominantly affect older females. Though often asymptomatic, larger ICAAs may cause compressive symptoms, thromboembolism, ischaemic stroke, transient ischaemic attacks (TIA), or massive bleeding upon rupture. The prevalence of ischaemic stroke or TIA in ICAA patients ranges from 3-6.3%. Contributing factors include congenital conditions, trauma, cranial surgeries, radiation, and infections. We report a 42-year-old woman with an acute frontal lobe infarction due to an ICAA, which subsequently led to fatal intracranial haemorrhage. Early diagnosis and timely intervention are critical to reduce the mortality and morbidity associated with ICAAs and their complications.

Keywords: internal carotid artery aneurysms, ischaemic stroke, intracranial haemorrhage

Introduction

Internal carotid artery aneurysms (ICAA) are a rare occurrence more commonly seen in females and has an increased risk with advancing age.(1) Unruptured intracranial aneurysms (UIA) are reported in 1.5% -1.8% of the general population.(2) While Most patients with ICAAs' are asymptomatic, some may exhibit compressive symptoms due the large aneurysms with compression of the adjacent cranial nerves. Others may cause thromboembolism leading to ischaemic stroke or transient ischaemic attacks (TIA) or massive bleeding due to the rupture of ICAA. (3) The prevalence of ischaemic stroke or TIA is 3-6.3% in patients with ICAA .(4)

The main aetiologies of ICAAs' are congenital, head trauma, cranial surgeries, radiation and infections such as tuberculosis, chronic otitis media, invasive fungal sinusitis or osteomyelitis of the skull base.(5) Non-traumatic ICAAs' are extremely rare. Digital subtraction angiography is considered as the gold standard diagnostic tool.(6)

We report a case of a 42-year-old woman with an acute frontal lobe infarction in the presence of ICAA which was later complicated with a fatal intracranial haemorrhage.

Case presentation

A 42-year-old woman presented with an acute onset headache for one day. She denied having fever, limb weakness or slurred speech. She did not have recent head trauma, but attributed it to mechanical type pain. . She was previously healthy and did not have a family history of vascular anomalies or coagulopathies. She was a non-smoker and did not consume alcohol or illicit drugs.

Upon admission she was afebrile and alert, her blood pressure was 130/80 mmHg and pulse rate was 84 bpm. Abdominal, cardiovascular and respiratory examinations were unremarkable. Her neurological examination was normal with preserved tone, reflexes, power in bilateral upper and lower limbs

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and negative Babinski reflex. There were no signs of meningeal irritation, and her Glasgow coma scale was 15/15.

Her haematological, biochemical investigations and coagulation profile were normal. Two-dimensional echocardiogram and electrocardiogram were also normal. Summary of investigations are shown in table1.

Despite adequate analgesics, her headache gradually worsened. The non-contrast computed tomography (NCCT) brain was done, which revealed the presence of an acute infarction involving the left frontal lobe. She was started on aspirin 75 mg and atorvastatin 40 mg. Magnetic resonance imaging of the brain and cranial angiography were arranged to rule out underlying vascular anomalies. It revealed the acute frontal lobe infarction (figure-1) and left ICAA at the level of siphon (figure-2). It was later confirmed by DSA as a left ICA saccular aneurysm at the communicating segment. After excluding possible risk factors, it was decided that the ICAA was responsible for the ischaemic stroke in the index case. After withholding antiplatelets she was transferred for endovascular coil embolization which was scheduled to be done in two weeks due to limited resources. While waiting for endovascular intervention she was admitted to the emergency department one week after the discharge with a history of fall and reduced level of consciousness. An urgent NCCT-brain revealed the presence of an intracranial haemorrhage (ICH) (figure 3) and subarachnoid hemorrhage (SAH)(Figure-4) with a GCS of 7/15. She was intubated and transferred for neurosurgical intensive care where she succumbed to the disease one week later.

Discussion

Formation of thrombosis within an aneurysm was detected in 76% of aneurysms of diameters over 25 mm and 48% in the 20-25mm range.(8) The main risk factors are the ratio between aneurysmal volume and the neck size, age of the aneurysm and intrasaccular changes such as reduced blood flow, increased viscosity and turbulent blood flow which lead to endothelial damage causing platelet aggregation and thrombi formation. This would result in distal embolization which could clinically manifest as an ischaemic stroke or TIA.(9)

Long term follow-up of the patients with ischemic stroke due to ICAAs revealed that the recurrent rate was low, and symptoms are transient, carrying a good prognosis. Surgical intervention in patients with ICAA revealed a lower recurrence rate but failed to

Table 1 - Summary of laboratory and other investigation

Investigation	Result
Full blood count	WBC-8x 10^9/L, Hb- 11.2 g/dL, PLT- 345x 10^9/L
Liver functions	AST- 23 U/L (15-43) ALT 42 U/L (11-63)
Renal functions	S. Cr - 76 micomol/L (65-90)
Serum electrolytes	Na-137 mmol/L (136-145) K- 4.2 mmol/L (3.5-5.1)
APTT	34 s (25-35 s)
PT/INR	PT- 11.4s (11-13 s) INR- 0.95
Anti cardiolipin antibody	Negative
Beta 2 glycoprotein antibody	Negative
Urine, serum homocysteine	Normal
NCCT brain	Left frontal lobe infarction
MR-angiography	Left sided ICA aneurysm at the siphon
DSA	Saccular aneurysm of Left ICA

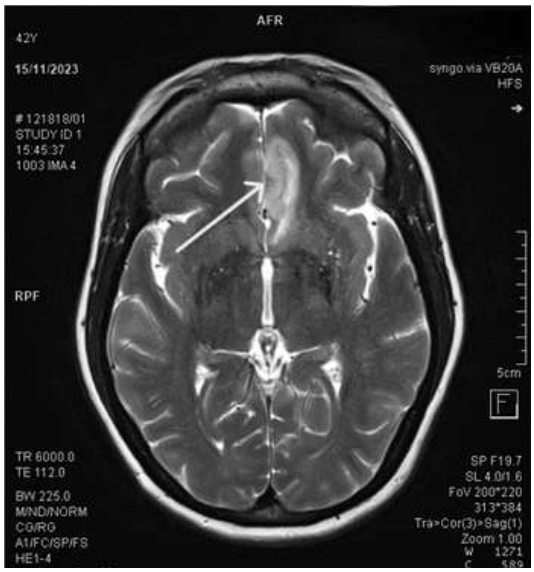

Figure 1 - MRI brain (arrow) showing left-sided gyri recti infarction

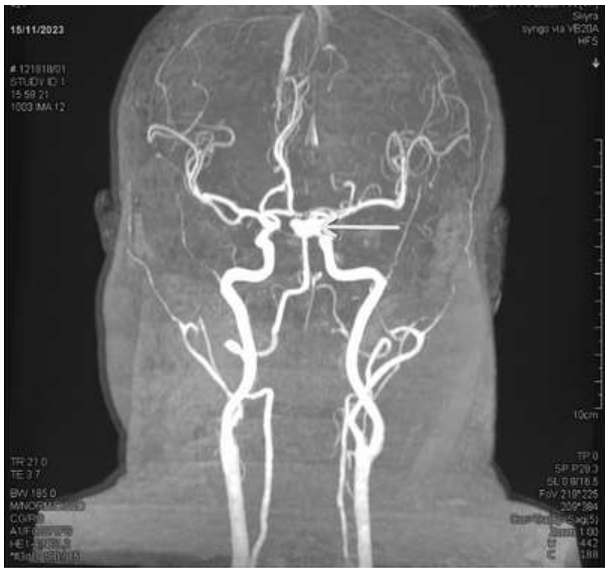

Figure 2 - MRA showing Left internal carotid artery aneurysm at the siphon

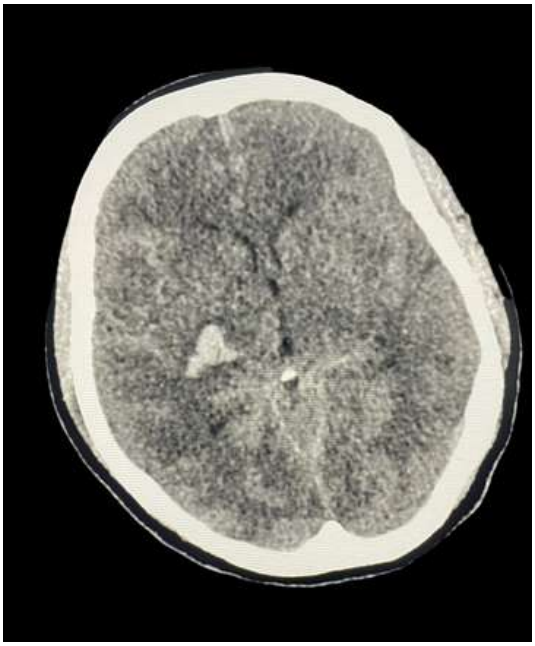

Figure 3 - NCCT brain revealing intracranial hemorrhage on the right side

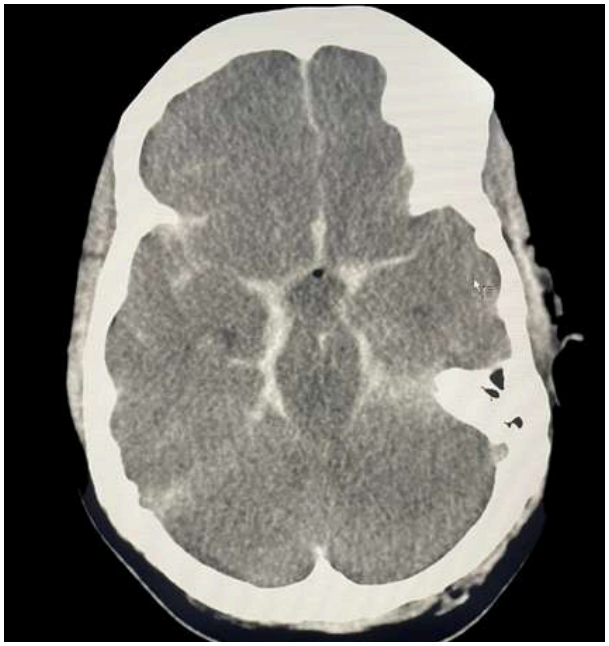

Figure 4 - NCCT brain showing diffuse SAH

demonstrate superiority over conservative management due to the intra and post operative complications.(10) Antiplatelets such as aspirin inhibit platelet aggregation within the aneurysmal sac, reducing the risk of thrombosis. The risk of SAH due to aspirin is not clearly identified yet.(11) Antiplatelets are required to be withdrawn 1 week prior to surgical intervention and can be restarted 2 days after the surgery. Low molecular dextran and nimodipine could also be used to improve microcirculation.(12)

The large ICAAs carry a higher risk of rupture. The annual rupture risk is 100% for diameters of >40 mm, 34.3% for 25-29 mm, 30% for 17 mm and 0.3% 3mm. Past history of SAH, uncontrolled hypertension and their location in the anterior communicating artery are independent risk factors of rupture which warrant follow-up imaging at appropriate intervals and early surgical intervention.(13)

The management of ICAAs' can be occlusive or reconstructive.(14) Occlusion of the parent artery can be achieved by surgical ligation or endovascularly by balloon catheters or coil embolization. Due to the anatomical inaccessibility and fragility of aneurysms, endovascular approach is preferable currently over surgical ligation or clipping. Occlusion of the parent vessel can lead to adverse effects such as ischaemic strokes if there is not enough collateral blood flow in the circle of Willis. Therefore, a temporary balloon occlusive test is performed to demonstrate the collateral flow. If the test is positive, it is safe to proceed with the occlusive surgery either endovascularly or surgically.(15) If the test is negative reconstructive surgery could be performed by placing a flow diverter with or without embolization.(16) Despite a positive occlusive test, 5-22% of patients may develop adverse events such as ischaemic strokes.(17)

In literature, there has been a young man with an ICAA who presented with an embolic stroke following a long-distance race. It was considered that heavy physical exertion, Valsalva maneuvers and acute dehydration could precipitate the formation of thrombosis within the saccular aneurysms.(18) The index case also presented with a thromboembolism following physical exertion, making primary physicians consider the possibility of vascular anomalies if patients present with ischaemic strokes in such circumstances.

The index case presented with acute severe headache following a physical exertion, in the absence of any other neurological deficit. As she did not respond to conventional analgesics and experienced worsening of symptoms. NCCT brain followed by MRI and MRA revealed the presence of acute ischemic stroke and left sided ICAA at the siphon, which was later confirmed by DSA. While waiting for the endovascular therapy she was admitted to the emergency department with an ICH and succumbed to the disease while receiving ICU care.

Conclusion

Prompt diagnosis of the intracranial artery aneurysms in ischaemic strokes, especially without major risk factors, is crucial. Timely surgical or endovascular interventions minimize mortality and morbidity. The case highlights the importance of timely intervention and necessity to optimize management strategies for ICAAs.

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest

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Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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CASE REPORT

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Priapism as the first presentation of chronic myeloid leukaemia in an otherwise healthy young man

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Abstract

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm of older adults which usually presents in its chronic phase with symptoms related to increased synthesis of the myeloid cell line and suppression of erythropoiesis. This case describes a 23-year-old previously healthy man who presented with priapism and had hepatomegaly and massive splenomegaly. His full blood count had a leukocyte count of 507x10^3/uL, haemoglobin of 7.1g/dL and platelet count of 854x10^3/uL. His blood picture and bone marrow biopsy revealed CML in chronic phase. He underwent immediate needle aspiration of the corpora cavernosa and leukapheresis. Priapism can be a rare presentation of CML and when present is common in younger adults.

Keywords: chronic myeloid leukaemia, haematological malignancy, priapism, malignant priapism, leukapheresis

Introduction

Chronic myeloid leukaemia is a myeloproliferative neoplasm defined by the presence of the Philadelphia chromosome. It has a slow progressive course, and if left untreated it could evolve through

1. Chronic phase
2. Accelerated phase
3. Blast crisis – may transform to acute leukaemias- 75% myeloid 25% lymphoid or myelofibrosis.

They usually present in the chronic phase and patients may or may not be symptomatic. Common presenting symptoms are symptomatic anaemia, abdominal discomfort due to splenomegaly, weight loss, fever and sweating in the absence of infection. Headache or priapism due to hyperleukocytosis, bruising and bleeding are uncommon. The EUTOS population-based registry designed to analyse the incidence and clinical characteristics of 2904 CML patients across 20 European countries revealed the median age of CML patients to be 55 years.(1)

We report a case of priapism as the first presentation of CML in an otherwise healthy young man.

Case presentation

We present a case of a 23-year-old previously healthy man who presented with priapism for 18 hours. He complained of a painful sustained erection with no involvement of the glans. His first presentation was to a local hospital where needle aspiration of nearly 250ml of sludged blood in the corpora cavernosa was done and the patient was transferred to a tertiary care hospital following the availability of his full blood count.

He was a healthy adolescent whose only complaint was loss of appetite over a month's duration with no loss of weight, evening pyrexia or night sweats. Neither did he give a history suggestive of anaemia, thrombocytopenia or abdominal discomfort. He gave no history of use of any medication including anti-psychotics or phosphodiesterase inhibitors that could

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cause priapism. Neither did he have a recent history of perineal trauma or any significant family history of haematological malignancies.

On examination, he was afebrile but pale with 2 palpable inguinal lymph nodes measuring 1cm×1cm. On abdominal examination he had a massive spleen crossing the midline with mild hepatomegaly and a half erect penis with some swelling not involving the glans.

His investigations revealed a full blood count with a total white blood cell count of $507x10^3$/uL, haemoglobin of 7.1 g/dL and platelet count of $854x10^3$/uL. His blood picture revealed Chronic Myeloid Leukaemia in the chronic phase. His tumour lysis screening revealed normal serum potassium, normal serum creatinine with an elevated serum inorganic phosphate level of 5.9 mg/dL (2.5-4.5) and a marginally low Calcium of 8.6 mg/dL (8.8-10.6). His ultrasound scan of the abdomen revealed an enlarged liver of 17 cm, a massive splenomegaly of 20.2 cm with no intra-abdominal lymphadenopathy, and a few subcentimeter bilateral inguinal lymphadenopathy. His bone marrow biopsy confirmed Chronic Myeloid Leukaemia in chronic phase and karyotyping revealed 46 XY with a Philadelphia chromosome in all spread.

Following admission, he underwent urgent leukapheresis via an internal jugular vascular catheter with the transfusion of 1 pint of red cell concentrate during the procedure and removal of 294 mL of buffy coat. As he had undergone needle aspiration at the local hospital, his priapism had resolved by then and the genitourological surgery team decided to manage it conservatively and to review following leukapheresis. He was concurrently started on oral Hydroxyurea at an initial dose of 2g daily, oral allopurinol 100mg tds and hyperhydration with intravenous fluids. With the first cycle of leukapheresis his symptoms resolved, and his WBC count also gradually decreased and showed good response to hydroxyurea. Therefore, the patient was continued on oral medication. Following availability of his karyotyping, patient was started on Imatinib as targeted therapy.

Discussion

Chronic Myeloid Leukaemia is a haematological malignancy commonly seen in the older population. The EUTOS population-based registry of CML patients concluded that the incidence of CML was a minimum in very young adults (20-29 years old) at 0.39 new cases per 100,000 (0.47 in males, 0. 29 in females) and that the incidence was highest in senior adults of 70 years or more at 1.52 per 100,000 inhabitants (2.08 in males, and 1.18 in females) culminating at a median age of 55 years.(1)

Priapism is considered a surgical emergency where there is a persistent erection of the penis lasting for more than 4 hours.(2) The overall incidence is at 0.73 to 5.4 cases per 100,000 men per year.(3) The priapism can be ischaemic or non ischaemic. Among the causes of priapism 65% cases are idiopathic, 20% related to haematological disorders such as sickle cell disease and other causes such as medications (phosphodiesterase inhibitors, intracavernosal injections) and malignancies, which account for 15%. Malignant priapism due to leukaemia however accounts only for 0.7%; out of which 50% is due to Chronic Myeloid Leukaemia.(4,5) Similarly, only less than 3% of CML presentations are with priapism.(4)

A systematic review done by Elrazi Ali et al on priapism in CML had reviewed 68 articles which included 102 patients worldwide. It noted that priapism as the first presentation of CML was less but it was infrequently reported during the start of treatment, following the cessation of medication and post splenectomy. This study also noted that the mean age for presentation with priapism in CML was 27.4 years tallying with our patient. Interestingly most patients (>50%) had been Asian and 27.4% had developed permanent damage to penile function.(6)

Conclusion

Priapism, even though a common presentation to surgical units, could have underlying medical conditions as causative factors. Even though CML is a malignancy of adults it can be seen in the younger population and could have atypical presentations such as priapism at the time of presentation in the absence of other clinical symptoms. Therefore, patients need a thorough history and basic investigations to guide the evaluation alongside acute treatment of the surgical emergency.

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest

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CASE REPORT

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Melioidosis presenting with acalculous cholecystitis and acute pyelonephritis

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Abstract

Melioidosis is an infection caused by a gram-negative bacterium, which is widely distributed in fresh surface water and soil in endemic regions. Melioidosis occurs predominantly in Southeast Asia, South Asia, northern Australia and China. Fatal melioidosis commonly occurs in individuals with specific comorbidities including diabetes mellitus, harmful use of alcohol, chronic lung disease and chronic kidney disease. The most common acute manifestation is pneumonia. Other sites of infection include skin, soft tissue and genitourinary tract. We present a case of melioidosis in a 52-year-old farmer presenting with acalculous cholecystitis and acute pyelonephritis which was successfully treated with antibiotics.

Keywords: melioidosis, acalculous cholecystitis, acute pyelonephritis

Introduction

Melioidosis is a highly fatal infectious disease brought on by *Burkholderia pseudomallei* bacteria. The pathogen, which is a saprophyte in tropical and subtropical water and soil, is contracted through ingestion, inhalation, or injection, particularly during the rainy season. The clinical spectrum is broad and varies from acute fulminant sickness to latent infection with eventual reactivation. The majority of patients have a predisposing factor. The mainstay of treatment is intravenous (IV) antibiotics along with supportive care, surgical abscess drainage and management of underlying risk factors.(1)

Here we report a case of a middle-aged man presenting with fever and abdominal pain for one month who was diagnosed to have melioidosis with acalculous cholecystitis and acute pyelonephritis. He achieved complete recovery following treatment with IV antibiotics.

Case presentation

A 52-year-old Sri Lankan man with a background history of poorly controlled type 2 diabetes mellitus presented with fever, persistent epigastric pain, nausea, vomiting and regurgitation for one month. On examination he was haemodynamically stable. His body temperature was 37.7°C. Lung auscultation revealed bilateral scattered coarse crepitations. Examination of the abdomen revealed tenderness in the right hypochondriac region.

On admission white cell count was 29.28 x 10^9/L, haemoglobin 12.9 g/dL and platelets 270x 10^9/L. Blood picture revealed chronic bacterial infection/sepsis. C-reactive protein was 248.6 mg/L. Procalcitonin was 35.15 ng/mL. Aspartate transaminase was 166 U/L, alanine transaminase 164 U/L, total protein 6 g/dL, total bilirubin 13.13 micromol/L, alkaline phosphatase 206.2 U/L, gamma glutamyl transferase 174.9 U/L, albumin 3.1 g/dL and globulin 3.1 mg/L. Renal functions and serum electrolytes were normal. Chest x-ray revealed left upper lobe and right lower lobe consolidations. Ultrasound scan of the abdomen and kidneys revealed acalculous cholecystitis and right sided acute pyelonephritis. Urine full report showed 10-12 pus cells, few epithelial cells and 2-3 red cells. He was

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managed for a possible sepsis of chest or abdominal origin with IV meropenem 1 g 8 hourly.

Computed tomography (CT) of the chest done on day 2 of admission revealed multifocal consolidations in lungs likely secondary to melioidosis (figure 1).

CT abdomen and CT kidneys, ureters and bladder confirmed acalculous cholecystitis and acute pyelonephritis. The patient was reviewed by the surgical team and the decision was made to manage acalculous cholecystitis with IV antibiotics.

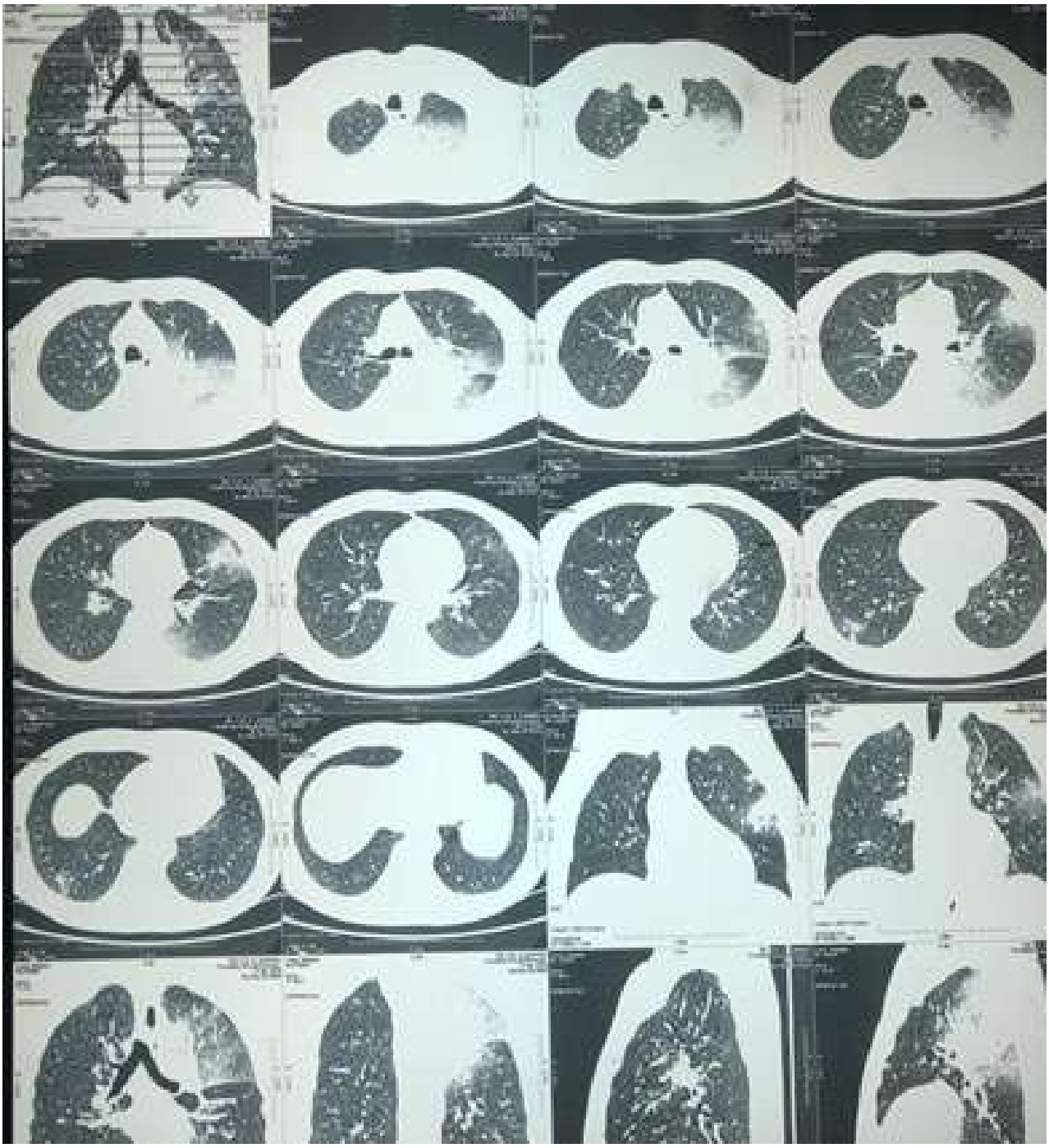

Figure 1 - CT Chest showing multifocal consolidative opacities in the lungs

Blood culture was positive for *Burkholderia pseudomallei*. The diagnosis was confirmed as melioidosis with acalculous cholecystitis and acute pyelonephritis. Following microbiology input meropenem was continued and oral co-trimoxazole 960 mg 6 hourly was added. Diabetes mellitus was managed with insulin.

Following 2 weeks on IV antibiotics, his symptoms and inflammatory markers improved. He was discharged with oral co-trimoxazole for 3 months. Three months later, on review at the medical clinic, repeat CT revealed partial resolution of the lung consolidation and a normal gallbladder.

Discussion

Similar to our case, the majority of melioidosis cases occur in those who frequently encounter soil and water. In addition, the prevalence of disease rises during the rainy season, when paddy farmers are frequently and continuously in touch with contaminated soil and water.(2) Although the incidence of melioidosis increases between the ages of 40 and 60 years, it can occur at any age.(2)

The clinical spectrum varies from acute septicaemic form to a latent asymptomatic form which is found incidentally in patients who have lived in endemic areas even years after they have left the area.(1) The principal presentations of melioidosis include pneumonia, genitourinary infection, skin infection, septic arthritis, osteomyelitis and internal organ abscesses.(3) In 2022, Vithana et al reported a case of melioidosis complicated with myositis.(4) This case was about a 45-year-old Sri Lankan man who presented with a tender, right thigh lump and raised inflammatory markers. He was found to have a large intramuscular abscess with myonecrosis. Pus culture was positive for *B. pseudomallei*. The patient successfully recovered with drainage and IV antibiotics. Pathirage et al from Sri Lanka reported a case of melioidosis presenting with multiple abscesses at different sites of the body.(5) In contrast to this our patient's imaging did not reveal any abscess formation in solid organs, such as the liver, spleen, prostate, or lung. In 2018, a case of melioidosis in a middle-aged Chinese man presenting with acalculous cholecystitis was reported. Interestingly, this patient had a positive bile fluid culture. In contrast to our patient this patient had an urgent cholecystectomy and was treated with meropenem for 1 month. followed by another 3 months of eradication therapy.(6)

Tajudin et al reported a case of a 45-year-old Malay woman who was diagnosed to have melioidosis with acute cholangitis.(7) In 2023 a case of melioidosis with acute cholangitis and septic arthritis was reported. This patient was treated with left ankle arthrotomy, washout and IV antibiotics.(8) Shaaban et al reported a case of reactivation of latent melioidosis presenting with acute pyelonephritis and bacteraemia.(9) This was an Indian patient who migrated to the USA. Similar to our case this patient had a background history of diabetes mellitus.

Diagnosing melioidosis in a non-endemic setting requires a high index of suspicion.(2) Melioidosis should be considered as a differential diagnosis in a patient presenting with fever, a history of residing in or visiting a melioidosis endemic area, an occupation that includes contact with soil or water that could harbour *B. pseudomallei* and the presence of predisposing comorbidities such as diabetes mellitus and chronic kidney disease.(2) Our patient was a farmer who had a background history of diabetes mellitus. *Burkholderia pseudomallei* can be isolated by culture or identified by PCR from a variety of specimens such as cerebrospinal fluid, blood, pus, sputum, urine, and throat swabs.(1) Non-specific laboratory findings include neutrophil leukocytosis, raised c-reactive protein, anaemia and transaminitis.(1) As discussed in the above case reports melioidosis can present with a variety of systemic manifestations including abscesses at different sites of the body, bone and joint involvement and acute cholangitis. However, cases of melioidosis presenting with both acalculous cholecystitis and acute pyelonephritis are rare in available literature. We report this case to demonstrate that acalculous cholecystitis is a rare manifestation of melioidosis.

The required duration of antibiotics for melioidosis is 12-20 weeks or longer if clinically indicated.(10) The use of ceftazidime or a carbapenem antibiotic for initial parenteral therapy is supported by clinical trial evidence and should be given for a minimum of 10–14 days. This should be followed by a protracted course of oral antibiotic treatment using trimethoprim-sulfamethoxazole (TMP-SMX) with or without doxycycline. For children, pregnant women, and patients who are intolerant to first-line treatment, amoxicillin-clavulanate is an alternative.(10)

Conclusion

Melioidosis should be considered as a differential diagnosis in patients with predisposing factors, presenting with prolonged fever, along with a history of contact with soil or travel to an endemic area. Confirmation of the diagnosis requires laboratory support and a high degree of clinical suspicion. Early identification and prompt treatment is mandatory to prevent morbidity and mortality.

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest

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CASE REPORT

Asian J Intern Med. 2025 Jan-Feb; 4(1)

Alkaptonuria: a rare genetic disorder diagnosed in an elderly female

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Abstract

Alkaptonuria is a rare autosomal recessive disorder of phenylalanine/ tyrosine metabolism. We present a case report of a 78-year-old woman treated for urosepsis complicated due to renal stones and found to have alkaptonuria. Alkaptonuria is common among children and young adults but in our case it was detected in an elderly female.

Keywords: alkaptonuria, homogentisic acid, ochronosis, vitamin C, nitisinone

Introduction

Alkaptonuria or black urine disease is a very rare inherited disorder of amino acid phenyl-alanine tyrosine metabolism in which there is a deficiency of an enzyme homogentisate 1,2 dioxygenase - HGD, leading to the accumulation of homogentisic acid in connective tissue . Classically, due to excess Homogentisic acid [HGA] patients pass urine, which upon exposure to sunlight for several hours, turns brown or black (figure 2A, 2B). This feature can be present from birth but often is ignored. Later in life patients develop other symptoms mainly due to deposition of HGA in collagenous tissues which is called ochronosis (figure 1C). This can lead to ochronotic osteoarthropathy , valvular calcifications, renal stones, dark pigmentation of skin and sclera (figure 1A and B). HGA can crystallize and contribute to the formation of kidney stones particularly calcium oxalate stones.(3,4) Patients also have a higher risk than the general population to develop renal stones and recurrent urinary tract infections and complications.(5) Diagnosis is usually made through urine tests that measure the levels of homogentisic acid. Alkaptonuria does not affect life expectancy though it has an impact on quality of life. However basic urinary investigations such as the Benedict test supports the clinical suspicion.

Treatment of Alkaptonuria focuses on symptomatic management including pain relief physiotherapy and dietary adjustment to reduce protein intake as there is currently no definitive protocol of management available.(6) Reducing protein intake minimises the accumulation of HGA since it originates from amino acid metabolism. Avoiding high phenylalanine-containing foods (e.g., meat,fish, dairy products) can help to decrease HGA levels. Increasing intake of fruits and vegetables which are generally low in protein and high in antioxidants are also helpful.(7) Staying hydrated helps dilute urine and reduce likelihood of urine stone formation. Nitisinone is an approved treatment for hereditary tyrosinemia type I, which is currently under investigation as a treatment option for AKU. Clinical trials with nitisinone are ongoing and have shown some encouragement.(8)

Case presentation

A 78-year- old woman from Northern Part of Sri Lanka presented with fever and chills, lower abdominal pain and difficulty in passing urine for one week. She was diagnosed to have bladder and distal ureteric calculi. She was discharged following lithotripsy treatment and stenting of the right side ureter.

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She was readmitted after two weeks with worsening renal functions and new onset confusion. She was treated with intravenous fluids and appropriate intravenous antibiotics .We decided to revisit her history and clinical features since we noticed bilateral scleral and dark ear pigmentation. Upon further questioning we found that she had knee joint problems needing a walking stick to mobilise. These joint problems often made her reluctant to walk at night and she used a urinal. Accidently the caregiver had noticed her urine to be dark-coloured while cleaning her urinal, but had not sought medical care for the above. They have also noted a dark staining in her undergarments but not given attention. With the above information, investigations were carried out to confirm alkaptonuria.

Meanwhile we restricted her protein intake and started on high dose vitamin C and she gradually improved. Her urine for organic acid test showed a massive peak of 2,5-dihydroxy phenyl acetic acid [homogentisic acid]. In a patient with characteristic clinical features this confirms the diagnosis of alkaptonuria. We arranged medical clinic follow-up for the patient.

Discussion

In our case it was an incidental finding to detect features suggestive of alkaptonuria. During her clinic visits we found that she is completely asymptomatic while adhering to high dose vitamin C supplements and dietary protein restriction. One of the main problems in treating alkaptonuria is that we don't have any definite treatment protocol.(10)The dietary restriction may have poor compliance in the long term.(10) This protein restriction strategy seems to be less practical in the adult population compared to pediatric population.(11) Intradermal Vitamin C has

Figure 2 - **A an B:** Scleral Pigmentation; **C:** Ear Pigmentation

Figure 2 - **A:** 1st urine sample.; **B:** After few hours of sun exposure.

Table 1 - Routine hematological biochemical and microbiological investigations

Hematology	**Unit**	**Result**	**Reference range**
White cell count	10^3/L	12.89	4.0-10.0
Neutrophils	%	74.6	50.0-70.0
Lymphocytes	%	16.9	20.0-40.0
Monocytes	%	4.5	3.0-12.0
Eosinophils	%	3.6	0.5-5.0
Red cell count	10^6/L	3.43	3.5-5.0
Hemoglobin	g/dL	10.1	11.0-16.0
Hematocrit	%	31.8	37-54
Mean corpuscular Volume	fL	92.7	80-100
Mean corpuscular Hb	pg	29.5	27.0-34.0
Platelets	10^3/L	375	150-450
ESR	mm in 1st hour	95	<35
Biochemistry			
Creatinine	mol/l	102	53-98
Uric Acid	µmol/L	165	149-369
Sodium	mmol/L	141	135-145
Pottasium	mmol/L	4.7	3.5-5.10
LDH	U/L	296	120-246
Total calcium	mmol/L	2.50	2.20-2.70
Albumin	g/L	35.10	35-50
Corrected calcium	mmol/L	2.62	2.2-2.7
Magnesium	mmol/L	1.00	0.6-1.0
Phosphorus	mmol/L	0.80	1.12-1.45
Alkaline phosphatase	U/L	84	46-116
Total Protein	g/L	76	64-82
Creatinine Kinase	U/L	35	30-135
AST	U/L	32	15-37
ALT	U/L	26	16-63
Total bilirubin	µmol/L	13.5	0-17
Direct bilirubin	µmol/L		0-3
C-reactive protein	mg/L	350-> 156-> 60-> 52-> 17	0-5

Table 1 - Routine hematological biochemical and microbiological investigations (continued)

Biochemistry	Unit	Result	Reference range
Cholesterol	mmol/L	3.4	<5.18
HDL cholesterol	mmo/L	0.75	<1.3
Triglycerides	mmo/L	2.09	<1.7
LDL-C	mmo/L	1.70	<2.59
TSH	mIU/L	2.582	0.4-4.0
Urine Ketone bodies		Negative	
Urine Culture ABST		Candida species	
Urine for reducing substances		Black colour precipitate	
Urine for organic acid analysis		Massive peak of 2,5 dihydroxy phenylacetic acid [Homogenisitic Acid]	

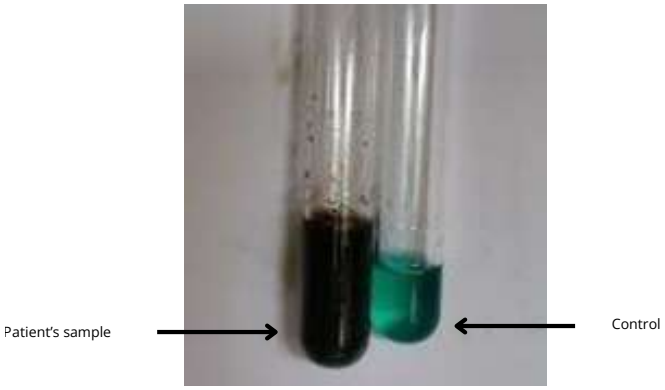

Figure 3 - Benedict's test black color precipitate (supports clinical suspicion of alkaptonuria)

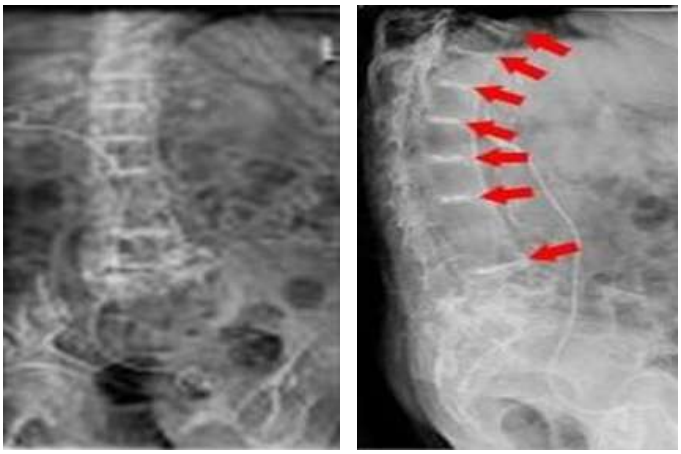

Figure 4 - Inter vertebral disc calcifications

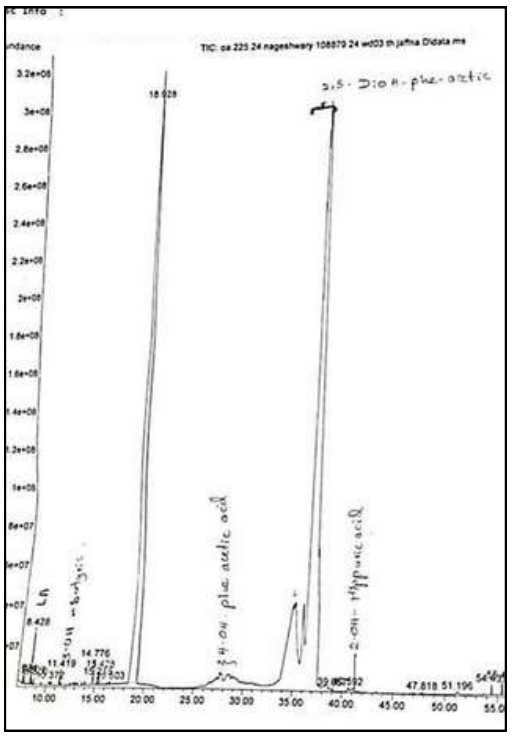

Figure 5

Organic acid analysis by gas chromatography: massive peak of 2,5dihydroxy phenyl acetic acid (Homogenisitic acid) confirms diagnosis of alkaptonuria

been used to treat exogenous ochronosis but these studies require long term research with a higher number of patients to establish efficacy.(9) Nitisinone inhibits 4-hydroxyphenyl pyruvate dioxygenase which is one of the enzyme linked to tyrosine degradation, which results in decrease production of homogentisic acid.

Conclusion

In this case we learnt the existence of late presentation of cases that may be missed though they have urinary symptoms that many people do not attribute to the underlying musculoskeletal symptoms. The availability of urine organic acid analysis by Gas chromatography-mass spectrometry helps in confirming the diagnosis in resource limited settings in SriLanka. Currently management focuses on alleviating symptoms this may include pain management for arthritis and lifestyle adjustments. Ongoing research aims to explore potential treatments including dietary restrictions and development of enzyme replacement therapies. It's a rare disease and symptoms and signs are subtle we have to have high degree of suspicion to diagnose this condition.

Declarations

Author contributions
Sumeda madhuwantha: identification of findings in the patient and planning investigation; Srivickneswaran Ghetheeswaran: giving guidance through whole process and authorisation of specific investigations; E Jasinghe: providing all necessary definitive biochemical investigations to confirm diagnosis; R Mathanky: carrying out all the necessary biochemical investigations.

Conflicts of interest
The authors declare that they have no conflicts of interest

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Ethical considerations
Consent of the patient taken regarding photos and content

Co-authors have approved the revisions
Data can be accessed for academic purposes

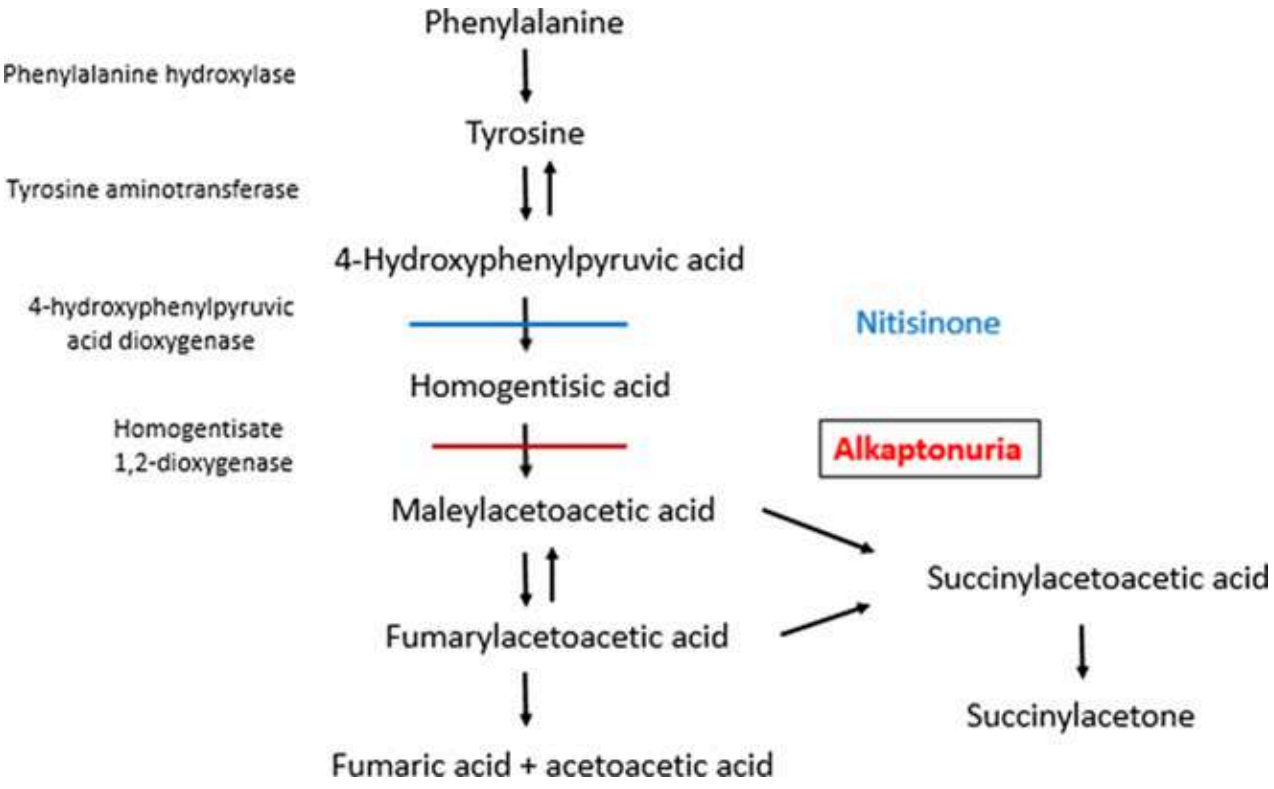

Figure 6 - Nitisinone inhibits 4-hydroxyphenyl pyruvate dioxygenase which is one of the enzyme linked to tyrosine degradation, which results in decrease production of homogentisic acid

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11. The success of dietary Protein restriction is age dependan V de Haas1 E.Carbasius Weber JB de Klerk ,H DBakker, G smit, W A Huijbers,M Duran, B T Poll-The
12. Preventive use of nitisinone in alkaptonuria patients Bruce H. R. Wolffenbuttel, M. Rebecca Heiner-Fokkema & Francjan J. van Sprons

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CASE REPORT

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Unusual presentation of Takayasu Arteritis during pregnancy mimicking peripartum cardiomyopathy

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Abstract

Takayasu arteritis (TA) is a chronic inflammatory vasculitis affecting medium and large arteries predominantly in young women which can result in lethal complications. The pathology involves mononuclear cell infiltration and granulomatous inflammation in the arterial wall, arterial thickening, stenosis, occlusion and aneurysmal dilation. During the acute phase, patients may experience non-specific constitutional symptoms which can pose significant diagnostic dilemmas. Here we describe a 33-year-old woman who presented with generalised weakness, fatigue, and malaise who was treated for peripartum cardiomyopathy and subsequently suspected to have TA based on an incidental finding of circumferential wall thickening of the carotid arteries on an ultrasound scan of thyroid. An aortogram confirmed the characteristic features of TA. Prompt diagnosis and intervention are essential to prevent life-threatening complications of this relatively rare condition.

Keywords: Takayasu arteritis, medium and large vessel vasculitis, peripartum cardiomyopathy

Introduction

Takayasu arteritis (TA) is a rare vasculitis that affects large arteries, causing granulomatous inflammation, leading to complications such as stenosis, occlusion, and aneurysmal dilation. Advanced stages may result in life-threatening complications like cerebral thrombosis, haemorrhage, myocardial infarction, aneurysm rupture, pulmonary and systemic hypertension, or organ failure due to compromised blood flow.(1) The incidence of stenosis or occlusion and aneurysm formation has regional variation.(2,3) TA was first described by Mikito Takayasu in 1908. (4,5) A noteworthy correlation exists between retinal artery and large artery involvement in TA. Retinal microaneurysms serve as a prognostic indicator of disease severity.(6) Updated criteria by the American College of Rheumatology published in 2022 has improved the accuracy of diagnosis.(7) Magnetic resonance arteriography(MRA) is now considered to be the preferred non-invasive imaging technique, with computed tomography angiography(CTA) and ultrasound considered as alternatives.(8) Fluorodeoxyglucose positron emission tomography (FDG-PET) helps to measure vascular inflammation and assess disease activity.(9)

Biopsies reveal adventitial inflammation, elastic tissue destruction in media, neovascularisation of intima and media.(10) Macrophages play a crucial role in inflammation and remodeling.(11) First-line treatments include steroids and methotrexate.(14) For severe cases, Tumor necrosis factor (TNF) inhibitors and Janus Kinase (JAK) inhibitors are recommended. Disease activity is assessed using clinical indices and biomarkers.(15)

Case presentation

A 33-year-old woman diagnosed to have dilated cardiomyopathy, diabetes mellitus and bronchial asthma who has undergone evaluation for

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persistently elevated inflammatory markers since 2019 presented with generalized malaise and weakness for two weeks. She did not have loss of weight or appetite, night sweats or fever. There were no features suggestive of connective tissue diseases or autoimmune disorders. She had no contact history of tuberculosis or history suggestive of high-risk behavior. An intermittent cough was noted and treated as bronchial asthma since 2019. She had undergone elective caesarean section in 2020 at 32+4 weeks of gestation due to severe left ventricular dysfunction with pulmonary hypertension. There was no significant allergic history or family history noted.

Physical examination during the initial evaluation was unremarkable except for bilateral thyroid nodules with elevated blood pressure. In this presentation, her body temperature was 38.2°C, and her heart rate was 96 beats per minute. Examinations of the chest and precordium were unremarkable

Table 1 summarises baseline investigations performed during the course of the illness. Again the investigations revealed very high inflammatory markers with anaemia. Further investigations were performed to identify a cause. ECG showed T inversions in anterolateral chest leads. Trans-thoracic echocardiography demonstrated global hypokinesia with severe left ventricular dysfunction with an ejection fraction of 35% which could not be attributed to an underlying cause.

Blood picture showed anaemia of chronic disease and serum protein electrophoresis consistent with chronic inflammation. Blood cultures, venereal disease screening and autoimmune serological tests and chronic granulomatous disease screenings were unrewarding. Her renal, thyroid and liver profiles were normal except for a reversed albumin-globulin ratio.

Ultrasound scan of the neck showed small TR3 nodules in both thyroid lobes with an incidental finding of circumferential wall thickening of carotid arteries which raised the possibility of an underlying large vessel vasculitis. Carotid duplex showed bilateral diffuse circumferential wall thickening of common carotid arteries with approximately 50% stenosis.

Patient was reexamined based on the ultrasound scan findings which revealed a striking difference in blood pressures between the right and left arms. Her systolic blood pressure in the left arm was between 90-100 mmHg while diastolic blood pressure was 80 mmHg. In her right arm, the systolic blood pressure was 140 and the diastolic blood pressure was 70 mmHg. The brachial and radial pulses on her left were feeble but normal in character. Carotid and subclavian artery bruits were present on the left side.

The CT Aortogram carried out showed circumferential wall thickening of the aorta involving the aortic arch up to the bifurcation, right brachiocephalic trunk, bilateral common carotid, proximal internal carotid and subclavian arteries.

Table 1 - Summary of investigations

Investigation	Reference range	05/04 2019	19/09 2020	23/02 2024	27/06 2024	11/09 2024	21/09 2024
WBC (10^9/L)	4-10	9.04	9.14	9.30	9.03	9.15	9.92
Neutrophil (%)	50-70	64	60	48	60	62	64
Lymphocyte (%)	20-40	33	34	36	38	32	33
Hemoglobin (g/dL)	11-15	9.4	11.3	10.8	9.4	10.5	11.8
MCV (fL)	80-100	77	76.6	81.2	77.4	76.9	75.3
MCH (pg)	27-34	28.6	26.2	28.6	27.4	24.3	24.6
RDW (%)	11-16	14	16.4	17.2	16	18.2	19.3
Platelets (10^9/L)	150-450	532	447	494	532	489	488
ESR (mm/1st hour)	<20	140	139	117	140	80	20
CRP (mg/L)	0-3	182	160	145	147	127.4	10.2

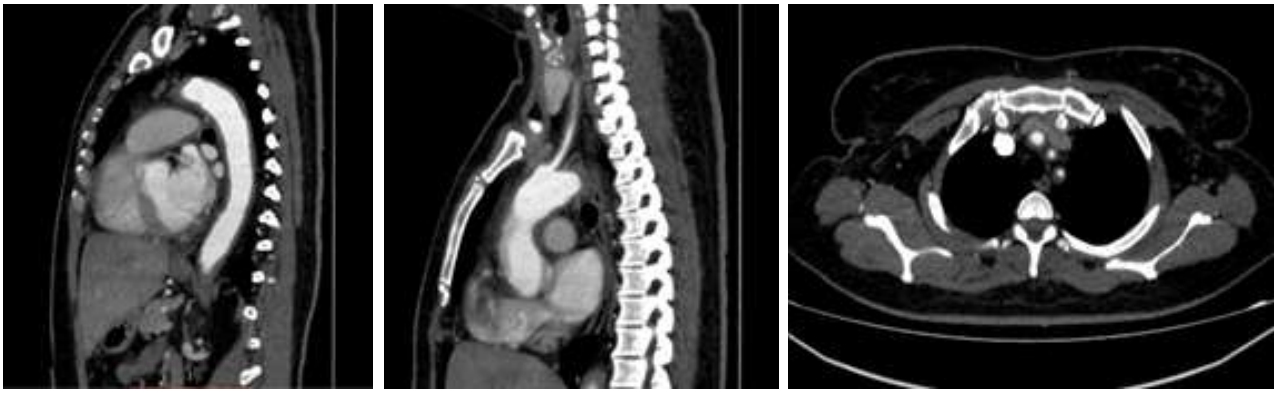
Mild wall thickening is observed in the bilateral common iliac, proximal superior mesenteric, bilateral renal arteries. There is moderate luminal narrowing of the proximal coeliac trunk at the origin (figure 1).

She was treated with a tapering regimen of oral prednisolone which started at 60 mg mane, azathioprine 100 mg daily and with other supportive measures after which she became asymptomatic and her inflammatory markers became normal gradually over three weeks. Oral prednisolone was tapered at an interval of every two weeks. She remained symptom-free following discharge. A repeat 2D echocardiogram showed an ejection fraction of 65%. A coronary angiogram was not performed since the patient refused.

Figure 2 outlines the chronology of evaluation since 2019.

Discussion

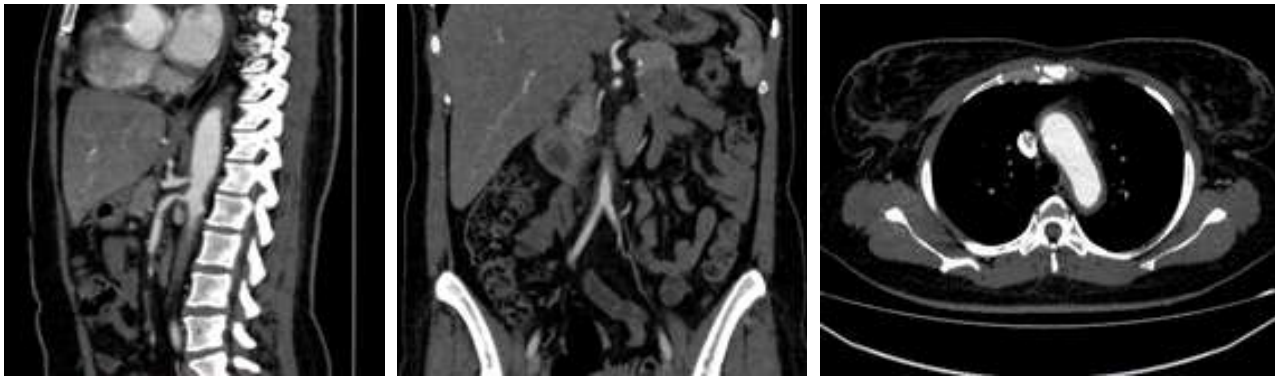
Diagnosis of TA is challenging and involves ruling out similar aetiopathology such as atherosclerosis, fibromuscular dysplasia, tuberculosis, syphilis, systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, Marfan syndrome and giant cell arteritis. (12,13) The gold standard diagnostic tool is angiography, although non-invasive techniques like Doppler ultrasound and magnetic resonance angiography (MRA) are also highly effective.(5,8) Criteria by American College of Rheumatology (ACR)



Descending thoracic aorta (sagittal)

Left common carotid artery (sagittal)

Branches of aortic arch (axial)



Coeliac trunk and SMA origin from the abdominal aorta (sagittal)

Aortic bifurcation (coronal)

Arch of aorta (axial)

Figure 1 - CT aortogram demonstrating luminal wall thickening

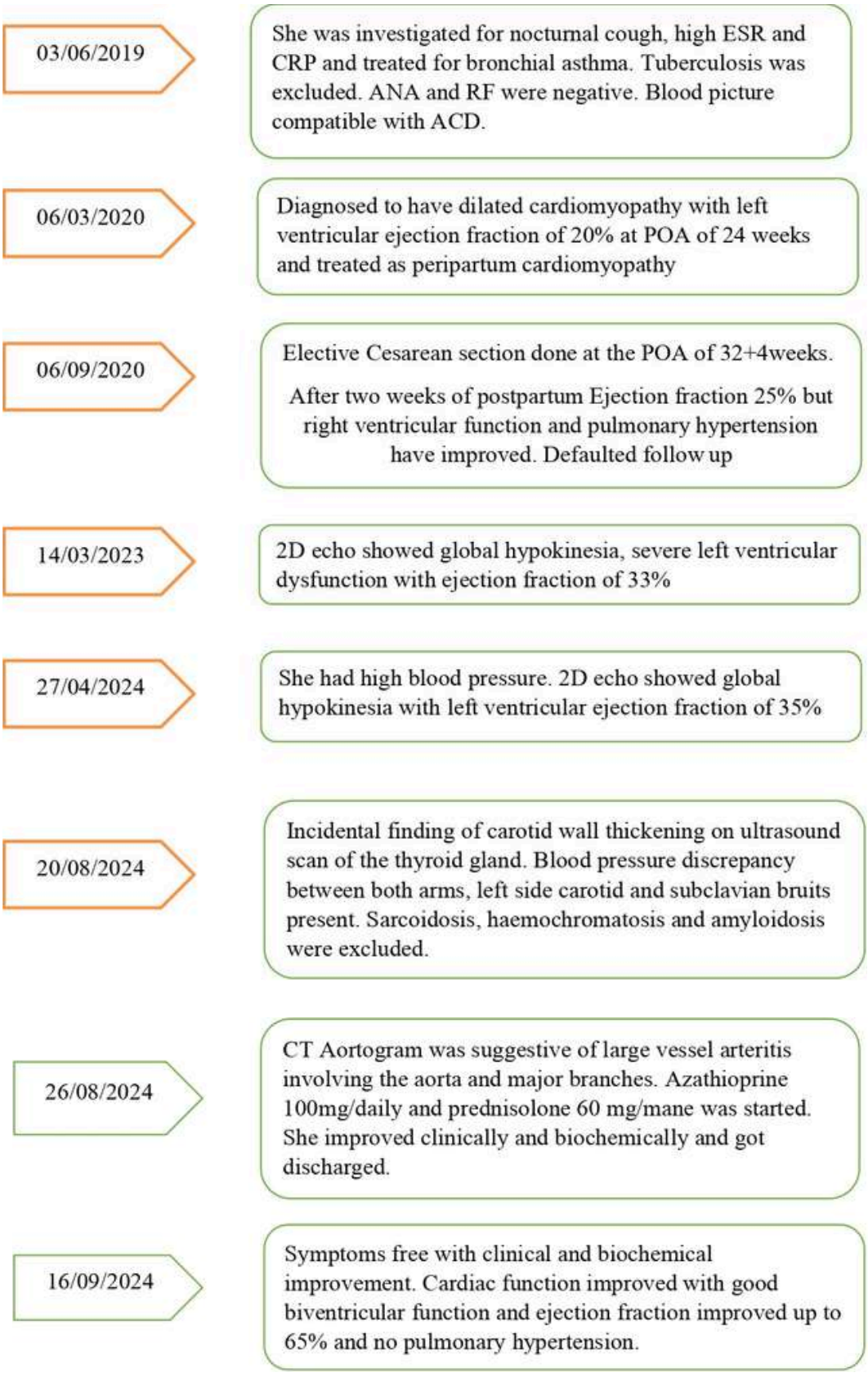


Figure 2 - Chronology of evaluation since 2019

for Takayasu arteritis show a sensitivity of 90.5% and a specificity of 97.8%. Additionally, elevated acute phase reactants (ESR,CRP) are often present, supporting the diagnosis.(6)

This case highlights the importance of challenges encountered in early detection of TA when it presents with non-specific symptoms. In this case, the differential diagnoses included other primary vasculitides, which do not present with a discrepancy in blood pressures between the arms, which is a key feature in TA. This specific physical sign would be easily missed unless looked for in particular. TA primarily affects large vessels and their branches, with symptoms corresponding to the specific vessels involved. In this case there were no significant occlusive symptoms except for the discrepancy in blood pressures between the arms.

The cornerstone of management focuses on minimising narrowing of vessels rendered with immunosuppression and systemic corticosteroids. (14) Surgical or endovascular interventions may be considered in severe cases to restore blood flow and prevent further complications.(16)

Conclusion

This case report illustrates the challenges in diagnosing vasculitis when a patient presents with nonspecific manifestations that mimic other systemic illnesses. TA is one such condition that could pose a challenge in diagnosis as it is predominant in young females where other autoimmune diseases and pregnancy related conditions are common. Non-invasive imaging studies are proven to be beneficial in picking up vital pathology like TA even in low resource settings, and should be sorted whenever possible.

Declarations

Conflicts of interest
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CASE REPORT

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An amyopathic presentation of anti-PL-7 antisynthetase syndrome

Wijesena KDRS[1]*, Karunathilaka H[1], De Silva M[1], Premaratne BG[1], Senevirathne IN[1]

Abstract

Anti-PL 7 anti-synthetase syndrome (ASS) is a rare cause of interstitial lung disease (ILD). A 52-year-old woman presented with worsening dyspnoea and exertional desaturation after a flu-like episode without any evidence of muscle involvement. She had a skin rash diagnosed as pemphigus foliaceus but had no evidence of cutaneous manifestations of ASS. Her HRCT scan of the chest showed fibrotic ILD. Anti-PL-7 antibody and anti-Ro-52 were positive in the myositis antibody panel. She was treated with immunosuppressants for which she showed a rapid response. In patients presenting with worsening respiratory symptoms mimicking infection, ILD should be considered together with secondary causes of ILD including ASS even in the absence of clinical features of ASS or myositis.

Keywords: antisynthetase syndrome, Anti-PL-7 antibody, Anti-Ro antibody, Anti-Ro-52 antibody, interstitial lung disease

Introduction

Antisynthetase syndrome (ASS) is a rare autoimmune disease characterised by interstitial lung disease (ILD) and/or inflammatory myositis, with positive antisynthetase antibodies (ASA). Out of the ASA, anti-Jo-1 is the most common, and anti-PL-7 is rare. Anti-Ro and more specifically anti-Ro-52 are the most common myositis-associated antibodies.(1) Because of the rarity of anti-PL-7, little is known about the clinical manifestations of ASS associated with anti-PL-7 antibodies.

We present a case of a middle-aged woman evaluated for dyspnoea with lung crepitations after a febrile illness without myositis. Evaluation of the aetiology of her dyspnoea using imaging modalities and extended antibody panels helped narrow down the differential diagnoses culminating in a diagnosis of anti-PL-7 ASS. Treatment of ASS is with immunosuppressants.(2) The prognosis for ASS is worse than other inflammatory myopathies that do not have ASA.(3) Early diagnosis and treatment are needed to avoid the detrimental effects of lung fibrosis. This case highlights why ASS should be considered in patients with ILD or antibiotic-resistant pneumonia when other diagnoses have been ruled out.

Case presentation

A 52-year-old previously well woman presented with worsening shortness of breath for 1 week. One month prior to admission she had a high-grade fever and on day 2 of the fever, she had had a generalised blistering rash with oral ulcers evolving to erythematous plaque formation. Her full blood count (FBC) had been within normal limits and her C-reactive protein (CRP) was 155 mg/L (0-5 mg/L). She was treated with oral antibiotics and oral acyclovir, suspecting varicella infection. The skin lesions settled with scaling. Skin biopsy was confirmed to be pemphigus foliaceous. Subsequently she developed gradual onset shortness of breath on exertion with a

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When we saw her in the fourth week of the illness, she was breathless even at rest. She did not have cough, orthopnoea, paroxysmal nocturnal dyspnoea, or lower limb swelling. She denied small joint arthritis, Raynaud's phenomenon, sicca symptoms, or photosensitive rashes. She had no muscle pain, weakness, or constitutional symptoms. She denied occupational or household exposure to allergens. On examination, she had a scaly skin rash over the body, and oral ulcers which were healing. There were no nail changes, Gottron's papules/sign, or mechanic hands. She had significant crepitations in bilateral lung bases. On air oxygen saturation (SpO2) was 99% which dropped to 80% with minimal exertion. Resting arterial blood gas revealed; pH 7.44 (7.35-7.45), partial pressure of oxygen 81 mmHg (80-100 mmHg), partial pressure of carbon dioxide 36 mmHg (35-45 mmHg) and HCO3 25 mmol/L (22-26 mmol/L).

FBC revealed; white blood cells 7.27×10^3/uL (4-11×10^3/uL), haemoglobin 11 g/dL (11.5-16 g/dL) and platelets 307×10^3/uL (150-400×10^3/uL). CRP was 2 mg/L and the erythrocyte sedimentation rate (ESR) was 46 mm/ 1st hour (<30). Serum procalcitonin level was <0.04 ng/mL (<0.05 is normal). Chest x-ray (CXR) revealed increased alveolar shadows in bilateral lung bases (figure 1). Sputum culture and sputum for acid fast bacilli were negative. The 2-dimensional echocardiogram revealed an ejection fraction of 60%, a tricuspid regurgitation pressure gradient (TRPG) of 22 mmHg, and normal bi-ventricular function. COVID PCR was negative. Pneumocystis jirovecii (PJP) was not detected on toluidine blue stain. She was treated with antibiotics for atypical pneumonia with no response.

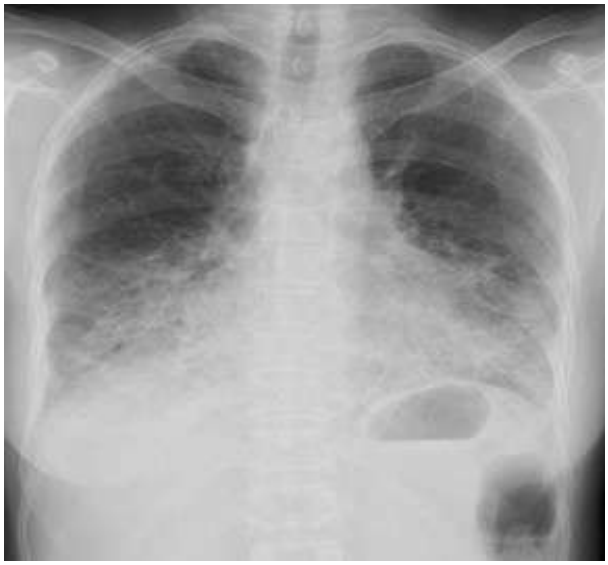

Figure 1 - Chest radiograph: bilateral shadows

HRCT of the chest showed areas of traction bronchiectasis, septal thickening, parenchymal fibrosis involving the middle lobe of the right lung, the lingual segment of the lung, bilateral lung bases, apical segment of the right upper lobe, and a small area of pneumomediastinum suggestive of fibrotic ILD (figure 2). She was unable to perform spirometry.

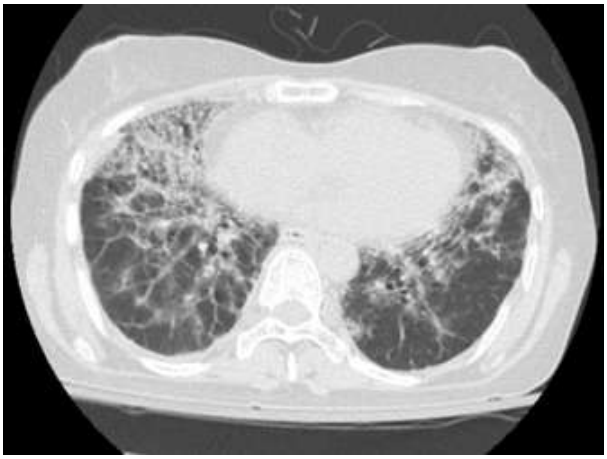

Figure 2 - HRCT chest: fibrotic ILD

The patient did not have features of myositis, idiopathic ILD, hypomyopathic dermatomyositis (DM)/ polymyositis (PM). Hence ASS or evolving connective tissue disease with rapidly progressive ILD were considered as the differential diagnoses. The autoimmune panel showed positive ANA with a titre of 1:640. Her C3 level was 166 mg/dL (87- 200 mg/dL), and C4 level was 34 mg/dL (19- 52 mg/dL). Out of the extractable nuclear antigen panel, SS-A/Ro antibody and Ro-52 antibodies were strongly positive. Anti-Jo-1 was negative. Rheumatoid factor level was 18 IU/mL (<14 IU/mL) while creatine kinase level was 16 U/L (29 – 168 U/L). There was no electromyographic evidence of myopathy or myositis. Repeat HRCT chest done after 2 weeks showed worsening fibrotic changes of early usual interstitial pneumonia (UIP)/ secondary fibrotic nonspecific interstitial pneumonia (NSIP) changes with no evidence of residual pneumomediastinum. Dermatological opinion was sought. She had no cutaneous manifestations of dermatomyositis or anti synthetase syndrome.

Bronchoscopy revealed chronic changes with thin secretions in the mucosa. Pyogenic culture, tuberculosis studies, PJP stain, and fungal cultures of bronchoalveolar lavage were negative. Aspergillus galactomannan antigen was absent. Cytology revealed 90% alveolar macrophages.

After excluding possible infection and considering an autoimmune aetiology, she was treated with intravenous methylprednisolone pulses, 1 g daily for 3 days, followed by oral prednisolone and oral mycophenolate mofetil (MMF). Her shortness of breath and lung signs showed a dramatic improvement.

Subsequently, an extended myositis profile was done for 16 antigens including anti MDA 5. Out of them, anti-PL-7 and anti-Ro-52 were positive. Lower lip biopsy excluded Sjogren's syndrome. Age-appropriate cancer screening excluded paraneoplastic processes.

Following two weeks of treatment, her SpO2 after exertion improved to 98%. She was able to perform her daily activities without limitation. However, the HRCT chest done after two months did not show significant interval change radiographically. After 6 months, her condition was stable, and she did not develop symptoms of myositis during the follow-up period.

Discussion

ASS is a rare autoimmune disease with antibodies against aminoacyl transfer RNA (tRNA) synthetases (ARS). It is a form of idiopathic inflammatory myopathy that is now recognised as a separate entity and manifests interstitial lung disease more compared to DM and PM. The clinical features include ILD, non-erosive arthritis, myositis, Raynaud's phenomenon, unexplained fever, or mechanic's hands.(2)

According to evidence in ASS the prevalence of ILD (86%) is more common than the prevalence of myositis (73%) or arthralgia/arthritis (60%).(4) These patients may not have typical myopathic symptoms and the myositis may present later in the course of the disease causing diagnostic dilemmas like in the index case.(5) Our patient's presentation was unusual because she had a febrile illness with a skin rash suggestive of pemphigus foliaceous followed by respiratory symptoms which were attributed to atypical pneumonia. She did not have evidence of muscle involvement and had ILD as the only manifestation of ASS making the diagnosis challenging. There are two criteria available to aid the diagnosis of ASS which are mentioned in table 1.

In our patient, fever with rapidly progressive ILD, the positivity of PL-7 antibody and rapid clinical improvement with immunosuppressants supported the diagnosis of ASS. This case fulfilled the Connors criteria for the diagnosis of ASS.

Table 1 - Criteria for the diagnosis of antisynthetase syndrome (ASS)

Connors et al. diagnostic criteria (6)	**Solomon et al. diagnostic criteria (7)**
Definitive: the presence of ARS autoantibody	**Definitive:** the presence of ARS autoantibody
PLUS, one or more of the following:	*PLUS, two major or one major and two minor criteria*
• Interstitial lung disease	**Major:**
• Arthritis	• Interstitial lung disease
• Raynaud's phenomena	• Dermatomyositis or polymyositis by Bohan and Peter criteria
• Fever	**Minor:**
• Mechanic's hands	• Arthritis
	• Fever
	• Mechanic's hands

Out of the ASA, anti-PL-7 antibodies are rare and associated with severe ILD.(2) Interstitial lung disease (77%) was the most common manifestation of anti-PL-7 ASS followed by myositis (75%), and arthritis (56%).(8, 10-12) Autoantibodies against Ro-50 and more specifically Ro-52 (30%) were the most observed antibodies among patients with autoimmune myositis followed by Anti-Jo-1 (15%) and Anti-PL-7 (5%).(1) The degree of muscle involvement in PL-7 ASS is lower than in Jo-1 associated ASS.(2) PL-7 associated ILD development varies and sometimes can be initially misdiagnosed as pneumonia. NSIP or UIP subtypes were the HRCT findings in most cases. (9)

Guidelines recommend glucocorticoids as the first-line agent in the management of systemic autoimmune rheumatic diseases including ASS-associated ILD. MMF, azathioprine, rituximab, and cyclophosphamide are also first-line treatment options.(13) Additional immunosuppressants are needed as there can be a recurrence of lung disease with steroids alone.(2) The index patient responded well to a steroids and MMF combination.

Conclusion

PL-7 ASS is a rare autoimmune disease that can present as an atypical pneumonia without other ASS symptoms. ASS needs to be considered in the differential diagnoses for causes for ILD even in the absence of myositis. Positive anti-Ro and anti-Ro-52 may suggest an underlying autoimmune myositis. The extended myositis antibody panel will help to delineate the disease. Immunosuppressants are the mainstay of treatment for PL-7 ASS. Amyopathic ASS patients need to be followed up for later development of myositis.

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest

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CASE REPORT

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Kyphosis leading to platypnoea-orthodeoxia: an overlooked cause for dyspnoea and desaturation

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Abstract

Platypnoea-orthodeoxia syndrome is a rare cause of dyspnoea and desaturation. This case report describes a 72-year-old woman with kyphosis who presented with episodic dyspnoea at rest which worsened on exertion. She had a drop in oxygen saturation in the seated position and improvement in the supine position. Bubble contrast echo showed bubble crossing within 3 cardiac cycles suggestive of intracardiac right to left shunting of blood. Transesophageal echocardiogram confirmed the presence of a patent foramen ovale. As this is an overlooked cause for dyspnoea and desaturation, awareness of this condition and its association with kyphosis is important in the evaluation.

Keywords: platypnoea,orthodeoxia, kyphosis, patent foramen ovale

Introduction

Platypnoea-orthodeoxia syndrome (POS) is dyspnoea and hypoxaemia in upright position which is relieved in supine position. The presence of intracardiac or extracardiac shunts are the main mechanism of the condition.(1) Out of the intra cardiac causes patent foramen ovale (PFO) is the main cause. Kyphosis changes the heart anatomy making changes in the blood flow direction facilitating shunting through the PFO in the presence of normal right heart pressures.

Case presentation

A 72-year-old woman with a prominent kyphosis due to aging presented with episodic shortness of breath for a few months which was worsening over time. During some episodes she was short of breath even at rest as well as on exertion. She didn't notice significant relief or worsening in supine position. Her symptoms were not associated with cough, fever, orthopnoea, paroxysmal nocturnal dyspnoea or lower limb swelling. Along with that she had malaise, episodic migrainous type headache and episodic atypical chest pain at rest. She had had several hospital admissions, and she was treated for possible heart failure. She had a background history of hypertension, hyperlipidaemia, hypothyroidism, diabetes mellitus, and had had 3 transient ischemic attacks. She also had a history of an episode of non-ST elevation myocardial infarction (NSTEMI).

Her saturation was 83%-92% on air in the seated position. It improved with supplemental oxygen. Except for the kyphosis, her respiratory, cardiovascular, abdominal, and neurological system examinations were unremarkable. All the basic investigations were normal. Table 1 has results of further testing.

Incidentally we observed that her desaturation occurred only in seated position and was relieved in supine position. Supine saturation was 97-98%, which was confirmed by arterial blood gas analysis. There

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was more than a 5 mmHg drop of partial pressure of oxygen (PaO2) observed with the positional change. This postural deoxygenation was particularly noted after exertion and at times while she was at rest.

Bubble contrast echo with agitated saline in the resting position showed bubbles crossing within 3 cardiac cycles confirming an intracardiac shunt, possibly a patent foramen ovale (PFO). The anatomy of the heart was also observed to be altered due to her kyphoscoliosis. The presence of a PFO was confirmed by trans-oesophageal echocardiography (TOE)(figures 1 and 2). The cause for her dyspnoea and hypoxaemia was found to be a right to left shunt via the PFO in the presence of normal estimated pulmonary artery pressures. Flow through the PFO was enhanced on seated position due to the malpositioning of the heart due to kyphosis.

During her evaluation for dyspnoea she revealed the history of an episodic headache with imbalance, vertigo and dizziness over a few weeks with subtle cerebellar signs on examination. Magnetic resonance imaging (MRI) of the brain showed multiple lacunar infarctions of different ages in the left cerebellar hemisphere and left periventricular white matter. MR angiography (MRA) of the brain had diffuse atherosclerosis in cerebral arteries. The lower limb duplex scan excluded deep vein thrombosis. Coronary angiogram (CA) showed only minor coronary artery disease.

Considering the risk-benefit ratio of the procedure, age of the patient and impact of the symptoms on her life, it was decided not to go ahead with catheter closure of the shunt. The treatment of her comorbidities was optimised, and lifestyle modifications were reinforced. During follow-up she remained symptomatic but was able to carry out her basic daily activities.

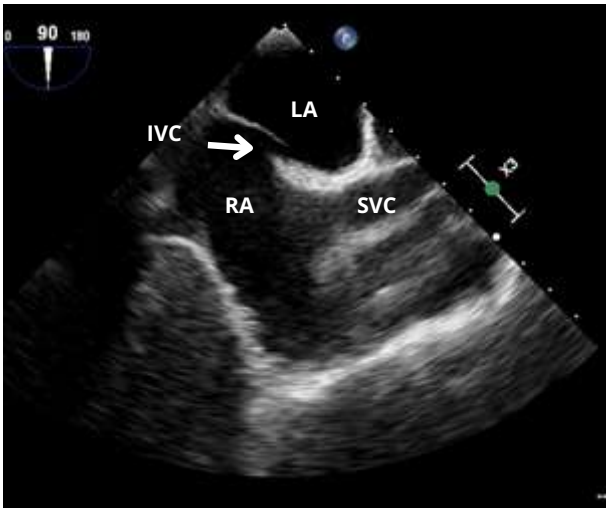

Figure 1 - Left atrium (LA), Right atrium (RA), Inferior vena cava (IVC), Superior vena cava (SVC). TOE image of the PFO. The arrow shows the IVC alignment facilitating blood flow which is directed towards the PFO

Table 1 - Investigations of the patient

Investigation	Results
Lung function test	No restriction. Mild upper airflow limitation. Forced vital capacity (FVC) 1.41 L (88%), Forced expiratory volume in first second (FEV1) 1.30 L (103%), FEV1/FVC 116%.
HRCT chest	Minimal honeycombing in bilateral lung bases, no generaliszed interstitial lung disease
CTPA	No evidence of pulmonary embolism or lung pathology that can affect oxygenation and no ascending aorta dilation
V/Q scan	Very low probability of pulmonary thrombo-embolism
2D echo	Ejection fraction of 60%, the tricuspid regurgitation pressure gradient (TRPG) of 18 mmHg, interatrial septal echo drop-out noted without obvious color crossing with good bi-ventricular function
Holter monitoring	Normal

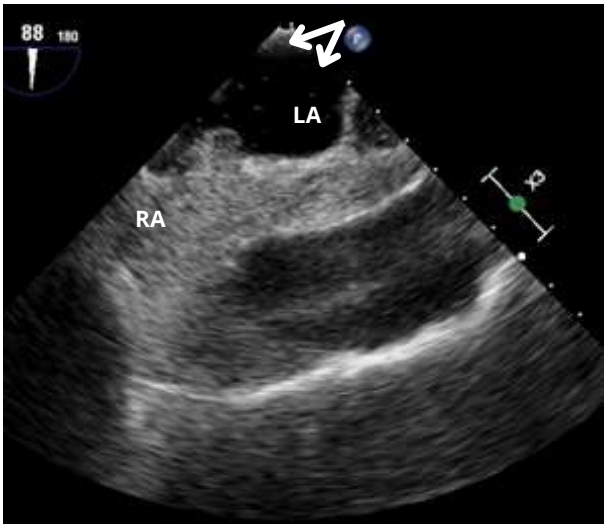

Figure 2 - TOE image of the RA filled with intravenously injected agitated saline microbubbles (arrows) which are appearing in the LA through the PFO within 3 cardiac cycles

Discussion

POS involves worsening dyspnoea (platypnoea) and arterial desaturation (orthodeoxia) while in the upright position. This drop in saturation is defined as a drop in PaO2 >4 mmHg or oxygen saturation >5% from supine to an upright position. According to the postulated pathophysiology, intracardiac communication between the two atria was the most common cause of POS. A PFO was reported as the main site of the communication between the 2 atria. The prevalence of PFO in the population could be as high as 25% but most will not get the shunting of blood as the left atrial pressure is higher than right atrial pressures. There needs to be a secondary anatomic or functional defect which facilitates the shunting of deoxygenated blood into the oxygenated blood in the presence of normal right heart pressures. This should be enhanced on upright posture to complete the symptomatology of the syndrome.(1)

Normally blood coming from the superior vena cava (SVC) flows in a downward direction in the anterior portion of the right atrium (RA) whereas blood coming from the inferior vena cava (IVC) flows in an upward direction in the posterior portion of the RA. In the presence of altered cardiac anatomy this flow structure may change and blood from the IVC tends to be directed towards the intracardiac communication and into the left atrium (LA). In patients with kyphosis, it is postulated that altered cardiac anatomy will make the ascending aorta and atrial septum more horizontal, facilitating the above mechanism.(1,2)

When POS is suspected, an echo with bubble contrast using intravenous agitated saline should be done in both supine and seated positions. Bubbles will cross within 3 cardiac cycles in the presence of intracardiac shunts. In our patient we excluded other causes of arterial desaturation such as pulmonary embolism, interstitial lung disease etc. The episodic nature of the symptoms of the index patient implies the shunting is dynamic. The worsening with exercise can be explained by the increased blood flow from the IVC during exertion.(3)

She got several lacunar infarcts in the brain which are unlikely to be caused by paradoxical embolism due to the shunt as we have excluded thrombosis in lower limbs and are most likely due to atherosclerosis. Embolic strokes are non-lacunar and in different vascular territories.(4) Cardiac emboli can cause infarcts involving the large vessels. She had other vascular risk factors and the MRA showed diffuse atherosclerosis.

Definitive treatment is percutaneous or surgical closure of the PFO. A meta-analysis of six randomised trials have shown reduced recurrent stroke risk in patients <60 years of age after mechanical closure of the PFO vs medical therapy.(5-10) PFO closure carries a risk of persistent atrial fibrillation and procedure related adverse events. Dyspnoea improvement after percutaneous closure of the PFO is observed in more than 95% of patients with a 10– 20% increase in oxygen saturations.(1)

The decision to correct the PFO is based on individual characteristics. In the index case, strokes were not an indication for PFO correction as she had multiple vascular risk factors. Dyspnoea and desaturation would have improved if the correction was done. The patient's main concern was the imbalance and even with the episodic desaturations, she was able to carry out her basic activities of daily living. Therefore, considering the age and other factors, the decision was made to follow up and observe.

Conclusion

This case illustrates a rare cause of dyspnoea and hypoxaemia due to kyphosis. When dealing with patients with unexplained dyspnoea, clinicians should be aware of platypnoea- orthodeoxia

syndrome and actively look for it. In the evaluation of dyspnoea both upright and supine oxygen saturation needs to be checked, and a bubble contrast echo is an essential investigation. More POS patients should be studied to completely understand the pathophysiology of the condition. Treatment differs as the cause for desaturation is different from case to case.

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest

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CASE REPORT

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Untwisting the story behind the femur fracture

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Abstract

Diagnosing Cushing syndrome can be challenging due to common symptoms in the general population, leading to a complex process. Here we present a case of Cushing disease in a middle aged man with delayed diagnosis following a femoral neck fracture, in the context of obesity, poorly controlled diabetes, hypertension and a history of tuberculosis. The patient was successfully treated with a positive outcome.

Keywords: Cushing syndrome, pathological femoral fracture, secondary osteoporosis

Introduction

Cushing syndrome is caused by prolonged exposure to excess cortisol either endogenous or exogenous. Cushing disease is the most common cause of endogenous Cushing syndrome caused by an adrenocorticotropic hormone (ACTH) secreting pituitary tumor.(1) Generally, patients experience excessive weight gain and a range of symptoms that are common in the general population. Untreated hypercortisolism leads to marked morbidity and mortality due to various complications.(2)

Even though it is difficult to suspect hypercortisolism at an early stage, early recognition and treatment are crucial to prevent disastrous complications as it is a treatable disease.

Case presentation

A 44-year-old man was admitted to the orthopaedic ward with a history of left-sided hip pain and difficulty in walking for a duration of 2 weeks. There was no history of back pain and faecal or urinary incontinence. He did not exhibit features suggestive of radiculopathy and had no history of trauma or falls. Radiographs revealed a fracture of the left neck of the femur, and he underwent arthroplasty.

He was referred to the endocrine unit for poorly controlled diabetes mellitus. He was obese with a recent BMI of 35 kg/m^2 and had gained 6 kg over the past 2 years. He had noticed increased generalised pigmentation, as well as pigmentation over the nails and knuckles recently.

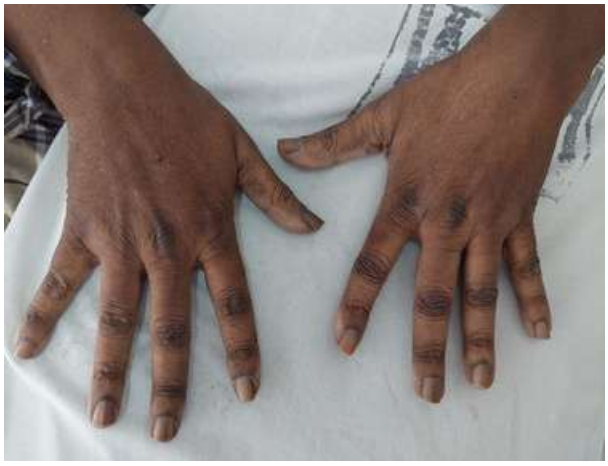

Figure 1 - Image showing pigmentation of the nails and knuckles of the hand

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He had been diagnosed with type 2 diabetes mellitus and hypertension 4 years ago. He experienced severe osmotic symptoms and had poorly controlled blood sugar levels, even with insulin therapy with an HbA1c of 12.5%. His blood pressure was also poorly controlled, requiring three antihypertensive medications. He was taking potassium supplements for hypokalaemia during his ward stay and had been treated for pulmonary tuberculosis twice in the recent past.

Given these manifestations, our suspicion turned towards hypercortisolism. Upon further questioning, he denied taking any medications, particularly steroids, and did not report sexual dysfunction. Clinically he was euthyroid, and the psychiatric evaluation did not reveal obvious psychiatric manifestations. He did not complain of any constitutional symptoms such as reduced appetite, or fever. Upon extended clinical examination, he did not exhibit facial plethora, wide purplish striae, bruising or proximal myopathy, aside from obesity and pigmentation over the nails and knuckles.

He was screened for Cushing syndrome and had a non-suppressed overnight dexamethasone test (ODST) and two-day low-dose dexamethasone suppression test (LDDST). He was further subjected to an adrenocorticotropic hormone (ACTH) test, and diagnosed with ACTH-dependent Cushing syndrome with an ACTH level of 97.5 pg/mL. MRI-pituitary gland revealed a pituitary macroadenoma (60 mm x 60 mm x 58 mm) with suprasellar invasion. His preoperative visual perimetry assessment was normal. The DXA scan revealed a Z score of -2.1 at the neck of the right femur, indicating osteoporosis.

In parallel, he was evaluated on the causes for fragility fractures. A CECT chest-abdomen-pelvis, showed an old fracture in the ramus of the pubis without any features suggestive of malignancies.

He underwent a transsphenoidal hypophysectomy (TSS) with perioperative steroid cover. Due to high cortisol levels throughout the day, he was treated with fluconazole 100 mg twice daily while monitoring for side effects. Following the TSS, he achieved

Table 1 - Summary of investigations

Investigations	Results	Reference
ODST (nmol/L)	684	<50
LDDST (nmol/L)	600	<50
9am Cortisol (nmol/L)	841	118-618
ACTH (pg/mL)	97.5	7.2-63.6
Prolactin (mIU/L)	388	73-412
TSH (mu/L)	0.89	0.5-4.7
Free T4 (ng/dL)	0.79	0.7-2.0
Testosterone (nmol/L)	2.96	9-35
HbA1C (%)	12.5	<6.5
Serum sodium (mmol/L)	140	136-145
Serum Potassium (mmol/L)	2.3	3.5-5.1
Serum creatinine (mg/dL)	0.80	0.57-1.1
LDL cholesterol (mg/dL)	205	
ESR (mm/1st hour)	20	

ODST- overnight dexamethasone test, LDDST- low-dose dexamethasone suppression test, ACTH- adrenocorticotropic hormone

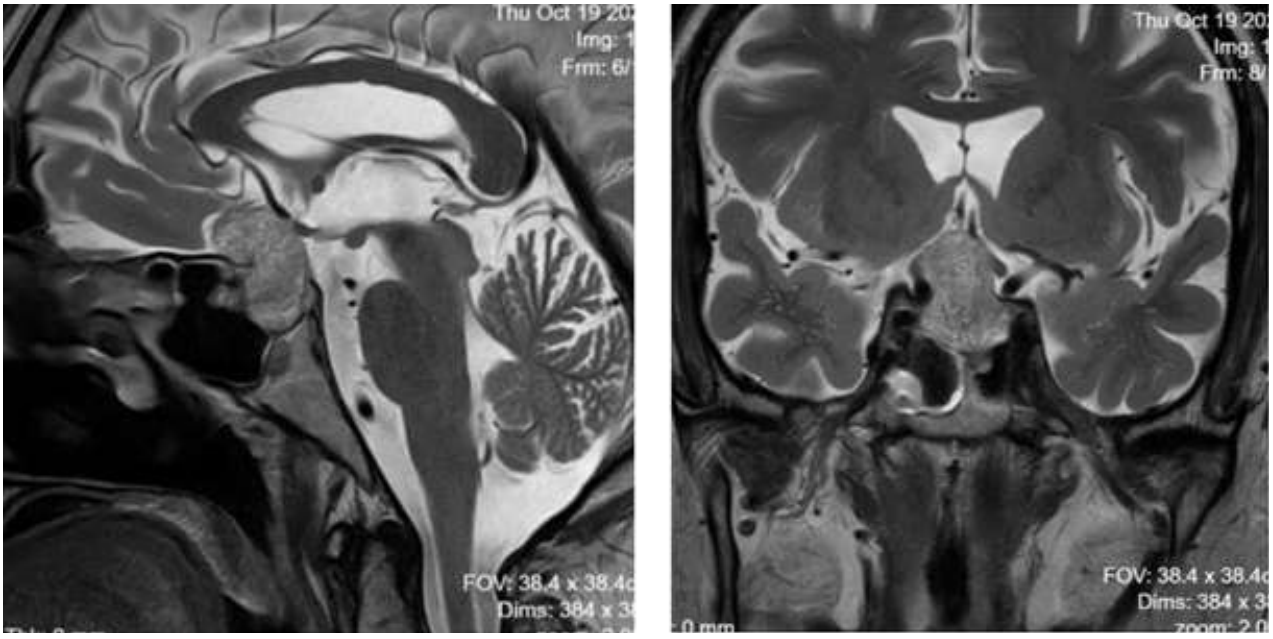

Figure 2 - MRI pituitary gland images showing a pituitary macroadenoma

remission with a postoperative cortisol level of 40 nmol/L after discontinuing steroids, with a residual tumor measuring 22 x 12x 12 mm^3. Thyroid and testosterone replacement therapy was started following surgery, while steroids were continued. The hypothalamic pituitary axis (HPA) was monitored for recovery and the recurrence of Cushing disease.

Histology revealed features of an ACTH secreting pituitary macroadenoma of high proliferation potential with a Ki67 index of 4.5% and was referred to radiotherapy. Six months post-surgery, his blood sugar and blood pressure were completely normal without any medications, and he is currently independently mobile.

Discussion

Cushing disease is a chronic condition in which excess ACTH is secreted from a pituitary adenoma. Establishing the diagnosis is often challenging because some of the features such as obesity, diabetes, and hypertension, are common in the general population. However, features like proximal myopathy, bruising, wide striae and facial plethora are considered discriminatory.(2)

The disease presents a wide spectrum of manifestations, ranging from subclinical to an overt syndrome depending on the duration and intensity of excess cortisol. It is an insidious, progressive disease that develops over years.(3)

Untreated hypercortisolism leads to high mortality and morbidity due to metabolic, cardiovascular, infectious, musculoskeletal including osteopenia and osteoporosis, thromboembolic and psychiatric manifestations.(2) A key clinical indicator of excess cortisol is the simultaneous appearance of new symptoms, and/or the progressive severity of existing symptoms over time. Prompt diagnosis and optimal management are essential to prevent devastating complications.

In our patient, obesity, pigmentation, diabetes, hypertension, dyslipidaemia and two episodes of tuberculosis occurred in the context of hypercortisolism. Unfortunately, Cushing syndrome was suspected only after a fragility fracture.

Diagnosis of Cushing syndrome is established when at least two different highly sensitive screening tests are abnormal after excluding physiological hypercortisolism. These screening tests include ODST, LDDST, urinary free cortisol or late night salivary cortisol. After establishing a diagnosis, the next step is performing an ACTH level to distinguish between ACTH dependent and independent causes. Patients with high ACTH levels (>20 pg/mL) have ACTH-dependent Cushing syndrome. The majority of ACTH-dependent Cushing syndrome cases are due to Cushing disease caused by pituitary adenoma rather than an ectopic cause. MRI-pituitary gland is the imaging of choice for detecting an ACTH-secreting pituitary adenoma.(4,5)

Treatment of Cushing syndrome involves a multidisciplinary team approach including an endocrinologist, neurosurgeon, radiologist and an oncologist. TSS is the initial treatment of choice for Cushing disease. A cortisol level of <55 nmol/L at 9 AM, 48 hours post-surgery after discontinuing hydrocortisone for 24 hours, indicates remission.(6)
Medical treatment is useful to reduce the cortisol burden before definitive surgery. Steroidogenesis inhibitors at the adrenal gland are commonly used with observation for possible side effects. In our patient, we used fluconazole as ketoconazole is not readily available in Sri Lanka.(7)

Radiotherapy is recommended for patients with recurrent Cushing disease, progressively growing tumors or post-surgical remnants. In our patient, we recommended radiotherapy as an adjuvant to surgery due to a post-surgical remnant with a Ki67 index >3%, indicating further tumor growth and invasiveness.(8)

Monitoring symptoms, signs along with investigations for Cushing disease is necessary as it can recur.(9)

Conclusion

Although diagnosing Cushing disease is challenging, clinicians must have a low threshold to screen for it, as diagnosing it at an early stage prevents mortality and morbidity related to complications.

Declarations

Conflict of interest
The authors declare that they have no conflict of interest.

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CASE REPORT

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First presentation of acute intermittent porphyria with steroid-responsive encephalopathy associated with autoimmune thyroiditis

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Abstract

Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT), also called Hashimoto's encephalopathy (HE), a treatable disease, has a wide spectrum of clinical presentation and is therefore, often misdiagnosed. Acute intermittent porphyria (AIP) is a rare disease and its prevalence in Sri Lanka is unknown. Coexistence or precipitation of AIP with thyroid illness is reported mainly related to hyperthyroidism. Here we report a case of a young girl who presented with abdominal pain, seizures, hypertension, hyponatraemia and subtle features of hypothyroidism who was successfully treated for SREAT with first AIP flare. This case highlights the possibility of coexistence of two rare entities in a single patient.

Keywords: acute intermittent porphyria, steroid responsive encephalopathy associated with autoimmune thyroiditis, hypothyroidism

Introduction

Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is a rare association of encephalopathy or neuropsychiatric symptoms with thyroid disease with poorly understood pathogenesis. It is generally considered as a neuroimmunological illness rather than a direct effect of thyroid dysfunction.(1) Acute intermittent porphyria (AIP) is an autosomal dominant metabolic disorder due to deficiency of hydroxymethylbilane synthase (HMBS). According to literature around 90% of the AIP cases are clinically latent raising the importance of high clinical suspicion.(2) AIP is an extremely rare disease in Sri Lanka and often not considered as a priority in differential diagnosis and only few case reports have been published to date. (3,4) Coexistence or precipitation of AIP secondary to thyroid illness reported in literature is mainly related to hyperthyroidism.(5,6) Here we report a rare case of a young girl with an atypical presentation of SREAT with hypothyroidism which may have triggered a flare of latent AIP which was diagnosed during the same admission.

Case presentation

A 19-year-old girl from Galle, Southern Sri Lanka with a past history of recurrent self-resolving epigastric pain presented with severe abdominal pain and vomiting. Despite severe pain her abdomen was soft. She was treated for acute gastritis after excluding surgical causes and discharged. She was readmitted on the same day with a right sided focal onset tonic clonic seizure with secondary generalisation. On admission she was afebrile and her GCS was 15/15

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after recovering from the seizure. There were no features to suggest central nervous system (CNS) infection. Fundoscopy was normal. Blood pressure was 160/100 mmHg and pulse rate was 90 bpm. She had diffuse abdominal tenderness without guarding or rigidity and developed multiple seizures in between which she regained full consciousness but had fluctuating, disinhibited behaviour.

Cerebrospinal fluid analysis and inflammatory markers excluded central nervous system infection. Preliminary imaging with the NCCT brain was normal. MRI brain showed two T1W1 hypointense and T2WI/FLAIR hyperintense juxtacortical lesions. Electroencephalogram (EEG) showed regular polymorphic delta activity with background delta slowing which could be due to encephalopathy. As she had irregular menstrual cycles and constipation, thyroid profile was performed which showed TSH >100 mU/L which was repeated and confirmed. Antithyroid antibodies (anti-TPO antibodies) were >140 IU/L while thyroid scan showed mild thyroiditis.

Acute porphyria was suspected due to abdominal pain, hypertension and serum sodium levels of 118 mmol/L. Qualitative Hoesch test for porphobilinogen in urine revealed a positive result prompting further evaluation for AIP. Total urinary porphyrins scanned with UV-VIS Spectrophotometer (model UV mini-1240) demonstrated a positive peak at 405 nm with a concentration of urine porphyrin: creatinine ratio of 1087 nmol/mmol (<35) and a scan of plasma for fluorescence utilising PerkinElmer Fluorescence Spectrometer LS 55 with excitation set at 405 nm resulted in a positive emission peak at 618 nm. All these biochemical markers indicated an acute porphyria, probably acute intermittent type. Refer to table 1 for a summary of investigations.

Initial seizures were managed with IV levetiracetam. With the confirmation of SREAT, thyroxine and IV methylprednisolone pulses were initiated which were converted to oral prednisolone after 5 days. Electrolyte imbalances were corrected, and the patient was adequately hydrated. After 48 hours of treatment, she completely recovered. She was discharged with thyroxine, and prednisolone and advised regarding identifying an AIP flare and precipitants. She was scheduled for follow-up at the clinic level.

The patient became euthyroid after 6 weeks of treatment. Prednisolone was tailed off over a period of two months. Repeat MRI brain was normal suggesting response to steroids. After 3 months of follow up with good treatment adherence she readmitted with severe abdominal pain, vomiting and hiccups for two days preceded by generalised ill health for one week precipitated due to an intentional low-calorie diet over a few days to reduce weight. She was successfully managed as for a flare of AIP with correction of electrolyte imbalances, hydration with 10% dextrose, IV labetalol for hypertension and close observation. She was discharged after 12 days of hospital stay.

Discussion

Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is a rare association of encephalopathy or neuropsychiatric symptoms with autoimmune thyroid disease. The estimated prevalence of SREAT is about two cases per 100,000 in the general population. There are no diagnostic criteria to diagnose SREAT. The diagnosis mainly depends on the presence of thyroid antibodies, suggestive clinical presentation, and exclusion of other causes of encephalopathy.(7)

In our case the patient presented with focal onset secondarily generalised seizures which is a known presentation of SREAT. A case series by Castillo et al. which studied the presentation and investigations of patients with SREAT has shown that 17% of patients had seizures as a presenting feature.(8) Generalised seizures are the most common type of seizures, however, partial seizures are not uncommon. Our patient had recent changes in menstrual cycles and constipation which were suggestive of hypothyroidism but had not been screened.

MRI findings in SREAT can be normal or nonspecific. MRI is normal in approximately 74% of patients with SREAT. Generalised cerebral atrophy, diffuse increased signal on T2-weighted and FLAIR images in subcortical white matter, and dural enhancement are the common findings in the MRI in the remaining patients. Cerebellar T2 hyperintense lesions or atrophy are rarely seen.(8) Our patient's lesions on MRI were in favour of both SREAT or multiple sclerosis. However, we did not consider multiple sclerosis as the primary diagnosis since the other clinical and biochemical evidence were not suggestive.

Although our patient's seizures and abnormal behaviour could be explained with SREAT, her recurrent abdominal pain with transient hypertension and hyponatraemia remained

Table 1 - Summary of investigations

Investigation	Result	Reference range (SI unit)
hemoglobin (g/dL)	10.2	12 – 16
white cell count (/ µL)	8900	4500 – 11000
platelet (/ µL)	248000	157000 – 371000
ESR (mm/ 1st hour)	17	<20
Serum sodium (mmol/L)	118	135-145
Serum potassium (mmol/L)	3.9	3.5 - 4.5
Serum calcium (mg/dL)	8.9	8.5-10.2
Serum magnesium (mg/dL)	1.2	1.46 - 2.68
Serum TSH (mU/L)	>100	0.4 – 4.0
Thyroid peroxidase antibodies (IU/mL)	>140	< 30
ANA titre	1:640 nuclear pattern, antibody target DFS 70	< 1:80
Urine porphobilinogen	positive	
Cerebrospinal fluid analysis		
Protein (mg/100mL)	48	15-60
glucose (mg/100mL)	90 (RBS – 118)	50-80 (>2/3RBS)
polymorphs	Nil	0
lymphocytes	Nil	0-5
red cells	23	0
HSV PCR	negative	
VZV PCR	negative	
CMV PCR	negative	
Bacterial culture	no growth	

ESR- erythrocyte sedimentation rate, TSH- thyroid stimulating hormone, ANA- anti nuclear antigen, CSF- cerebrospinal fluid, HSV – herpes simplex virus, VZV – varicella zoster virus, CMV- cytomegalovirus, PCR- polymerase chain reaction

unexplained. Latent AIP may be precipitated by thyroid illness but mostly discussed with hyperthyroidism or normal thyroid status.(9,10) Interestingly, our patient was hypothyroid, which is rarely documented in the literature. Diagnosing AIP in the early course of the illness was important as many antiepileptics precipitate flares of AIP. Of the electrolyte imbalances mentioned in the literature hyponatraemia is the commonest and is explained by syndrome of inappropriate ADH secretion.(3) Correction of electrolytes and carbohydrate loading to downregulate aminolevulinate synthase 1 enzyme is the mainstay of treatment. Our patient successfully responded to electrolyte correction, hydration with 10% dextrose infusion and a high carbohydrate diet.

Conclusion

This case highlights a rare presentation of a flare of latent AIP possibly triggered by SREAT. While AIP flares are known to be triggered by various factors, the role of SREAT as a potential precipitant remains unclear. Given the rarity of this association, further studies may be warranted to explore the underlying mechanisms and establish SREAT as a possible trigger for AIP exacerbations. Although rare, diseases like AIP should be duly considered in clinical context. Diagnosing AIP is challenging in a country like Sri Lanka with minimum diagnostic facilities. After exclusion of the common causes of acute altered mental status and seizures, early workup for treatable rare causes such as SREAT can help rapid recovery and avoid complications.

Declarations

Author contributions
History taking, examination, necessary investigations, management, daily monitoring of the patient and writing of the manuscript done by de Zoysa MWK. Uluwattage W and Jasinge E supervised the management and guided through the case and EWB Edirisinghe was a major contributor in writing the manuscript. All authors read and approved of the final manuscript.

Conflict of interest
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(1) Answer B - Subdural haemorrhage

Subdural haemorrhage (SDH) is a collection of blood accumulating in the potential space between the arachnoid mater and meningeal (visceral) layer of the dura mater. It is a common neurosurgical emergency with high rates of morbidity and mortality. The aetiology of SDH is either traumatic or nontraumatic where traumatic causes are the commonest. This can happen in all age groups, from intrauterine life to the elderly, with mortality ranging from 50% to 90%.

Acute SDH develops when there are sudden acceleration or deceleration forces which result in stretching or tearing of bridging cortical veins of the brain, which cross the subdural space to drain into an adjacent dural sinus.

In imaging, non-contrast CT (NCCT) is the modality of choice in the initial evaluation because of its frequent availability, rapid imaging time, and noninvasive nature. MRI generally has a limited role in the evaluation of acute SDH, mainly due to non-availability in most emergency units and the high image acquisition time. However, MRI may depict secondary causes for SDH, such as dural-based meningioma, haemangiopericytoma, and metastasis. Furthermore, MRI may be valuable in determining the age of the haematoma, which is important for patient management and medicolegal purposes. Changes in MRI image signal intensity in T1W and T2W sequences at various time stages of intracranial haemorrhage are described in table 1.

Table 1 - Changes in MRI image signal intensity in T1W and T2W sequences at various time stages of intracranial haemorrhage

Stage of Bleeding	Age of Blood	Blood Product	T1W Signal
Hyperacute	<24 hours	Intracellular oxyhaemoglobin	Isointense
Acute	1 to 2 days	Intracellular deoxyhaemoglobin	Iso to Hypointense
Early subacute	3 to 7 days	Intracellular methaemoglobin	Hyperintense
Late subacute	1 to 4 weeks	Extracellular methaemoglobin	Hyperintense
Chronic	After 4 weeks	Haemosiderin	Hypointense
Stage of Bleeding	Age of Blood	Blood Product	T1W Signal

(2) Answer E - Pulmonary embolism

Pulmonary thromboembolism (PTE) is a common and life-threatening venous thromboembolic condition characterised by the embolic occlusion of the pulmonary artery or its branches by a thrombus that originates elsewhere. This condition usually results from deep venous thrombi originating in the lower extremities. Definitive diagnosis of PTE significantly depends on various imaging modalities.

CXR is a routine investigation for patients with shortness of breath and chest discomfort in many emergency settings. The CXR is neither sensitive nor specific for acute PTE. However, it can be used to exclude many differential diagnoses of PTE, such as acute pulmonary oedema, pneumonia, and

pneumothorax. Other observed CXR abnormalities include pulmonary infiltrates, segmental atelectasis, pulmonary congestion, elevated hemidiaphragm, pleural effusion, Palla's sign (enlargement of the right descending pulmonary artery proximal to the obstruction, giving rise to a "sausage" appearance), Westermark sign (focal peripheral hyperlucency due to oligaemia), and Hampton's hump (Peripheral wedge-shaped airspace opacity, indicating lung segmental infarction.

Computed tomography pulmonary angiogram (CTPA) is the imaging modality of choice for acute PTE, with a sensitivity of 83% and specificity of 96%. A classic CTPA finding of acute PTE is a low-dense filling defect within a pulmonary artery branch surrounded by high-contrast material. When a cross-section of this filling defect is imaged in CTPA, it is called a "polo mint" sign (Figure B) and, when imaged through the long axis of the vessel, a "tram track sign." When a large thrombus lodges at the pulmonary artery bifurcation and extends to the main pulmonary arteries, it is called a "Saddle Pulmonary Embolism." Peripheral pulmonary infarction due to a thrombus appears as a wedge-shaped area of central ground glass appearance and peripheral consolidation in the lung window of CTPA. This sign is called "reverse-halo" or "atoll sign." Other CTPA signs include pleural effusion and features of right heart strain such as an increased right ventricle (RV)/left ventricle (LV) ratio, enlargement of the pulmonary trunk > 29 mm, flattening of the interventricular septum, and reflux of contrast material into the inferior vena cava and hepatic veins. In chronic PTE, the pulmonary vessels are usually narrower and show abnormal tapering, mosaic perfusion, band-like opacities, and bronchial dilation in lung parenchyma.

Magnetic resonance pulmonary angiography (MRPA) is a useful substitute for CTPA in pregnancy, patients with contraindications to iodinated contrast, severe renal insufficiency, untreated hyperthyroidism, and young patients.

(3) Answer A - Brain metastasis

Brain metastases account for approximately 25-50% of intracranial tumours. Since brain metastasis can mimic a broad range of differential diagnoses, a thorough history, physical examination, and careful interpretation of imaging findings are crucial. The top four primary cancers with a propensity for cerebral metastasis include lung, breast, melanoma, and colorectal carcinoma. While magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT) in detecting brain metastases, CT plays a vital role in the initial diagnosis due to its wide availability, short scanning time, and cost-effectiveness.

Brain metastases are commonly identified at the junctions of grey and white matter and between major arterial territories. Approximately 80% of lesions occur in the cerebral hemispheres, 15% in the cerebellum, and 3% in the basal ganglia. Lesions may appear as solitary or multiple in imaging. In non-contrast CT scans, metastases may exhibit isodensity, hypodensity, or hyperdensity (in the case of melanoma), along with varying surrounding vasogenic oedema and mass effect. Conversely, CT enhancement patterns may display uniform, nodular, or ring patterns.

Metastases typically appear iso- or hypointense on T1-weighted images, hyperintense on T2-weighted images, and demonstrate contrast enhancement. Haemorrhagic metastases may exhibit hyperintensity on T1-weighted images depending on the age of the haemorrhage. Metastasis usually does not demonstrate diffusion restriction on apparent diffusion coefficient (ADC) / diffusion weighted imaging (DWI) images.

(4) Answer D - Dengue haemorrhagic fever

Ultrasonography is one of the most frequently used non-invasive radiological investigations in dengue fever. There are multiple thoracic and abdominal manifestations detected in dengue haemorrhagic fever.

Thoracic manifestations

- **Pleural effusion:** Ultrasonically, it can detect an effusion as small as 20 mL. Pleural effusions are more frequently encountered on the right-side than the left-side. Pleural effusion predicts the severity of the illness and commonly occurs when platelet count is < 40,000.
- **Compressive atelectasis of the lower lobes of the lungs**
- **Pericardial effusion:** This is an uncommon manifestation and usually self-limiting. However, gross pericardial effusion leading to cardiac tamponade in severe dengue has been reported.

Abdominal manifestations

- **Hepatic manifestations:** hepatomegaly, altered liver echotexture, periportal oedema which manifests as periportal halo and hepatic subcapsular fluid.
- **Splenic manifestations:** splenomegaly, splenic subcapsular haemorrhages, splenic ruptures, and splenic infarction.
- **Gallbladder manifestations:** gallbladder wall thickening is frequently observed in the leaking stage and is a highly reliable ultrasonographic indicator to evaluate the severity of the disease.
- **Ascites:** ascites is a common manifestation, typically occurring during the third to fifth day of the illness. Initially, fluid can be detected in the pouch of Morison, and later, it may accumulate in the pelvis. The free fluid is typically reabsorbed within 12–24 hours once the leakage ceases.
- **Other manifestations:** acute pancreatitis, appendicitis and abdominal wall haematoma have been reported.

(5) Answer D - Sigmoid volvulus

A sigmoid volvulus (SV) occurs when the sigmoid colon twists around its own mesentery, resulting in a closed-loop obstruction. Typically, SV affects elderly males with a history of chronic constipation and neurological conditions like Parkinson's disease. A supine abdominal X-ray reveals a gas-filled, significantly dilated, ahaustral left-side large bowel loop originating from the pelvis and extending cranially. This classic X-ray appearance is referred to as the “coffee bean appearance.” SV can manifest with other appearances, including an “inverted U- or V-shaped sign,” the "white stripe sign," or the “Frimann-Dahl sign,” characterised by three dense lines formed by the walls of interposed sigmoid loops converging at the site of obstruction. Other signs include the “liver overlap sign,” where the apex of the sigmoid loop projects over the liver shadow in the right hypochondrium, and the “northern exposure sign,” where the apex of the sigmoid volvulus is detected above the transverse colonic loop in a supine X-ray abdomen. A plain X-ray abdomen provides a diagnostic yield in 57%–90% of patients.
In SV, abdominal CT findings include dilated gas-filled loops without haustra, the “whirl sign” indicating twisted mesentery bowel and vessels near the base of the volvulus, the “bird beak sign” characterised by progressive tapering of afferent and efferent limbs leading into the twist, the “split wall sign” depicting the separation of the walls of a single loop due to mesenteric fat indenting the bowel wall, and the “steel pan sign,” where gas-filled bowel loops in axial section resemble the percussion instrument known as a steelpan.

(6) Answer B - Left dense middle cerebral artery sign

The dense middle cerebral artery sign is a hyperdense middle cerebral artery (MCA) compared to the contralateral MCA in a non-contrast CT (NCCT) brain. Hyperdensity in CT is due to the dense intraluminal high globin-concentrated thrombus obstruction at the MCA in early MCA territory cerebral infarction. This radiological sign provides early diagnosis (within 90 minutes after vascular occlusion) before the brain damage develops, and the infarct becomes visible in the NCCT. Therefore, early tPA and mechanical thrombectomy can be applied to reduce morbidity and mortality.

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