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The role of precision medicine in healthcare

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

Definition and overview

Precision medicine is an emerging approach that takes into account an individual's variability in genes, environment, and lifestyle in disease treatment and prevention. (1,2)

Instead of the traditional one-size-fits-all approach, precision medicine aims to tailor medical treatment and prevention strategies to the specific characteristics of each individual. By taking into account unique variations in genes, environments, and lifestyles of an individual, this approach allows healthcare providers to better predict which treatment and prevention strategies will be most appropriate and effective for a particular patient, leading to improved outcomes and reduced side effects.

The terms "precision medicine" and "personalised medicine" show considerable overlap and are used interchangeably. "Precision medicine" appears to better capture the focus on treating and preventing diseases based on genetic, lifestyle-related, and environmental factors(3) as opposed to "personalised medicine" which incorporates dimensions beyond therapeutics, addressing the patient's social environment, cultural values etc. The term "personalised medicine" is also given a different interpretation which aligns with "holistic care" in traditional medicine. Therefore depending on context it may be considered an older term and a precursor to "precision medicine".

The ultimate goal of precision medicine is to provide the right treatment to the right patient at the right time, leading to better patient outcomes and a more efficient healthcare system(4,5,6)

History

From the discovery of the structure of DNA by Watson and Crick in 1953 to DNA sequencing by Sanger in 1977, culminating in the Human Genome Project launched in the 1990s, the concept of precision medicine has gradually established itself.

Research on Mendelian genetics and patterns of inheritance set the stage for the current knowledge in complex interactions between multiple genes in the development of disease. It also brought to light the diversity in the manifestation of the same genetic mutation due to variation in gene expression.(5) It is apparent therefore that the predictive ability of genetics alone in determining disease causation is relatively modest. Consequently, there arose a need for new technologies and approaches in the field of medicine.

Pharmacogenomics emerged as a response to such need and is a field that explores how an individual's genetic inheritance affects the body's response to drugs.(7)

The term "precision medicine" gained prominence in 2015 with the launch of the precision medicine initiative in the United State of America which aims to advance the treatment of diseases such as cancer and diabetes.(8) Since then the field of precision medicine has received much attention and has shown rapid development up to date.

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Precision medicine over Traditional Medicine/Evidence-based medicine

Traditional medicine follows a uniform treatment approach where the same drug is prescribed to all patients for a particular illness. These interventions are based on evidence from research that are generalised to the population at large. However, this approach poses challenges as not all patients respond equally to the drug. Some may not respond at all while others may experience adverse effects. These differences in individual responses could be attributed to genetic variations, age, gender, lifestyle choices, race, ethnicity, concurrent medications, underlying health conditions, environmental factors, and more. This not only leads to drug wastage but also increases costs and reduces satisfaction among patients and healthcare providers.

Precision medicine addresses these challenges by considering the diverse genetic, socio-environmental, and lifestyle factors within subpopulations to tailor specific therapies. It focuses on accurately measuring molecular, environmental, and behavioural contributors to health and disease, leading to more precise diagnostics, targeted disease prevention strategies, individualised treatment selection, and the development of innovative therapies.(5)

The role of AI in precision medicine

Precision medicine requires the analysis of large volumes of diverse data in order to deliver the desired outcome. The advancements in artificial intelligence (AI) with technologies of machine learning, neural networks, etc. demonstrates great promise in this context by making it a tool to handle such data efficiently, effectively and accurately.

The integration of AI and precision medicine thus shows significant potential to revolutionise healthcare as evidenced by AI application in the field of radiogenomics. Here associations between cancer imaging characteristics and genetic factors are studied to predict a patient's risk of developing complications from radiotherapy. This interdisciplinary approach has shown promise in various types of cancer, including glioma, breast cancer, liver cancer, and colorectal cancer.(6)

Application of precision medicine in different disciplines

The successful application of precision medicine is apparent in almost all disciplines in medicine. Some prominent discoveries and applications are discussed below under each discipline.

Oncology

Molecular testing has allowed for precise subtyping of cancers based on genetic abnormalities, leading to the development of targeted therapies tailored to individual patients.

For example, specific mutations like EGFR in lung cancer have led to the emergence of targeted therapies such as osimertinib (an EGFR inhibitor) that shows improved outcomes compared to traditional treatments.

Molecular profiling has also proven beneficial in breast cancer. Targeted therapies for HER-2 positive breast cancer, hormone receptor positive breast cancer, BRCA gene mutations are now available and applied with success and reduced side effects.

Mutations in many genes such as VEGF, EGFR, BRAF, HER-2, NTRK, etc. are implicated in colorectal cancer and targeted therapies to inhibit the activity of these genes are used successfully.

In addition to targeted therapies, genetic sequencing also provides prognostic information to guide treatment strategies. Tools that analyse and sequence individual tumour biology has led to the development of several prognostic kits, such as Oncotype DX, Mammostrat, and EndoPredict analyses, which stratify a patient's risk of future cancer recurrence (9, 10).

Radiology

Developments in imaging, which is part and parcel of the armamentarium of precision medicine, have considerably contributed to improved diagnostics. For example imaging modalities such as positron emission tomography indicate the metabolic activity of disease and is capable of guiding the management plan and detecting recurrence of cancer prior to the emergence of symptoms in cases of Hodgkin's Lymphoma (11,12).

Cardiology

Revolutionary advancements have taken place in the context of precision medicine in cardiology. Pharmacogenomics have enabled to demonstrate how polymorphisms in key genes, such as CYP2C9, CYP2C19, VKORC1 and SLCO1B1, significantly impact

the outcomes of treatment with clopidogrel, warfarin and simvastatin.(13) PCSK9 inhibitors in the management of hyperlipidaemia are another example of targeted cardiovascular therapeutics.

The more common cardiovascular diseases such as hypertension, atrial fibrillation and coronary artery disease occur in part due to an accumulation of thousands of small effect size genetic variants known as single nucleotide polymorphisms. Precision medicine helps in identifying the nuances in gene expression of these polygenic diseases, and applying both curative and preventive strategies tailored to the patient. (14)

Wearable health technology has significantly advanced precision medicine and has transformed insights into cardiovascular health redefining how risk stratification, diagnosis, therapy and monitoring takes place.(15)

Respiratory Medicine

Increased understanding of the immuno-pathophysiology of asthma has enabled the identification of multiple disease endotypes through clinical biomarkers such as sputum and blood eosinophils, serum IgE and fractional exhaled nitric oxide (FeNO). It is now possible to consider the individual pheno-endotype of the patient when planning treatment strategies. For example omalizumab (anti-IgE) is approved for allergic asthma patients with high IgE serum values while mepolizumab, reslizumab and benralizumab (anti-IL-5/Rα) are used for patients with severe eosinophilic asthma.Dupilumab (anti-IL-4Rα) is used for patients with high eosinophil and/or FeNO values. It is evidenced by clinical trials that these drugs reduce the number of exacerbations and are also instrumental in limiting the exposure to long-term oral corticosteroids and stabilising respiratory function, improving the overall asthma control.(16)

Application of similar successful targeted therapies are observed in many other respiratory disorders like chronic obstructive pulmonary disease, interstitial lung disease, bronchiectasis, etc.

Gastroenterology

Patients with monogenic inflammatory bowel disease (mIBD) have the opportunity of receiving genotype-guided therapy with the advent of precision medicine in addressing molecular aetiologies related to gastrointestinal disease.(17)

Neurology

Treating neurological diseases such as epilepsy, neurodegenerative disorders, movement disorders, etc. has proved challenging due to the diverse presentations, diverse response to treatment and adverse effects experienced when prescribing from the limited choice of drugs available.

Precision medicine therefore presents a great opportunity in the field of neurology in optimising diagnostics and treatment to achieve better patient outcomes. With advancements in gene sequencing it has been possible to identify the pathophysiological mechanisms of various epilepsy syndromes at a molecular level. The use of retigabine (ezogabine), a positive allosteric modulator of KCNQ2–5 (Kv7.2–7.5) ion channels, in KCNQ2-associated encephalopathy is a great example of the level of accuracy in therapy that can be achieved with precision medicine approaches.(18)

The use of neuromodulation in place of surgical resection in treating refractory epilepsy syndromes also demonstrates the revolutionary care possible with advances in precision medicine.(19)

Precision medicine and population health

Precision medicine can also be adapted for population-based strategies, emphasising a significant preventive aspect. It promotes patient engagement in both research and healthcare, giving rise to the concept of "preventive, personalised, precise, population-based, and participatory medicine."(5)

Precision medicine has some important implications in communicable diseases such as influenza, HIV and Ebola where identification of resistant strains aids in formulating effective treatment strategies. Genetic sequencing extends beyond therapeutics and is capable of facilitating disease surveillance as demonstrated in a study on drug-resistant tuberculosis where genetic analysis combined with epidemiological methods enhanced disease mapping and informed public health policies.(20)

Overall, by leveraging genetic insights and molecular data, precision medicine has the potential to revolutionise healthcare by improving patient outcomes and advancing personalised medicine practices.(20)

Considerations, challenges and limitations in the practice of precision medicine

While precision medicine aims to improve disease classification and treatment precision, several considerations need addressing.

Firstly, the value of enhancing disease classification lies in the availability of effective therapies. Without viable treatment options, improved disease understanding may offer limited benefits to patients. The challenge remains evident in conditions like Huntington's disease, where genetic testing is available, but treatment options are limited to symptomatic and supportive care. Additionally, the cost and time associated with developing targeted therapies based on precise diagnoses pose significant challenges.

Secondly, the financial implications of precise disease stratification and personalised treatments raise concerns about efficiency and clinical benefits. While targeting specific genetic or molecular aberrations may offer tailored therapies, the cost and resource-intensive nature of development and implementation need careful consideration.

Lastly, the complex nature of molecular classifications within diseases may strain existing healthcare systems, potentially fragmenting disease management based on molecular subtypes rather than organ systems. This can introduce inefficiencies and challenges in delivering holistic healthcare services, emphasising the need for careful integration of precision medicine approaches within existing healthcare frameworks.(2)

Summary

Precision medicine has taken root and is growing deep and wide with the aid of new technologies related to AI and advancements in molecular typing. Its effects are apparent in almost all disciplines of medicine showing great promise in achieving highly personalised and precise diagnoses and therapies. However, it is important to be mindful of the gap between the outcomes and investments in precision medicine so as to avoid unnecessary strain on the healthcare system and providers.

Precision medicine overall, has aided us in climbing out of the one-size-fits-all way of practice, opening an avenue of optimal healthcare for all.

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Medical complications among acute leukaemia patients receiving inward induction chemotherapy at haemato-oncology section of the National Cancer Institute, Sri Lanka

Wariyapperuma UM[1*], Madawala P[2]

Abstract

Introduction: Acute leukaemias are complicated with numerous disease and treatment related medical complications. Infection is one of the major complications and is related to chemotherapy associated-neutropaenia. This study aims to identify medical complications in acute leukaemia patients during the induction chemotherapy period.

Results: Medical complications were observed in patients receiving induction chemotherapy N=50. Infections and electrolyte disturbances were the most frequently observed complications (74% each) followed by chemotherapy induced neutropaenia (38%), alteration of liver functions (32%), steroid induced hyperglycaemia (28%) and bleeding (16%). Thrombosis and tumour lysis were detected at lesser frequencies (4% each). Among infections, the majority showed evidence of blood stream infection (27%) followed by pulmonary infections (24.3%). Gram negative organisms were the most frequently identified pathogen. Among the electrolyte disturbances, hypokalaemia (48%), hyponatraemia (48%), and hypocalcaemia (44%) were more prevalent. Mean duration from initiation of chemotherapy to neutrophil nadir was 10.05 days.

Conclusions: Patients with acute leukaemia encounter a multitude of disease and treatment related medical complications during induction chemotherapy. Infection is the most common complication with higher rates of bacteraemia and gram-negative sepsis. This is likely to be a result of treatment related neutropaenia. However, further focused studies on neutropaenic sepsis during induction chemotherapy are recommended. Clinical vigilance, strict and improved infection control strategies are necessary to improve the outcome of these patients.

Keywords: acute leukaemia, induction chemotherapy, neutropaenia, medical complications

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Introduction

Globally, malignancy poses an enormous burden on society. Cancer incidence and mortality are on the rise and contributory factors are multifactorial. Demographic transition towards an ageing population, together with increasing prevalence of non-communicable diseases and established risk factors such as smoking, overweight, physical inactivity are among the leading contributory factors. About 14.1 million new cancer cases and 8.2 million deaths occurred worldwide in 2012.(1) Over the years, the burden has shifted to less developed countries, which currently account for about 57% of cases and 65% of cancer deaths worldwide.(1)

Among the malignancies, solid organ malignancies are more prevalent than haematological malignancies. This trend is observed among the Sri Lankan population as well.(2) However, the incidence of lymphoid and myeloid leukaemia is rising with the adult population being more affected.(2) Though the trend is rising, overall survival of leukaemia is better than that of most solid organ malignancies.(3)

Among the haematological malignancies, acute leukemias which consist of acute myeloid leukaemia (AML) and acute lymphocytic leukaemia (ALL) are complicated with numerous disease and treatment related medical complications.(4-10) Infection is one of the major complications and is related to chemotherapy associated neutropaenia.(11) Metabolic disturbances are also very frequent and usually result from vomiting, diarrhoea, renal dysfunction or as a side effect of chemotherapy, antibiotics or diuretic use. Tumour lysis syndrome is a disease specific as well as treatment related complication giving rise to a myriad of metabolic disturbances which include hyperuricaemia, hyperphosphataemia, hyperkalaemia, hypocalcaemia and ultimately renal insufficiency.(9) Bleeding is another medical complication which can result from thrombocytopaenia, platelet dysfunction or disorders of coagulation. Disseminated intravascular coagulation is seen with all leukaemia subtypes, especially in patients with acute promyelocytic leukaemia. Leukaemia related hyperleukocytosis and leukocytosis can present with respiratory and neurological distress and is a medical emergency.(10) Leukaemic patients are at high risk of venous thrombosis and associated complications like pulmonary embolism.(5) Lactic acidosis, acute pulmonary failure and neutropaenic enterocolitis are among other less frequent medical complications. (4,8)

These medical complications, if anticipated, detected and managed properly will have a major impact on survival of these patients. Therefore, as physicians, it is of utmost importance to be aware of the prevalence, existing deficiencies and proper management of these medical complications among the local population in order to provide the optimal care for the patients. Under such circumstances, this study aims to identify disease and treatment related medical complications among acute leukaemia patients during inward induction chemotherapy.

Methods

This is a descriptive cross-sectional study carried out from December 2018 to May 2019 in the Hemato-Oncology sections at the National Cancer Institute Sri Lanka. Out of 212 acute leukaemia patients receiving inward treatment during the study period, the patients receiving induction chemotherapy regimen were only 50 and all of them were recruited to the study.

Data was collected via interviews and bedhead tickets. Informed consent was obtained from the patients. SPSS version 21 software was used to analyse data. Patients were followed up throughout the period of inward chemotherapy, which varied from 7-21 days depending on the chemotherapy regimen.

Results

Majority of the patients (66%) receiving induction chemotherapy were without prior medical comorbidities. Diabetes was observed in 6% and hypertension in 2% and the remaining 26% had other comorbidities like asthma, heart disease etc. None of them had chronic kidney disease.

Figure 1 summarises the main medical complications among the patients (N=50) receiving inward induction chemotherapy. Infections and electrolyte disturbances were the most frequently observed complications (74% each) followed by chemotherapy induced neutropaenia (38%).

Evidence of infections was defined as the presence of one or more of fever, elevated c-reactive protein (CRP), positive cultures or a clinically identifiable infective focus. Out of the 50 patients, 37 (74%) had evidence of infection at some point during induction chemotherapy. Among the 37 patients with evidence of infection, 23 (62.1%) had fever and 36 (97.3%) had elevated CRP levels.

Table 1 demonstrates the focus of infection among the 37 patients who had evidence of infection. Majority showed evidence of blood stream infection 10 (27%) followed by pulmonary 9 (24.3%) infections. In another significant proportion, 8 (21.6%), the focus was not identified.

In the 37 patients with evidence of infection, 10 (27%) had positive blood cultures. The majority 5 (50%) were gram negative pathogens. None of the fungal cultures were noted to be positive during the study period. This is shown in table 2. Urine culture alone was positive for gram negative organisms in 2 patients.

Table 3 shows the patterns of antibiotics used in patients with evidence of infection. The majority [30 out of 37 (81.1%)] were treated with the combination of beta-lactam or cephalosporin with antipseudomonal cover and an aminoglycoside. Addition of gram-positive cover in 13 (35.1%) and antifungal cover in 6 (16.2%) was utilised less frequently.

Detailed analysis of neutropaenia during induction chemotherapy revealed that 40% had disease related neutropaenia prior to initiation of chemotherapy. Chemotherapy induced neutropaenia was present in 38 %. According to the absolute neutrophil count (ANC) they were categorised as mild (ANC 1-1.5, in 6%), moderate (ANC 1- 0.5, in 20%) and severe (ANC <0.5, in 12%). Mean duration from initiation of chemotherapy to lowest neutrophil count (i.e neutrophil nadir) was 10.05 days (95% CI 7.71-12.4).

Among the electrolyte disturbances, hypokalaemia (48%), hyponatraemia (48%), hypocalcaemia (44%) were the most prevalent (figure 2).

Alteration of liver transaminases and serum bilirubin levels were seen in 16 (32%) out of the 50 patients in induction chemotherapy. Among these 16 patients, 14 (87.5%) were ALL patients and only 2 (12.5%) were AML patients. No cases of acute liver failure were documented.

Bleeding was exclusively seen among AML patients

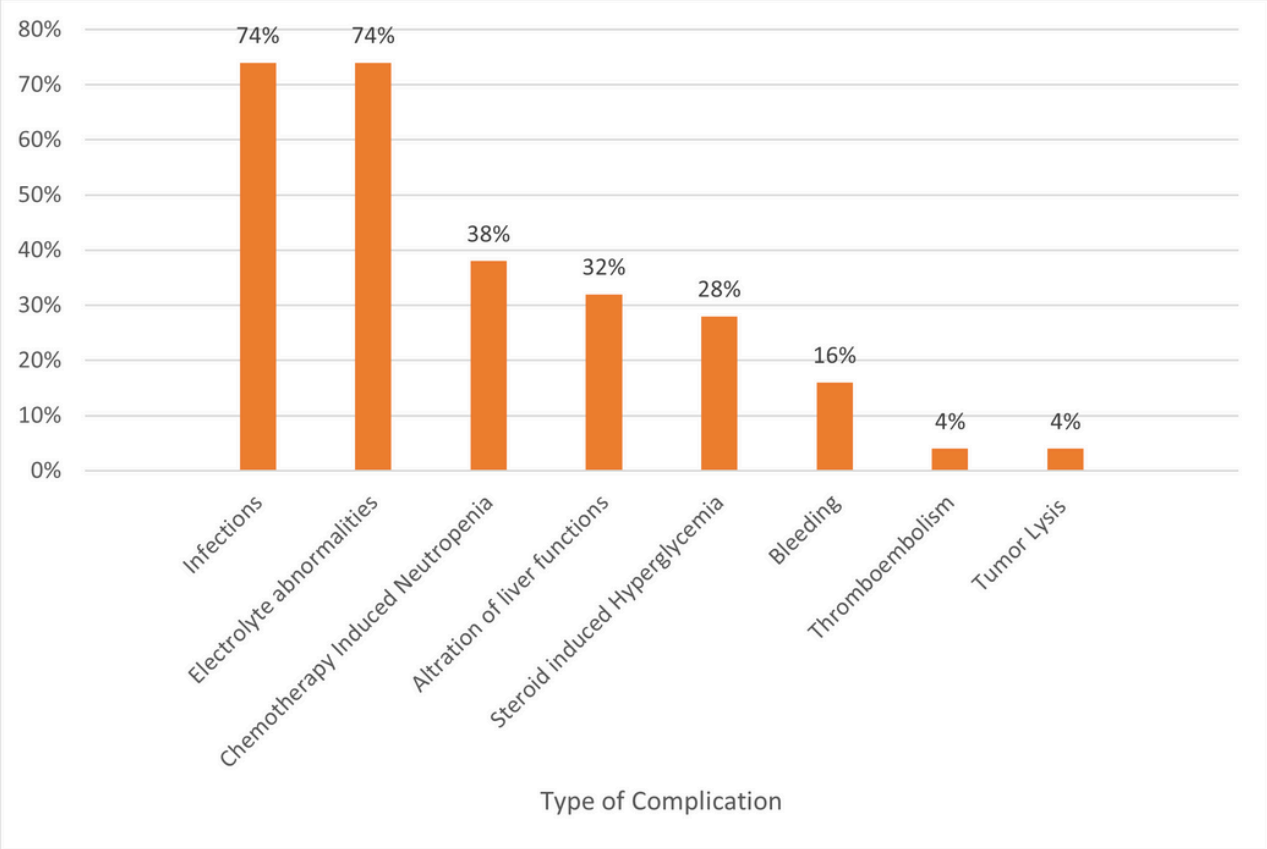

Figure 1 - Most common medical complications among the acute leukaemia patients receiving induction chemotherapy regimen. N=50

Table 1 - Focus of infection among the patients who had evidence of infection

Focus of Infection	n	percentage (%)
Bacteremia	10	27
Pulmonary	9	24.3
Unidentified	8	21.6
Soft Tissue	5	13.5
GI	2	5.4
GU	2	5.4
Multiple	1	2.7
n=37, GI - Gastrointestinal, GU - Genitourinary		

Table 2 - Microorganisms identified from blood cultures

Organism Isolated	n	percentage (%)
Gram Positive	**4**	**40**
Coagulase Negative *Staphylococcus*	2	20
Methicillin Resistant *Staphylococcus aureus* (MRSA)	1	10
Enterococci	1	10
Gram Negative	**5**	**50**
Escherichia coli	1	10
Pseudomonas aeruginosa	1	10
Not Specified	3	30
Mixed Gram positive and Gram Negative	**1**	**10**
Coagulase Negative *Staphylococcus* and Gram - Bacilli	1	10
Fungal	**0**	**0**
n=10		

Table 3 - Antibiotics used in patients with evidence of infection

Antibiotic Regimen	n	percentage (%)
Single Antibiotic	4	10.8
Beta-lactam or Cephalosporin with antipseudomonal cover+ Aminoglycoside	30	81.1
Other Combinations	3	8.1
Addition of Gram + cover	13	35.1
Addition of antifungal cover	6	16.2
n=37		

and all the reported thrombosis episodes were among ALL patients. There were no reported cases of pulmonary embolism. Bleeding events mainly comprised melaena, epistaxis or skin bruising. The two thrombotic episodes consisted of thrombosis of subclavian vein and inferior vena cava.

Discussion

This study findings highlight important medical complications of acute leukaemia patients during induction chemotherapy. neutropaenia, neutropaenia induced sepsis and disturbances in electrolyte composition are the main complications detected. These complications are mainly related to the induction chemotherapy regimen received by the patient.

There are different types of chemotherapy regimens for the patient with acute leukaemia receiving inward treatment. The first chemotherapy regimen following diagnosis is the induction chemotherapy followed by consolidation/intensification and a separate regimen for patients with relapse. The maintenance course of chemotherapy is given on an outpatient basis at clinic level. Majority of the patients receiving induction chemotherapy developed medical complications in comparison to patients receiving other regimens. Creutzig et al has also noted the complications, in particular the infections to be more common during the induction period and that neutropaenic sepsis leading to fatal infection as the main cause of death in AML patients rather than the progression of the leukaemic process.(12)

Around 74% of patients developed infections following induction chemotherapy. Other studies carried out in the same context reported similar high rates of infections.(12,13) A study by Yang et al revealed a rate of infection of 82.2% during induction therapy in acute leukaemia.(13) Lungs were the main focus of infection in several studies.(11,13) In contrast, our study showed a higher rate of bacteremia (27%) overtaking pulmonary infections (24.3%). Inadequate facilities to properly isolate patients with neutropaenia, and poor infection control methods are the likely reasons for this observation which needs to be further evaluated. In another significant proportion, the site of infection was unclear (21.6%). This can be explained by the phenomenon of "febrile neutropaenia" defined as occurrence of fever during a period of significant neutropaenia often without an identifiable source of infection.(14) The predominance of gram-negative organisms identified from blood cultures are in keeping with the results from Yang et al(13) however the fact that none of the fungal cultures were positive must be highlighted. All the patients who received

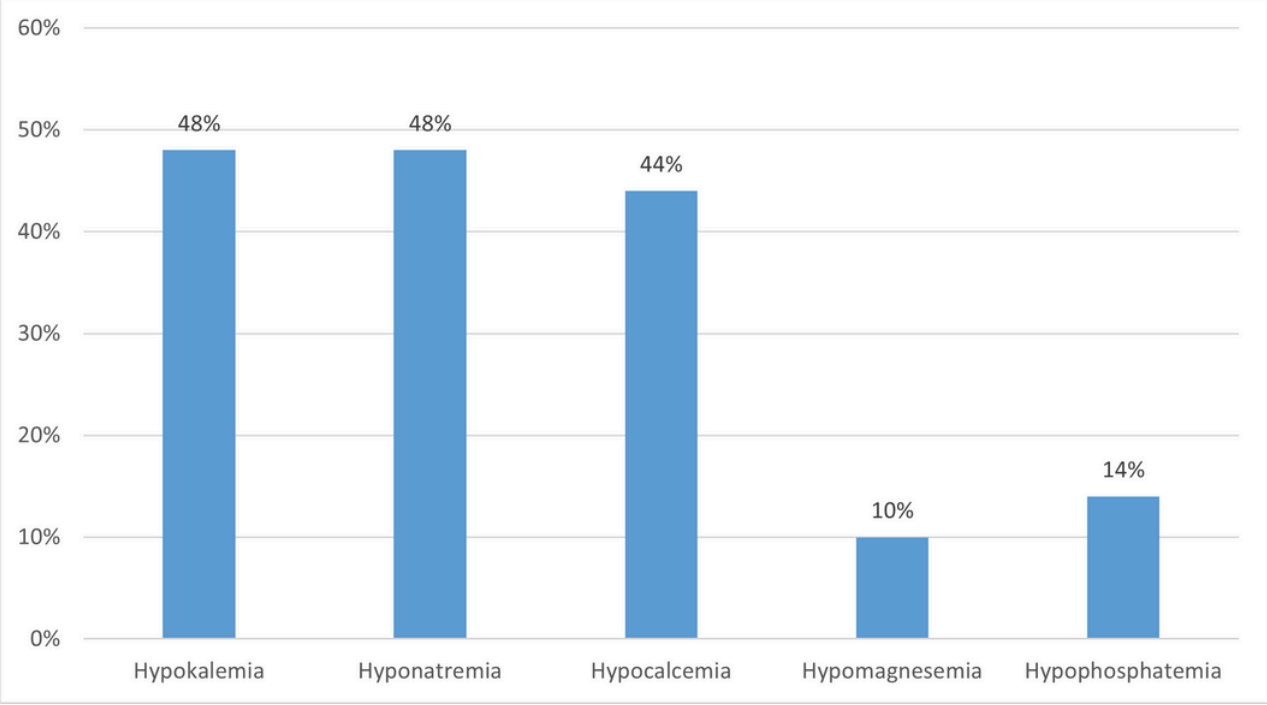

Figure 2 - Common electrolyte imbalances during induction chemotherapy. N=50

antibiotics did so either due to presence of infections or febrile neutropaenic episodes. Antibiotic prophylaxis is not used during induction chemotherapy. The decision to add gram positive cover is based on positive cultures, or clinical suspicion. Antifungal treatment is added for persistent or recurrent fevers with neutropaenia. This practice is in keeping with the 2016 National Guideline on empirical and prophylactic use of antibiotics.(15)

Neutropaenia following induction chemotherapy is a well-documented complication. In this study the reported mean duration of induction to neutrophil nadir level of 10.05 days (95% CI 7.71- 12.4) is in keeping with the study by Han et al(16) where the duration was less than or equal to ten days. However, this study did not assess the correlation between timing of neutropaenia and occurrence of infection.

The literature shows numerous electrolyte and acid-base disturbances in acute leukaemia patients.(14,15) Filippatos et al found an array of electrolyte abnormalities in the clinical setting of acute leukaemia, attributable to the disease process itself and/or to the treatment strategies.(17) Multitude of electrolyte disturbances were the focus of research by Sean O'Regan et al where pathogenesis of which was again based on the leukemic process and chemotherapy protocols.(18) The disturbances were particularly seen in relation to potassium, sodium, calcium, phosphorus and magnesium homeostasis as well as in the acid base status. In this study, hypokalaemia was most frequently observed along with hyponatraemia, hypophosphataemia, hypocalcaemia, hypomagnesaemia and acid base disturbances at lesser frequencies. Leukaemia and lysozyme induced tubular damage, cytotoxic drugs and antibiotics, syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypoalbuminaemia and malnutrition are among the numerous underlying pathogenic mechanisms. This study population exhibited a high frequency of hypokalaemia in keeping with other studies. There was also a higher incidence of hyponatraemia and hypocalcaemia. Acid base status was not routinely measured unless a disturbance was clinically suspected, hence the study failed to characterise such details.

Liver dysfunction in acute leukaemia is multifactorial. Leukaemic infiltration, drug induced liver failure (antifungals and chemotherapy) and bacterial and fungal infections are among the leading causes. The finding of altered liver functions at a high rate in ALL patients in our study is supported by Thiele et al(19) where liver infiltration was seen in >95% of ALL patients compared to only 75% in AML. The use of methotrexate in the treatment regimen of ALL is another contributory factor which was observed during the study which can explain the higher incidence in ALL patients.

Glucocorticoids are routinely used as a part of acute leukaemia treatment regimens and the finding of a significant proportion (28%) of glucocorticoid induced hyperglycaemia is well documented. According to Harris et al the reported frequency is much higher (77.8%).(20)

The thrombotic events were much less (4%) compared with other studies(21) where the rate has been around 43% in adult ALL patients. Similarly, tumour lysis syndrome (TLS) was observed less frequently. Wasim et al(22) documented a 14% incidence with a similar sample size. Further evaluation is needed in this regard to identify the contributory factors for the above observations.

Conclusion

Patients with acute leukaemia encounter a multitude of disease and treatment related medical complications during induction chemotherapy. Infection is the most common complication with higher rates of bacteraemia and gram-negative sepsis observed in this study. Higher infection rate is likely to be a result of treatment related neutropaenia. However, further focused studies on neutropaenic sepsis during induction chemotherapy are recommended to evaluate this further. Assessment of demographic characteristics and comparison of age-related mortality outcomes in the induction chemotherapy group is also recommended for future studies. Clinical vigilance, strict and improved infection control strategies are necessary to improve the outcome of these patients.

Declarations

Author contributions

UMW conceived the original study idea and contributed to research designing. UMW contributed to literature review and collected information. UMW reviewed the collected data for analysis, contributed to the data analysis and drafted the manuscript. PM guided as senior author in data analysis, preparing the manuscript and corrected the manuscript. All the authors revised and approved the final manuscript.

Conflicts of Interests

There are no conflicts of interest. All the authors declare that they have no competing interests.

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Student performance in anatomy examinations depending on the modes of learning/teaching: onsite or online

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Abstract

Introduction: Traditionally, anatomy is a subject that involves a hands-on lab-based component using embalmed cadavers and histology slides. Due to the COVID-19 pandemic there were many changes to Sri Lankan medical education. This study analysed the effect on student performance in anatomy teaching/ learning methods with the start of COVID-19 pandemic in a Sri Lankan medical faculty.

Methods: Three student groups with completely onsite (Batch A), transition to online midway through the semester (Batch B), and almost completely online (Batch C) were included. Their second-semester examination performance was analysed in total and component-wise [multiple-choice questions (MCQ), short-answer questions (SAQ) and objective-structured practical exams (OSPE I – Projections, OSPE II – Gross spot]. Descriptive analysis, Kruskal-Wallis and Dwass-Steel-Critchlow-Fligner tests were used for comparison.

Results: Allocated proportions for MCQ:SAQ:OSPE were 30:40:30. Mean MCQ marks of batches A, B, C were 14.8, 14.9, 16.4 and mean SAQ marks were 24, 25.1, 24 respectively with significant differences in both [MCQ-H(2)=29.1, p=< .001, SAQ- H(2)=11.3, p= .003). With MCQs batch C had the best performance (p=< .001), whereas batch B had better performance than batch A (p< .001) in SAQs. Mean OSPE marks were 24.8, 17.4, 20.7 with a significant difference (H(2)=334.8, p=< .001). Batch B had lower performance than batch A and C(< .001), while batch A had performed better than batch C (< .001) in OSPEs.

Conclusion: MCQ performance was better in online learners while OSPE performance, which reflects the understanding of the three dimensional structure was better in onsite learners. This highlights the value of receiving hands-on experience with cadavers and histology practicals.

Keywords: anatomy, medical education, online learning, onsite learning, cadaveric dissections

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Introduction

Learning and teaching Anatomy cannot be accomplished solely through books. Since the beginning of medical education, teaching this basic science of medicine involved cadaver-based dissections to familiarise and get hands-on experience with the human body.(1) Across various techniques of teaching and learning, this physical and practical approach remains widely used even today, as a reliable method for studying normal and variant anatomy and understanding the three-dimensional structure and relationships of the human body.(2,3) This hands-on experience is either a whole-body dissection or faculty-guided demonstrations on prosected cadavers. Either way, they both have heavy in-person interactions.(1) However, due to the reduced availability of donated cadavers and the higher intake of students to the faculties, anatomy education with cadaver dissection has been greatly reduced.(4) With the advancement of technology and newer technical tools, the way of anatomy teaching and learning is constantly changing and we can find many medical schools that have replaced cadaver dissection with a digital experience partially or completely.(1) These newer tools (e.g., virtual models of the human body/virtual anatomy table, 3D printing, dissection software programmes) can aid the perception of knowledge from different viewpoints as well as facilitate understanding of the three-dimensional structure of the human body, although expensive.(3,4)

In the literature, six methods/techniques of anatomy education have been mentioned: in-person lectures, cadaveric dissection, inspection of prosected specimens, using models, living and radiological anatomy teaching, and computer-based learning that includes recorded lectures, videos, audio and anatomy software.(2,4) These can further be classified as onsite/face-to-face, blended, and online teaching models. In onsite education, students are present in a classroom/ lecture hall/ laboratory and experience learning on the site while a teacher/instructor teaches/guides them through the study materials. In online education, learning occurs via online platforms such as Moodle, Zoom, etc. Blended learning involves both onsite and online teaching/learning activities.(5)

General evaluation of anatomy knowledge is by several types of assessments: theory knowledge by written examinations based on multiple choice questions (MCQ)/ single best answer type questions (SBA), short answer questions (SAQ), or essays while practical/clinical application of this core knowledge is tested by oral examination (VIVA), spot tests, objective structured practical examinations (OSPE), or objective structured clinical examinations (OSCE).(6) These evaluation domains are in line with the first and second tiers of Miller's pyramid (first tier - knowledge tested by written exams and MCQs, second tier - application of knowledge assessed by essays, clinical problem-solving exercises and extended MCQs) that was introduced for the assessment of clinical competency by George Miller in 1990.(7)

Novel coronavirus or COVID-19 started as an outbreak in Wuhan City, China in December 2019 and soon spread into a worldwide pandemic to affect every socio-economic level and had a great impact on the education systems of the world.(8) Sri Lanka, as a low-middle income country faced many difficulties. The transformation caused by the COVID-19 pandemic across the globe affected almost all educational institutes including universities which rapidly converted to online delivery of education and assessments. The situation provided an opportunity to modify and design the future anatomy curriculum and its delivery(1,3) and this was the case for other subjects in Sri Lankan schools and universities.

Although several studies in Sri Lanka assess the student practices, perception and attitudes towards online learning, to the best of our knowledge student performance depending on the mode of learning has not been previously evaluated in the country.(9-11)
The main objective of this study was to compare the total and differential marks obtained for different components of one module of the anatomy examination (MCQ, SAQ and OSPEs) among three batches that had different modes of teaching/learning methods as completely onsite (Batch A), transition to online mid semester (Batch B) and almost completely online (Batch C).

Methods

This was a descriptive cross-sectional study that involved the anatomy marks of three batches of first-year medical students at the same university in Sri Lanka. We used year 1 semester 2 examination marks that were held at the end of the thorax-abdomen module. The three batches were named Batch A (completely onsite learning before the pandemic), Batch B (transitioned to online learning mid-semester), and Batch C (completely online learning with two weeks of expedited onsite practicals).

The total population of the three batches that faced

the end-semester examination for the module on thorax and abdomen was included and the students who failed to face the examination were excluded. After applying inclusion and exclusion criteria Batch A had 205 students, Batch B had 204 students, and Batch C had 241 students.

Ethical approval was obtained from the Ethical Review Committee, Faculty of Medicine, University of Peradeniya (ERC no: 2023/EC/63). Statistical analysis was done with the Jamovi (version 2.3) Computer Software. Descriptive analysis included mean, standard deviation, and minimum and maximum values. Mean marks obtained by batches A, B, and C for components of MCQ, SAQ, and OSPE I and II including projections and cadaver-based spots were compared using the non-parametric Kruskal-Wallis test as the Shapiro-Wilks normality test was not fulfilled by each of the groups ($p<0.05$). The Dwass-Steel-Critchlow-Fligner (DSCF) test was used for the pairwise comparison of the groups.

Results

Proportions of marks allocated for MCQ:SAQ:OSPE in this module examination were 30:40:30. Mean MCQ marks were 14.8 (SD ±3.29) , 14.9 (SD ±3.22), and 16.4 (SD ±4.19) , mean SAQ marks were 24.0 (SD ±3.88) , 25.1 (SD ±5.15), and 24.0 (SD ±5.56) and mean OSPE marks were 24.8 (SD ±3.18), 17.4 (SD ±3.05), and 20.7 (SD ±3.66) for batch A,B,C respectively. Mean total marks for batch A,B,C were 63.4 (SD ±8.95), 57.3 (SD ± 9.96), and 61.0 (SD ±12) Full descriptive analysis of the marks is shown in table 1.

Detailed analysis for comparison of the different components of the examination using Kruskall-Wallis test and DSCF pairwise comparison of marks among three batches are shown in tables 2 and 3 respectively. Accordingly, the mean MCQ marks of batches A, B, C showed a significant difference ($H(2)=29.1$, $p=< .001$), with batch C showing the best performance ($p=< .001$), and batch B had better performance compared to batch A although statistically not significant ($p= .886$). Mean SAQ marks also showed a significant difference ($H(2)=11.3$, $p= .003$), and here batch B had better performance than batch A ($p< .001$) and batch C ($p= .126$). Mean OSPE marks also showed a significant difference ($H(2)=334.8$, $p=< .001$), where batch B had significantly lower performance than batch A and C($< .001$), while batch A had performed better than batch B and C ($< .001$).

Discussion

As mentioned earlier, anatomy education has evolved from full on-site teaching-learning domain to blended learning during the past few decades. This change accelerated with the effects of COVID-19 pandemic, including the temporary lockdown of countries as per government regulations and the implementation of policies on physical distancing. The closure of educational institutes in response to the pandemic led to the use of online modes which were adapted in Sri Lanka as well.(8-10) The teaching and learning process continued through online platforms including evaluation where applicable.

Challenges during COVID-19 pandemic faced by Sri Lankan universities

COVID-19 pandemic necessitated the conversion of universities in Sri Lanka to the online format of teaching/learning with the rest of the world . Traditional medical education in the medical faculties

Table 1 - Descriptive analysis of MCQ, SAQ, OSPE and total marks of three batches

	MCQ			SAQ			OSPE			Total		
	A	B	C	A	B	C	A	B	C	A	B	C
N	203	208	245	203	208	245	203	208	245	203	208	245
Mean	14.8	14.9	16.4	24.0	25.1	24.0	24.8	17.4	20.7	63.4	57.3	61.0
SD	3.29	3.22	4.19	3.88	5.15	5.56	3.18	3.05	3.66	8.95	9.96	12.0
Minimum	7.00	5.00	3.00	8.00	0.00	3.00	6.00	0.00	6.00	23.0	7.00	12.0
Maximum	22.0	24.0	25.0	32.0	34.0	33.0	31.0	23.0	27.0	82.0	76.0	83.0

MCQ - multiple-choice questions, SAQ - short-answer questions, OSPE - objective-structured practical exams, N – number of students, SD – standard deviation

Table 2 - Kruskall-Wallis comparison of different components of the examination

Component	χ^2	df	p
MCQ	29.1	2	< .001
SAQ	11.3	2	0.003
OSPE	334.8	2	< .001
Total	**39.9**	**2**	**< .001**

MCQ - multiple-choice questions, SAQ - short-answer questions, OSPE - objective-structured practical examinations

Table 3 - Dwass-Steel-Critchlow-Fligner pairwise comparison of marks among three batches

Batch	MCQ (W, p)	SAQ (W, p)	OSPE (W, p)
A - B	0.664, .886	4.91, .001	-23.3, < .001
A - C	6.636, < .001	1.85, .389	-16.2, < .001
B - C	6.345, < .001	-2.75, .126	15.3, < .001

MCQ - multiple-choice questions, SAQ - short-answer questions, OSPE - objective-structured practical examinations

in Sri Lanka was based on onsite teaching and learning that expanded over a 5 - 5 ½ years including clinical and skill based exposure at skill laboratories and teaching hospitals. This is more so with the subject of anatomy in the first 1 ½ years. Onsite learning and group work aid the students with their leadership qualities, skills, attitudes, teamwork and professional development in addition to core subject knowledge.(8)

With the conversion, the academic staff adapted to online education. The particular medical faculty where the current study was done, anatomy educators used online real time and recorded lectures, videos, 3D animations, and explanatory videos of prosected specimens to teach anatomy to the students. Traditional tutorials were transformed into online tutorials where the students and the lecturer discuss the basic anatomy and related clinical components of the questions. Educators switched to distant learning platforms such as Zoom, Learning Management Systems (LMS), Whatsapp groups, Google classroom and Moodle to connect with students and upload the learning materials.

Lower economic status, which aggravated during the COVID-19 pandemic, poor internet connectivity especially in certain geographical locations in the country, lack of access to devices, disruptions to the academic calendar, and lack of opportunities for professional development were problems that students of higher educational institutions in healthcare encountered faced during online learning.(8-11) Furthermore, regarding online anatomy learning during the pandemic, the lack of onsite practicals, diminished socialization and lack of self-motivation had a significant impact on medical students.(9)

The effect of this change on student performance in Sri Lankan universities has not been studied up to now. The unexpected but valuable experience obtained through the unavoidable shift to online methods of teaching/learning provides useful insights into the effective use of these modalities in the future.

Online medical education

Online education can be asynchronous; where the transmission and receipt of information do not coincide (e.g., pre-recorded lectures, videos), synchronous; where all learners receive information simultaneously and communicate directly with each other (e.g., teleconferencing, instant messaging, internet chat forums) or hybrid, where there is a mix of asynchronous and synchronous learning. An online hybrid curriculum can offer a rich learning experience as it incorporates the best features of both learning modalities.(1) An educational intervention conducted

using the online platforms, in the field of surgery involving 1st year medical undergraduates up to postgraduate trainees in Sri Lanka received favourable feedback from the students(10), proving that online mode could provide useful in medical education. However, studies on student perception on converting to online anatomy learning during the COVID-19 pandemic reveal that although the overall attitude towards online learning was positive, most believe online education cannot completely replace the onsite mode, particularly when it comes to practical and clinical based components.(3,9,12) It should also be noted that medical students face several problems during the use of e-learning modalities such as, barriers to free access of material, internet related expenses and connection issues, distractions while using online resources, and inadequacy of storage space in devices.(11)

Assessment modalities in anatomy education

The assessment of anatomy knowledge in medical education includes evaluating theoretical and practical aspects. For theory, assessment modalities include multiple-choice questions (MCQ), and short answer questions (SAQ). The practical component involves cadaver-based spots, objective structured practical examinations (OSPEs), and oral examinations.(6)

A systematic review evaluating academic performance on anatomy between online and face-to-face teaching revealed no statistical difference between the two teaching methods, although a higher level of student satisfaction with face-to-face teaching was observed.(2)

Selected module and examination

This study looks at the differences in the student performance in the anatomy module of thorax and abdomen among three groups of students; those who had completely onsite learning before the pandemic, the students who had transitioned to online learning midway through the semester, and those who had completely online learning with only two weeks of sped up onsite practical sessions. Regardless of the mode of conduct of the course, the examination in this particular module was held physically at the faculty premises. So the students had to complete all the components of the examination in a similar manner.

When we look at the results obtained by these three batches who did the learning part in three different modes, Batch C, which had completely online learning, had the best performance (p=< .001) when it comes to MCQs. When considering SAQ marks, batch B, which had a transition from onsite to online mode had better performance than batch A (p< .001). Batch A, that had completely onsite education had the best performance when considering the OSPE component (< .001) while batch B had significantly lower performance compared to batches A and C (< .001). The performance varies across the components of the examination. The OSPE component was best performed by those who did onsite teaching/ learning activities. OSPEs are based on dissections and histology practicals. Those who had hands-on experience in the dissection room and practical classes did better with specimens at examinations. They have participated in small dissection group discussions, mock OSPEs, and bodyside tutorials during their dissection time which the complete online teaching/ learning group has missed. On the other hand, MCQ performance was best among those who did online teaching/ learning. Since they had very limited time with specimens, they may have invested greater time in studying books which must have aided with better performance in MCQs.

Similar to our study, Chang et al. in 2021, had evaluated student performance in lecture (theory) and laboratory (practical) components of anatomy examinations of two groups; one unaffected by COVID-19 and the other which faced the transition to modified learning during the pandemic . They showed a significant decrease in the performance in the laboratory component during the transition period compared to the unaffected group, although their performance had comparatively improved during the following examination.(13)

While not considering the different examination components, other studies on the comparison of onsite vs online anatomy education have shown a better student performance with online or hybrid education although their assessments were also conducted using online platforms in contrast to our study.(14,15) But in another study where students' perceptions were recorded regarding their academic performance before (onsite teaching) and during (online teaching) the pandemic, the numbers indicated their grades being higher, same or lower were equal even though the method of assessment was not mentioned.(16)

A systematic review on the COVID-19 pandemic and its effects on anatomy education state that cadaver dissection extends beyond just learning the human morphology and involves the touches, incisions, hands-on-skills and complex 3D-dimensional

structure understanding which is rather difficult through only online resources.(3)

However, highlighting the importance of adapting to newer technology while following traditional methods, a randomised-controlled trial comparing remote and onsite learning/teaching have found that both onsite team teaching and well-prepared recorded video teaching (vodcast) promotes better learning among medical and nursing students effectively, according to the participants' test result analysis.(16,17)

Conclusions and recommendations

The best MCQ performance observed among those who had mostly online learning shows that the use of digital resources could benefit the students. However, as a subject like anatomy is mainly based on the understanding of the three-dimensional structure, the best performance in the OSPEs among those who had completely onsite learning, suggests that hands-on experience may help to understand the subject in further depth. Moving forward, the integration of online activities while continuing the onsite methods are likely to lead to the improvement of teaching and learning anatomy among university students.

Limitations

As this study was done using the marks available, we didn't analyse the other factors that may have affected the teaching/ learning mode such as the quality of internet connection and availability of devices concerning Batch C and the number of students per dissection group in Batch A. The theory papers were scrutinised at the department and faculty level; however, difficulty indices were not calculated for each examination paper. The students were selected to the medical faculty based on their z-score at advanced level examination (bio science stream) and the cut off values lie within a more or less similar narrow range every year, but we didn't compare those values among the three student groups. These are the key drawbacks of this study.

Declarations

Author contributions
All authors contributed to the conceptualization and design of the study. MJSJ, EWK, RG, SR, BR, MK, and NY contributed to the acquisition of data. MW and EWK conducted the data analysis. MJSJ, EWK, RG and MW contributed to data interpretation and writing the manuscript. All authors read and approved the final manuscript.

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Prevalence and characteristics of chronic kidney disease in patients attending the nephrology clinics of the National Hospital of Sri Lanka: a cross-sectional study

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Abstract

Introduction: Chronic kidney disease (CKD) has become a major health concern on a global scale, and its impact is also significant in Sri Lanka. Diabetes mellitus and hypertension are identified as the main causes of CKD in Sri Lanka. Chronic kidney disease of unknown origin (CKDu) has undeniably surfaced as a substantial factor in the prevalence of CKD in recent decades, notably in specific geographic areas worldwide.

Methods: Over a course of three months, a descriptive cross-sectional study was carried out at the outpatient clinics of the National Hospital of Sri Lanka to describe the socio-demographic factors related to CKD and to understand the aetiological factors of the disease within CKD patients attending the clinics.

Results: The study involved 387 CKD patients, with an average age of 53 years. Males accounted for 62.8%. Of total participants, CKD Stage V with or without regular dialysis consisted of 26.5% and transplant patients consisted of 26.8%. Most (88.1%) patients were from the western province while 11.9% were from other provinces. The prevalence of CKD secondary to diabetes mellitus was 35.9% followed by hypertensive kidney disease (31.3%). The most common aetiology for CKD in the western province was diabetes mellitus (37.2%) followed by hypertension (31.5%). The prevalence of CKDu was 7.9% in the western province and 13.0 % in other regions. Diabetes mellitus ($p < .001$) and glomerulonephritis ($p < .001$) were significantly associated with age groups above and below 40 years.

Conclusion: This study highlights diabetes and hypertension as the predominant causes of CKD among patients in both the western province and other provinces of Sri Lanka. It also highlights the heightened prevalence of hypertensive kidney disease in the young population compared to previous studies.

Keywords: chronic kidney disease, chronic kidney disease of unknown origin, prevalence, aetiology

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Introduction

Chronic kidney disease (CKD), recognised as a burgeoning health concern globally due to its significant morbidity and mortality rates, is defined as structural or functional abnormalities in the kidneys lasting more than three months, with implications on one's health.(1) Within the current health dynamics and disease patterns, the prevalence of CKD has been increasing dramatically over the world. Based on recent statistics, the global prevalence of CKD stood at 9·1%, equivalent to approximately 700 million cases in the year 2017. Regrettably, this is a notable increase in the prevalence of CKD by 29.3% compared to the CKD prevalence in 1990.(2) Moreover, 1·2 million people had died from CKD, making it the 12th leading cause of death in the year 2017.(3)

There has also been an analogous increase in the incidence of CKD in the population in Sri Lanka. The background factors for this increase are diverse and highly heterogeneous and can be attributable to the increase in non-communicable diseases like diabetes mellitus and hypertension and the high incidence of CKD of unknown origin (CKDu) in certain areas of the country.(4) The overall outcome of this increase has been detrimental to the health care system in Sri Lanka, with the increasing demand for dialysis requirements as well as the medical management of the disease condition and its complications.

Despite extensive research in other countries related to sociodemographic factors and aetiological backgrounds of CKD, to date, in Sri Lanka, there is a paucity of studies dealing with those. Most of the Sri Lankan studies involved patients with CKD above stage III. Most available studies in Sri Lanka were conducted in the North Central region, where the CKDu is prevalent. In areas where CKDu is not prevalent, diabetes and hypertension emerge as the leading causes of CKD. Soon after the liberation of northern and eastern territories from the civil war, there was dissemination of the population to the western and central provinces to seek better specialised medical care. However, lately, more facilities for CKD patients were established in the major hospitals in the North Central province. Hence, the epidemiology of CKD is undergoing transformation in both CKDu and non-CKDu regions. To effectively address the increased incidence of CKD, it is important to have a clear picture of the sociodemographic variations and the aetiological factors linked to CKD. Therefore, to establish the grounds for early detection and prevention, identifying these antecedents will be of enormous value. Hence, there is a timely requirement for further studies to investigate more into the sociodemographic and aetiological factors of CKD to establish the trends and associations.

Methods

A hospital based, descriptive, cross-sectional survey was conducted among patients attending outpatient nephrology clinics at the National Hospital of Sri Lanka over a period of 3 months after their consent. The formula used to calculate the sample size is as follows:

$$n = \left(\frac{(z_{\alpha/2})(\sigma)}{E}\right)^2$$

Data was collected through an interviewer-administered questionnaire. The sources of data included patient interviews, diagnosis cards, clinic records, imaging reports and biopsy reports.

The probable aetiology of CKD was made according to the following criteria:

Diabetes was established as the cause of CKD if a patient had clinically and biochemically confirmed diabetes mellitus with either a prolonged duration of diabetes preceding the onset of CKD (minimum of five years) or the presence of diabetic retinopathy in the absence of indicators for any other aetiology.

In the absence of indicators for any other aetiologies, hypertension was regarded as the presumptive cause if a patient with CKD had hypertension associated with any of the following criteria: a long duration of hypertension (at least five years), presence of concentric left ventricular hypertrophy in the echocardiography, or the presence of hypertensive retinopathy at the time of CKD diagnosis. The diagnosis of glomerulonephritis was established based on the findings from renal biopsy.

CKDu was determined as the presumptive diagnosis based on the following criteria(16): when eGFR is less than 60 mL/min/1.7m^2, or when albuminuria is equal to or greater than 30 mg/g creatinine, or when proteinuria is equal to or greater than 150 mg/g creatinine. Exclusion criteria included a urine protein to creatinine ratio exceeding 3000 mg/g creatinine, patients with diabetes mellitus, patients with hypertension, those who experienced acute kidney injury necessitating dialysis, individuals over the age of 70 years, and the presence of clinical, laboratory, or ultrasound evidence indicating other known causes of CKD. Renal imaging and renal biopsy

reports were utilised in identification of other aetiologies.

The stage of CKD was determined by evaluating the estimated glomerular filtration rate (eGFR) in accordance with the KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease.(1) The eGFR was computed using the abbreviated modification of diet in renal disease (MDRD) equation.(10)

The distribution of sociodemographic characteristics of CKD patients has been presented as frequencies and percentages. The association between the aetiology of CKD and patient groups was evaluated using the chi-square test. A p-value of less than .05 was considered statistically significant.

Results

Out of the desired sample size of 427 only 387 responded to the study instrument yielding a response rate of 90.8%. The mean age of the study sample was 53 years with males comprising the majority at 62.8% (M: F=1.7:1).

Table 1 presents an overview of the various demographic factors of the study sample. In terms of gender distribution, males constituted a higher proportion at 62.8%. Most participants identified as Sinhalese with a significant minority being Sri Lankan Tamils. The majority of the participants were married accounting for 89.0% of the sample.

Most of the participants (88.1%) of this study resided in the Western Province.

Most patients (26.8%) were transplant patients, followed by Stage V with and without regular dialysis, I, II, IIIA, IV, IIIB (26.5%, 13.5%, 11.9%, 8.3%, 8.1%, 4.9%) respectively.

There was no family history of CKD in the majority which accounted for 323(84.6%) individuals. However, 59(15.4%) individuals reported a family history of CKD, predominantly affecting the 1st degree relatives.

Table 2 outlines the lifestyle factors associated with CKD. The majority were non-smokers (90.6%), with 9.4% reporting a significant smoking history of more than 10 pack years. Similarly, the majority did not consume alcohol, although 10.5% reported heavy alcohol consumption.

In terms of weight status, the majority, (61.5%), had normal weight, while a noteworthy minority were overweight (18.8%) and obese (6.4%).

Table 3 depicts the aetiological factors contributing to CKD. Diabetic nephropathy emerged as the most (35.9%) prevalent contributing factor, followed by hypertensive kidney disease (31.3%) . CKDu was the third most prevalent cause for CKD in the study population (8.5%).

Table 4 presents associations between the age and the aetiological factors of CKD. Diabetic nephropathy, glomerulonephritis and other hereditary nephropathies demonstrated a statistically significant association with age.

Table 5 depicts the comparison of aetiological factors of CKD between patients from the western province and elsewhere. Only chronic pyelonephritis showed a statistically significant difference with residence in the western province (p = .005).

Discussion

The increasing prevalence of CKD in Sri Lanka indeed presents a significant public health challenge, often described as reaching epidemic proportions.

Regarding sociodemographic factors associated with CKD, in our study, the mean age of the study population was 53 years, with males comprising the majority at 62.8% (M:F=1.7:1). This observation aligns with findings from a study conducted at the National Hospital of Sri Lanka in 2011, which revealed a mean age of 50.57 years with a male to female ratio of 2.1:1.(4).

In terms of educational levels, the highest reached by participants was passing the ordinary level examination, which was 45.1%. This is contrary to the findings of the research conducted by Lowe et al., in Kebithigollewa, where only 23.33% have passed ordinary level examination.(11) This difference can be well explained by the regional disparity of educational resources and inequality of economic distribution of the provinces.

The majority of patients (39%) had a monthly income of 25,000 Sri Lankan Rupees or less, underscoring the prevalence of disease in the low socioeconomic group. This is further solidified by the study conducted in Kebithigollewa by Lowe et al, where 46.67% had a monthly income of less than 10000 Sri Lankan Rupees.(11)

The study conducted in the North Central Province of

Table 1 - Socio-demography of the study population

Socio-demographic variable	n (%)
Gender	
Male	243 (62.8)
Female	144 (37.2)
Ethnicity	
Sinhala	317 (83.6)
Sri Lankan Tamil	39 (10.3)
Moor	21 (5.5)
Other	2 (0.5)
Marital status	
Married	341 (89.0)
Unmarried	32 (8.4)
Widowed	10 (2.6)
Education level	
Never had school education	4 (1.0)
Grade 01 to Grade 05	19 (4.9)
Grade 06 to Grade 11	69 (18.0)
Passed O/L	173 (45.1)
Passed A/L	94 (24.5)
Higher education up to diploma	7 (1.8)
Higher education up to degree and above	18 (4.7)
Monthly income	
Less than Rs 25000	149 (39.0)
Rs 25001 to Rs 35000	91 (23.8)
Rs 35001 to Rs 50000	81 (21.2)
Rs 50001 to Rs 80000	43 (11.3)
More than Rs 80000	18 (4.7)
Province of residence	
Western Province	341 (88.1)
Southern Province	5 (1.3)
Sabaragamuwa Province	17 (4.4)
Central Province	4 (1.0)
North western Province	14 (3.6)
North central Province	2 (0.5)
Eastern Province	4 (1.1)

Table 2 - Lifestyle factors related to chronic kidney disease of the study population

Lifestyle factors of patients with CKD	n (%)
Significant Smoking history (>10 pack year history)	
Yes	36 (9.4)
No	348 (90.6)
Heavy alcohol consumption (>14 units per week)	
Yes	40 (10.5)
No	341 (89.5)
BMI	
Underweight (≤18.5 kg/m^2)	50 (13.3)
Normal weight (>18.5≤25 kg/m^2)	232 (61.5)
Overweight (>25≤30 kg/m^2)	71 (18.8)
Obesity (>30 kg/m^2)	24 (6.4)

Table 3 - The frequencies of aetiological factors of chronic kidney disease in the study population

Aetiologies of chronic kidney disease	n (%)
Chronic pyelonephritis	14 (3.6)
CKDu	33 (8.5)
Diabetes mellitus	139 (35.9)
Glomerulonephritis	7 (1.8)
Hypertension	121 (31.3)
Miscellaneous	30 (7.8)
Obstructive nephropathy	7 (1.8)
Other hereditary nephropathies	26 (6.7)
Polycystic kidney disease	10 (2.6)
Total	387 (100)

Sri Lanka in 2019 revealed that the majority of CKDu patients were at stage IV (40%), with 31.8% and 24.5% in stages III and V, respectively.(6) The study conducted at the National Hospital of Sri Lanka by Wijewickrema et al. in 2011 revealed 54% of CKD stage V, 21% of CKD IV and 13% of CKD III. In the current study, most were post transplant patients (26.8%) while 26.5% were in CKD V with or without regular haemodialysis. Transplant patients attending to the dedicated post kidney transplant clinic at the national Hospital of Sri Lanka were enrolled into this study. Therefore, the proportion of transplant patients was comparatively higher. Unlike many studies in Sri Lanka that typically focused on patients with advanced CKD (beyond stage III), this research encompassed individuals across all stages of chronic kidney disease.(4,16) This broader inclusion allowed capturing patients with significant proteinuria with normal eGFR secondary to diabetes mellitus, and other glomerulopathies.

The study revealed a positive family history of CKD in

Table 4 - Association of the aetiology of chronic kidney disease with age groups

Aetiological factors	Age		p
	< 40 n (%)	≥ 40 n (%)	
Chronic pyelonephritis	3 (4.7)	11 (3.4)	0.71**
CKDu	7(10.9)	26(8.0)	0.450
Diabetes mellitus	6 (9.4)	133 (41.2)	<0.001
Glomerulonephritis	7 (10.9)	0 (0.0)	<0.001
Hypertension	20 (31.3)	101 (31.3)	0.99
Miscellaneous	8 (12.5)	22 (6.8)	0.12
Obstructive nephropathy	3 (4.7)	4 (1.2)	0.09**
Other hereditary nephropathies	8 (12.5)	18 (5.6)	0.04
Polycystic kidney disease	2 (3.1)	8 (2.5)	0.67**
Total	64 (16.5)	323 (83.5)	

Table 5 - Comparison of aetiology of chronic kidney disease between the western province and other provinces

Aetiologies	Province		p
	Western Province n (%)	Outside Western Province n (%)	
Chronic pyelonephritis	9 (2.6)	5 (10.9)	0.005
CKDu	27(7.9)	6(13.0)	0.243
Diabetes mellitus	127 (37.2)	12 (26.1)	0.139
Glomerulonephritis	6 (1.8)	1 (2.2)	0.591**
Hypertension	107 (31.5)	14 (30.4)	0.897
Miscellaneous	27 (7.9)	3 (6.5)	1.000**
Obstructive nephropathy	6 (1.8)	1 (2.2)	0.591**
Other hereditary nephropathies	23(6.7)	3 (6.5)	1.000**
Polycystic kidney disease	9 (2.6)	1 (2.2)	1.000**
Total	341 (88.1)	46 (11.9)	

15.4%. Out of them, 91.4% are first degree relatives. The study conducted by Lowe et al. in Kebithigollewa, which involved mainly CKDu patients, showed a strong family history of 60% among family members. (11) The strongly positive family history in Kebithigollewa suggests the possibility of genetic influences or shared exposure to common aetiological agents within family groups. In the current study, the positive family history can be mainly attributed to the familial preponderance of diabetes mellitus, hypertension, and hereditary nephropathies.

Smoking has been identified as a risk factor for CKD. A study by Sangmi et al. revealed that a longer duration of smoking was associated with a higher risk

of CKD progression.(12) Similarly, a retrospective case-control study among non-diabetic subjects has found that smoking more than 20 cigarettes per day was associated with an increased risk of chronic kidney disease.(13) A meta-analysis further supported these findings, indicating that both former and current smokers had increased odds of developing CKD.(8) In the current study sample, a notable minority, comprising 9.4%, reported significant smoking habits.

The effect of obesity on CKD has been highlighted by numerous studies in many countries. Ejerblad et al., discovered that people who were overweight at the age of 20 had a notable three-fold increase in the risk of chronic kidney disease compared to individuals with a BMI of less than 25.(7). The study conducted by Senevirathna et al. in Medawachchiya in 2011 unveiled a notable proportion of CKD patients in that cohort who were underweight.(14) This is consistent with the fact that the majority of patients in that study were from a low socioeconomic farming community. In contrast with Senevirathna et al. study, Lowe et al. study conducted in Kebithigollewa, revealed a majority in their study population was overweight.(11) Current study revealed that the majority (61.5%) of the study population was within normal weight and 6.4% are obese. This highlights the potential association of geographical and socioeconomic variation of prevalence of obesity and the composition of aetiology of CKD.

Diabetes and hypertension stand out as two of the most prevalent aetiological contributors to CKD in Sri Lanka in line with other Asian countries.(15) The epidemiology of the current study can be compared with two similar studies done at the National Hospital of Sri Lanka by Gooneratne et al. in 2006 and Wijewickrema et al. in 2011.(16,4) In all three studies the leading cause of CKD was diabetic nephropathy followed by hypertension. Hypertensive kidney disease has nearly doubled from Wijewickrema et al. study conducted in 2011 .

Only chronic pyelonephritis showed statistical significance with residence in the western province, with a p value of .005. However, diabetes and hypertension were the most prevalent leading causes of CKD in patients from both the western province and other regions. This underscores the increasing prevalence of diabetes and hypertension in both the western province and other provinces.

The difference in prevalence of CKDu in the western province as opposed to other regions did not show any statistical significance. The total prevalence of CKDu in the current population was only 8.5%, which was lower than the previous two studies conducted at the same institute (25.6% and 9.5%). The main reason for this could have been that the majority (88.1%) of the study population were from the western province compared to the two previous studies (Western province to elsewhere ratio of 7.4:1 (current study) vs 2.2:1 vs 1.4:1).

In the current study, the most common cause for CKD in patients younger than 40 years was hypertension (31.3%) followed by hereditary nephropathies (12.5%) and glomerulonephritis (10.9%). This contrasts with Wijewickrema et al. study, where glomerulonephritis was the commonest cause of CKD (42.6%) in patients younger than 40 years of age.(4) A few factors could have contributed to this difference. Firstly, the increased prevalence of hypertension in Sri Lanka according to Rannan-Eliya et al. study, which concluded that nearly one in three Sri Lankan adults have hypertension requiring treatment.(17) Secondly, CKD would have been diagnosed in some young patients when they were investigated for secondary hypertension. The probable origin of CKD might trace back to an unnoticed renal injury during childhood, complicating the investigation into its cause, especially when CKD has already progressed significantly. Additionally, there are limited indications for a renal biopsy due to its high complication rates.(18) Therefore, aetiology for most young patients' CKD would have been labelled as hypertension, without further investigations. Thirdly, the current study enrolled patients with all stages of CKD, which identified early stages of hypertensive kidney disease in a relatively young population. Furthermore, it's essential to recognize that certain aetiological factors, such as diabetes mellitus (p=< .001), glomerulonephritis (p=< .001), and other hereditary nephropathies (p= .045), are significantly associated with age groups above and below 40 years. This finding further strengthens the conclusions drawn in the study conducted by Wijewickrema et al. It adds additional support to the previously reported results, reinforcing the consistency and reliability of the findings across different studies.

Limitations

The scope of the study was confined to a single centre , and it was conducted during the peak of the COVID-19 pandemic, a time when patient clinic attendance was affected due to safety concerns and restrictions. Therefore, the study might have overlooked CKD patients who did not actively seek medical attention, thus limiting the comprehensive

understanding of the condition within the population. Pandemic could have influenced the study results by several other ways such as changing risk factors, socioeconomic factors and worsening health conditions due to severe COVID infection.

The study was limited to a short duration of three months and relied on a relatively small sample size. This constraint may have implications for the generalisability of the study findings. This is a cross-sectional study, which comes with several inherent limitations, such as limited causality and temporal ambiguity.

Conclusion

This study highlights diabetes and hypertension as the predominant causes of CKD among patients attending the Nephrology clinics at NHSL.

Moreover, the study sheds light on the heightened prevalence of hypertensive kidney disease in the young population compared to previous studies.

Recommendations

The findings of the current study emphasise the significant impact of diabetes and hypertension on renal health in the population. Addressing the prevention, early detection, and management of diabetes and hypertension is crucial in mitigating the burden of CKD and improving overall public health outcomes in the population. Further research and targeted interventions are warranted to effectively address the challenges posed by these leading aetiological factors of CKD in Sri Lanka.

To gain a comprehensive understanding of the true burden of chronic kidney disease in Sri Lanka, larger multicenter studies involving units caring for CKD patients in both CKD-u and non-CKD-u provinces are imperative. These studies would allow for a thorough assessment of the prevalence, distribution, and aetiological factors contributing to CKD across diverse regions of the country. Furthermore, this study highlights the importance of establishing renal registries in Sri Lanka which can typically collect and analyse data on patients with CKD, end-stage renal disease (ESRD), and those undergoing renal replacement therapy (RRT) such as dialysis or kidney transplantation.

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Deprescribing in an outpatient medical clinic at a tertiary care hospital in Sri Lanka

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Abstract

Introduction: Use of multiple concomitant medications or 'polypharmacy' is linked to decreased medication adherence, adverse drug reactions and increased financial burden on patients and the economy. Deprescribing by experienced healthcare personnel can ensure safe and effective use of medications. Many medications, prescribed during hospital stay or at clinic level are continued for unnecessarily long periods, highlighting the necessity for deprescribing. The objectives of this audit were to identify and deprescribe inappropriate medications in patients, identify their comorbidities and explore reasons for the inappropriate medication use.
Methods: This deprescribing audit was conducted by systematic sampling in selected adult patients >18 years, attending a medical clinic at National Hospital, Kandy over one month. The audit standard was the American Academy of Family Physicians (AAFP) '5-step process in deprescribing'. Our study was based only on the first 3 steps of the AAFP deprescribing process.
Results: Out of a total of 402 patients, deprescribing was carried out in 135 (33.58%). In this deprescribed group, 59.3% of patients were female and the mean age was 62.3 (±10.9) years. Furthermore, of the deprescribed patients, 52.6% had hypertension, 44.4% had ischaemic heart disease, and 34.1% had diabetes mellitus. The most deprescribed medication was antiplatelets (37.8%), followed by analgesics (24.4%) and diuretics (20%). A clear indication for using the drug was lacking in 68.9%, while 31.1% of patients continued taking the medication for longer than recommended.
Conclusions: In this audit, over one third of patients underwent deprescribing. It provides just a glimpse of the broader issue of inappropriate polypharmacy and the necessity of deprescribing. Future research involving multiple centres is recommended to enhance understanding of medication patterns necessitating deprescribing.

Key words: deprescribing, polypharmacy, inappropriate medications, multiple medications

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Introduction

The use of multiple medications, termed polypharmacy, is a serious problem in our healthcare system at present. In published literature, the term 'polypharmacy' has been given many definitions such as 'use of at least one potentially inappropriate drug', 'the presence of five/ six or more concurrent medications' or 'medication prescribed to treat the side effect of another medication' interchangeably.(1). The use of multiple or potentially inappropriate medications is linked to numerous adverse health outcomes, including diminished medication adherence, adverse drug reactions (ADRs)(2), increased risk of disability and hospitalisation(3) and increased healthcare utilisation.(4) According to statistics, nearly half of older adults are on five or more concomitant medications(5-7), and as many as 1 in 5 of these prescriptions is potentially inappropriate.(8) Moreover, ADRs account for more morbidity and mortality than most chronic diseases. (9,10)

Despite the fact that some conditions and patients need to be treated with multiple medications, it is the responsibility of the prescriber to use medicines appropriate to the patients' clinical needs, in doses that meet their individual requirements, for an adequate period, and at the lowest cost to them and their community.(11)

During a medications review, a clinician can identify the drugs which are no longer needed for the patient and 'deprescribe'. Deprescribing is a process of medication withdrawal, supervised by a healthcare professional to ensure safe and effective use of medications. This process requires knowledge, attention, time, and awareness of the issues associated with multiple medications.(12)

Kutner et al, found that discontinuation of statins in patients with a life expectancy of one year or less, improved quality of life, reduced medication burden, and reduced medication costs by $3.37 per day.(13) Another Australian study evaluated a hospital-based deprescribing intervention designed to reduce total drug burden.(14) No such studies have been done in Sri Lanka. Rising costs attributed to unnecessary medications represent a major concern achieving sustainable health care.

Other than the prescribers' awareness, there are tools to identify medications objectively for deprescribing. These tools attempt to address the polypharmacy burden, ADR risk, medication regimen optimization, and the decision-making required to implement the deprescribing process.(15) Clinicians must overcome the barriers of deprescribing by liaising with the other specialties, as well as the patient and their family.

In our practice, we have observed that many of our patients in the clinic setting are on multiple medications, prescribed during hospital stay or at the clinic, without being reviewed to evaluate the necessity of long-term continuation. Often these patients' medications are not reviewed until they are admitted with undue adverse reactions caused by inappropriate medications.

The primary objective of this audit was to identify and deprescribe inappropriate medications (i.e., medications not indicated, medications being used beyond the recommended duration, multiple medications with similar action, unnecessary vitamins etc.) in a sample of patients attending a medical clinic at National Hospital Kandy (NHK). Specific objectives included identifying the medications that needed deprescribing, evaluating the comorbidities of these patients, and exploring reasons for the inappropriate medication use.

Methods

The audit was conducted in adult patients aged 18 and above attending a weekly medical clinic at NHK over the course of one month. A systematic sampling method was utilised to select participants from the clinic's registry, where every third patient was chosen, and their medications were reviewed. We obtained informed consent from the patients whose medications needed to be deprescribed. The process of deprescribing was conducted by clinicians; consultant physicians and senior registrars, and registrars under the supervision of consultant physicians.

As the audit standard, we adhered to the American Academy of Family Physicians (AAFP) 5-step process in deprescribing.(16) The five steps are 1] identifying potentially inappropriate medications; 2] determining if the medication dosage can be reduced or the medication stopped; 3] planning tapering; 4] monitoring for discontinuation symptoms or the need to restart and support the patient; and 5] documenting outcomes. It was decided to carry out the first 3 steps initially and the next 2 steps during a follow-up period of six months. This paper describes only the first 3 steps.

Initially, potentially inappropriate medications were identified. Subsequently, decisions were made

regarding whether to omit or reduce the dose as necessary. In cases where immediate cessation was not practical or feasible, tapering off was performed. With regards to antiplatelets, the necessity of single antiplatelet therapy as primary prophylaxis or dual antiplatelets one year after acute coronary syndrome or revascularization was assessed according to the current guidelines.(17,18) Antiplatelets were discontinued in the absence of an indication to continue. Throughout this process, there was constant discussion with patients, explaining the reasons for deprescribing, and it was done only with their clear consent.

Data was collected using a validated interviewer-based questionnaire. Demographic information such as age and sex, comorbidities, deprescribed medications along with their classes, and reasons for continuation were collected from patients. Personal information such as names and addresses were not collected to ensure privacy. Institutional administrative and ethical approval were obtained. Numerical data was presented with means and standard deviations, while categorical data was presented as percentages. Data analysis was performed using SPSS statistical analysis software.

Results

Out of the 402 patients included in the study, deprescribing was carried out in 135 (33.58%) patients. Majority of these patients (59.3%) were female. The age range of deprescribed patients was 30-87 years, while the mean age was 62.3 (± 10.9) years.
Among the patients who had deprescribing, 52.6% were on treatment for hypertension, 44.4% had ischaemic heart disease, and 34.1% had diabetes mellitus (table 1).

The most deprescribed medication was antiplatelets (37.8% of patients). Diuretics, vitamins/ supplements, and acid-lowering medications were deprescribed in 20%, 12.6% and 11.9% respectively. Analgesics were omitted in 24.4% of patients (table 2).

Upon analysing the reasons for the deprescribed medications, the main reasons for deprescribing were as follows: 93 (68.9%) of patients lacked a clear indication for using or continuing the medication, and 42 (31.1%) of patients continued taking medication for a longer duration than recommended. Out of the patients who lacked a clear indication to continue, some were on vitamin supplements such as vitamins B, vitamin C, folate and calcium, and some were on antiplatelets for primary prevention which is no longer recommended in the current guidelines. Analgesics like gabapentin and amitriptyline, which can increase the risk of falls in the elderly, were also inappropriately used.

Majority of the patients who continued taking

Table 1 - Comorbidities among the patients who underwent deprescribing

Comorbidity	Number of patients (%)
Hypertension	71 (52.6)
Ischaemic heart disease	60 (44.4)
Diabetes	46 (34.1)
Stroke	18 (13.3)
Heart failure	10 (7.4)
Epilepsy	10 (7.4)
Chronic kidney disease	8 (5.9)
COPD and Asthma	4 (2.9)
Arthritis	2 (1.5)
Valvular heart disease	1 (0.7)
GORD	1 (0.7)

COPD - Chronic Obstructive Pulmonary Disease, GORD - Gastro-oesophageal Reflux Disease

Table 2 - Medications deprescribed

Medication	Number deprescribed %
Antiplatelets	***51 (37.8)***
Clopidogrel	34 (25.2)
Aspirin	17 (12.6)
Analgesics	***33 (24.4)***
Paracetamol	10 (7.4)
Diclofenac sodium	8 (5.9)
Gabapentin	8 (5.9)
Amitriptyline	7 (5.2)
Vitamins/ Supplements	***17 (12.6)***
Vitamin B	12 (8.9)
Vitamin C	2 (1.5)
Calcium	2 (1.5)
Folic acid	1 (0.7)
Acid-lowering medications	***16 (11.9)***
Omeprazole	12 (8.9)
Famotidine	4 (3.0)
Antiemetics	***7 (5.2)***
Domperidone	4 (3.0)
Prochlorperazine	3 (2.2)
Others	***11 (8.1)***
Betahistine	6 (4.4)
Cetirizine	2 (1.5)
Isosorbide mononitrate	1 (0.7)
Enalapril	1 (0.7)
Fluoxetine	1 (0.7)

medication for a longer duration than recommended, were on dual antiplatelets (aspirin and clopidogrel) after their revascularization or acute coronary syndrome. Medications such as omeprazole, famotidine, domperidone, and betahistine were continued for months to years.

Discussion

In our study, deprescribing was conducted in nearly one-third of the patients. The most commonly deprescribed medication was antiplatelets, followed by analgesics, diuretics and acid lowering medications.

Potentially inappropriate medication use presents a clinical challenge because we are more focused on improving the health of patients under our care by initiating medications rather than reducing the dose or discontinuation. However, we must appreciate that

one of the most important components of good prescribing is deprescribing.

Initially patients with hypertension or diabetes , had been prescribed aspirin for primary prophylaxis without adequate cardiovascular risk assessment. Wever, it is not recommended in the current guidelines.(17) Upon evaluating their cardiovascular risk, aspirin was discontinued in some patients.

Furthermore, patients who had acute coronary syndrome or who underwent revascularization were using dual antiplatelet therapy for several years without being reassessed, contrary to the current recommendation to discontinue one antiplatelet after a year.(18) Prolonged use of antiplatelets can potentially lead to adverse effects such as gastric irritation and life-threatening bleeding. We rectified the inappropriate antiplatelet therapy in these patients.

Acid-lowering medications, such as proton pump inhibitors (PPIs) that were started alongside antiplatelets for acute coronary syndrome had been continued for years, and some patients were taking over-the-counter PPIs on their own, without any review. These were deprescribed after explaining the potential harmful effects to the patients. In a study conducted in Slovenia, two third of hospitalised patients underwent deprescribing of inappropriate PPI.(19)

In our deprescribing process, we adhered to the first 3 steps of the 5 step deprescribing process outlined by the AAFP.(16) Current evidence indicates that most older adults would prefer to alleviate their medication burden and are receptive towards medication deprescribing.(20)

Halliday et al, assessed the safety of withdrawing heart failure medication in a randomised clinical trial involving patients with recovered (ejection fraction ≥50%) dilated cardiomyopathy. Although further research is necessary, this trial revealed that approximately 40% of participants experienced relapses when their heart failure medications were withdrawn, suggesting that long-term administration of these medications is often, though not always, necessary.(21) In the deprescribing process undertaken in our study, considering that patients may experience symptoms and relapses after deprescribing, they were advised to return if they encountered any issues.

Several tools, predominantly focused on care of older adults, are available to identify medications that may be appropriate for deprescribing.(22) The AGS Beers Criteria is an evidence-based, expert consensus list of medications that are often inappropriate in older adults due to excess risk of harm and/or limited benefits in this population.(23) For persons approaching end of life, the STOPP Frail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy) tool is a particularly useful reference.(24) A list of 'Modified STOPP/START criteria for Sri Lanka' has been developed. These criteria are currently being validated through a multi-center study.(25)

Barriers to deprescribing are multifactorial: resistance from patients and/or caregivers, beliefs regarding the consequences of deprescribing, inadequate organisational support for standardised medication review, a relative scarcity of evidence and/or guidelines on deprescribing, prescribers' behaviour such as inertia, and a lack of knowledge in deprescribing.(26-29) We faced considerable resistance from some patients when we tried to deprescribe their long-term medications, but after explaining the rationale of the decisions they understood and agreed with us.

Deprescribing is a complex process and demands the clinician spend a considerable time on each prescription. The limited time that can be allocated for an individual patient in our busy clinic settings is perhaps the most significant barrier in a country such as Sri Lanka.

Another instance where there is undue continuation of medications is when drugs have been prescribed by a specialist. In these situations, fellow colleagues and primary care clinicians may not be comfortable in deprescribing due to the subjective feeling of the need to honour professional hierarchies.(30,31) Therefore, effective communication and collaboration with patients, families, and other professionals is essential, if we are to achieve an effective deprescribing policy in Sri Lanka. Regular medication reviews, ideally annually or bi-annually, are crucial for patients with chronic conditions.

Limitations

As this study was conducted as an audit, the positive and/ or negative outcomes of deprescribing were not assessed, for which long-term follow-up is necessary. This study was conducted at a single medical unit in a tertiary care institution in Sri Lanka, providing just a glimpse of the broader issue of inappropriate polypharmacy and the necessity of deprescribing.

Conclusion

Deprescribing addresses polypharmacy challenges by prioritising ongoing treatment. Over one third of the patients included in this audit underwent deprescribing. These patients were either on long-term medications that were not indicated or taking medications beyond the recommended duration. The most common drug classes that were deprescribed included antiplatelets, analgesics and diuretics.

Recommendations

Follow-up of patients is necessary to identify the outcomes and address any adverse effects of deprescribing. Continuous auditing and deprescribing protocols are recommended across healthcare settings in Sri Lanka. Future research involving multiple centres could enhance understanding of medication patterns necessitating deprescribing. We would like to suggest authorities to strengthen local guidelines on deprescribing in order to benefit patients in the long run.

Declarations

Author contributions
All authors contributed to the conceptualization and design of the study. Perera UAWL, Jayasinghe IK,Wijesingha WMCR, Rathnayaka DL and Rupasinghe S contributed to the acquisition of data. Perera UAWL, Wijesingha WMCR and Abeywickrama UK conducted the data analysis. Perera UAWL, Jayasinghe IK and Abeywickrama UK 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 with respect to the research, authorship, and/or publication of this article.

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Knowledge and attitude regarding insulin therapy among patients treated with insulin for diabetes attending a tertiary care hospital in Sri Lanka

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Abstract

Introduction: The incidence of diabetes is rising in the South Asian region including Sri Lanka. Insulin is one of the therapeutic options which has a significant impact in optimal control of diabetes but lack of knowledge and negative attitudes among patients pose a significant barrier to proper adherence to insulin therapy. This study aims to assess the knowledge and attitudes towards insulin therapy among patients treated with insulin for diabetes attending National Hospital, Kandy and to assess the association of demographic parameters with knowledge and attitude scores.
Methods: An institution-based, descriptive, cross-sectional study was conducted which included 298 randomly selected patients with diabetes who are on insulin attending National Hospital, Kandy. They were assessed with a structured interviewer-administered questionnaire. The data was analysed using SPSS version 22.
Results: The knowledge scores of participants were 70%, 26.8% and 3% for good, moderate and inadequate, respectively. The majority (74%) had a favourable attitude towards insulin therapy. The mean knowledge and attitudes scores were 81.9% (95% CI: 79.5% to 84.3%) and 78.3% (95% CI: 73.5% to 83.1%), respectively. Being retired (p= .012) and being on insulin for more than 5 years (p = .028) were associated with a good knowledge score.
Conclusions Majority of the patients with diabetes assessed in the study had good knowledge and a favourable attitude regarding insulin therapy. It is therefore essential to maintain and reinforce the educational and training modalities made available for patients with diabetes.

Key words: insulin, diabetes mellitus, knowledge, attitude

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Introduction

The incidence of diabetes mellitus is rising globally, especially among populations of the South Asian region.(1) The trend is similar in Sri Lanka where local studies have exhibited a significant rise in the incidence of diabetes mellitus.(2) Prevalence of diabetes in Sri Lanka in 2021 was estimated to be 11.3% and it is predicted to increase to 13.9% by 2030.(2) Timely diagnosis and optimal control of blood sugar have proven to play a major role in minimising diabetes-related complications and reducing diabetes related morbidity and mortality.(3) Insulin is an essential agent in the management of all patients with type 1 diabetes and a considerable proportion of patients with type 2 diabetes. It has been shown that more than 30% of patients with diabetes are treated with insulin.(4)

A variety of misconceptions and a certain degree of stigma affect the receptiveness and compliance to insulin therapy.(5) Provision of adequate education on insulin therapy plays a pivotal role in improving treatment compliance and glycaemic control.(6) Numerous studies worldwide have demonstrated that knowledge and attitudes regarding insulin therapy is inadequate among significant proportions of patients who are on long term insulin. This is more frequently observed in developing nations such as India, Pakistan and Ethiopia.(4, 5, 7) In Sri Lanka there are multiple small-scale studies performed among patients with diabetes to assess their knowledge and attitude towards diabetes in general. Most of these studies are consistent with the findings of the studies performed in several other developing nations, demonstrating inadequate knowledge and unfavourable attitude in the majority.(8, 9)

Bedside and clinic-based patient education by well-trained healthcare staff can be easily implemented to improve knowledge and attitude regarding insulin therapy. This will have a positive impact in improving the compliance with insulin, resulting in better glycaemic control and minimising diabetes related complications.(10, 11) When the bigger picture is considered, in the long run, nation-wide effective awareness programmes and strategies will indirectly contribute to reducing the healthcare burden and costs to the country.

The objectives of our study were to assess the level of knowledge and attitude regarding insulin therapy among insulin treated patients with diabetes mellitus receiving treatment at National Hospital, Kandy and to ascertain if there is any significant association between the level of knowledge and attitude regarding insulin therapy with selected study variables.

Methods

Study design and population:
This was a cross-sectional study based at National Hospital, Kandy and was conducted from July to November 2020. The study population included randomly selected patients above the age of 18 years with diabetes who are on insulin therapy admitted to medical wards or those who attended general medical clinics at this hospital. Patients who are less than 18 years of age, patients with significant psychiatric disorders, newly diagnosed patients with diabetes and critically ill patients were excluded from the study. Ethical clearance for the study was granted by the Ethics Review Committee of National Hospital, Kandy.

Sample size calculation and sampling method:
The sample size was calculated using a single population proportion formula mentioned below, in which, *n* is the sample size, *Zα/2* is the confidence coefficient, *p* is the expected proportion of knowledge and attitude regarding insulin therapy and *D* is the level of precision.

$$n = \frac{(Z\alpha/2)2p(1-p)}{D^2}$$

As there was no accessible information to any large-scale studies published in Sri Lanka specifically on the topic of knowledge and attitudes regarding insulin therapy at the time when this study was conducted, the expected proportion of patients with good knowledge and attitudes (p) were adopted from a cross-sectional study conducted to assess the knowledge, attitude and practice related to diabetes mellitus among the general public in Southern Sri Lanka.(8) Accordingly, the expected proportions of good knowledge and attitudes (p) were taken as 77% and 10%, respectively. A precision level (D) of 5% and a confidence coefficient (Zα/2) of 1.96 were used.

The sample sizes calculated were 272 and 138 for knowledge and attitude, respectively. The study finally included 298 subjects who met all the inclusion and exclusion criteria. Convenience sampling was used considering its practical feasibility.

Data Collection:
Data was collected via a face-to-face interview. Trained interviewers (medical officers) administered a structured close-ended questionnaire which was developed based on a reliability and validity tested

questionnaire used in a similar study conducted in Ethiopia. The questionnaire was made available in Sinhala, Tamil and English languages. The questionnaire comprised three parts: background and demographic details, questions on knowledge regarding insulin therapy and questions on attitude regarding insulin therapy.

"Knowledge" was assessed using fifteen close-ended questions. Questions were on the areas of basic information about insulin, insulin injection technique, storage of insulin and hypoglycaemia. "Attitudes" were assessed using five closed-ended questions. Contents of the questionnaire were reviewed by experienced clinicians in the field for content validity and the questionnaire was pre-tested on a representative sample of patients in a pilot study.

One point was given to each correct answer in knowledge questions and for each positive response regarding attitudes. The total score in each section was converted to a percentage. The knowledge categories were defined as: a score of 0 to 49% as inadequate as 50-74% as moderate and above 74% as good. The attitude categories were defined as: a score of 0-69% as unfavourable and a score of more than 69% as favourable.

Table 1 - Frequency and percentages of demographic parameters

Demographic Parameter	Subcategories of the parameter	Percentage %	Frequency
Sex	Female	59.7	178
	Male	40.3	120
Ethnicity	Muslim	10.4	31
	Sinhalese	78.9	235
	Tamil	10.7	32
Marital Status	Divorced/Separated	1	3
	Married	83.2	248
	Unmarried/Single	11.7	35
	Widowed	4	12
Education status	Up to Grade 5	22.1	66
	Up to Grade O/L	47	140
	Up to Grade A/L	24.8	74
	Graduate	6	18
Employment status	Retired	24.5	73
	Unemployed	46.3	138
	Working full time	21.1	63
	Working part time	8.1	24
Family history of diabetes	No	45.6	136
	Yes	54.4	162
Duration of insulin therapy	< 1 year	11.1	33
	1-5 years	41.3	123
	> 5 years	47.7	142

Informed written consent was obtained from all the subjects enrolled in the study. Each study subject was given a unique identification number, and no patient-identifiable information was obtained.

Data Analysis:
Statistical analysis of data was performed using SPSS 22 software. The frequency and percentages of all study variables (descriptive statistics) were carried out first. Inferential statistics were used to assess the association between the dependent variables of knowledge/attitude score categories and the independent variables. Independent variables included: age, sex, marital status, level of education, ethnicity, employment status, family history of diabetes mellitus and duration of diabetes.

Multivariable logistic regression was used to determine the association between attitude score categories and independent variables. As there were more than two knowledge score categories, multimodal logistic regression was used to assess the association between knowledge score categories and the independent variables. A p value less than 0.05 was considered significant for all statistical analyses.

Results

The characteristics of the study population are summarised in table 1.

All study subjects were aware that insulin should be stored at a lower temperature. Interestingly, only 52% knew that there are different types of insulin. Outcome of the responses of each question in the knowledge section is shown in table 2.

Majority of the study population responded favourably to all questions pertaining to attitude towards insulin therapy. Percentages of positive and negative responses to each question on attitude towards insulin therapy is shown in table 3.

The final percentages and frequencies of knowledge and attitude score categories are summarised in table 4.

Percentage of the 'knowledge score' ranged from 46% to 100% with a mean score of 81.9% (95% CI: 79.5% to 84.3%) and the 'attitude score' ranged from 0% to 100% with a mean score of 78.3% (95% CI: 73.5% to

Table 2 - Responses to questions on knowledge regarding insulin therapy

Question	YES (%)	NO (%)
1. Do you know that diabetes mellitus results in high blood sugar?	98	2
2. Do you know that insulin is given in the form of an injection?	100	0
3. Do you know that there are different types of insulin?	52.3	47.7
4. Do you know the alternative treatments of diabetes mellitus?	94.0	6.0
5. Insulin vial is stored in a refrigerator or cold place?	100	0
6. Insulin injection is taken soon after or before taking a meal?	90.9	9.1
7. Sites for insulin injection are abdomen (around the umbilicus), thigh, upper arms?	99.0	1.0
8. The angle to administer insulin is 45°?	84	28.2
9. Do you know that the site of insulin injection should be changed regularly?	96.6	3.4
10. Do you know any strategy to remember insulin injections?	32.9	67.1
11. Do you know that insulin pen devices are available for easier injection of insulin?	69.1	30.9
12. Do you know that abnormally low blood sugar is a complication of insulin injection?	90.6	9.4
13. Do you know that the insulin vial should be examined before injection?	85.9	14.1
14. Do you know that a new needle should be used for at least every 2-3 doses?	68.1	31.9
15. Are you aware of symptoms caused by low blood sugar?	75.8	24.2

Table 3 - Percentages of positive and negative responses to questions on attitude towards insulin therapy

Question	YES (%)	NO (%)
1. Insulin frequently causes adverse health problems	22.5	77.5
2. Insulin is one of the best medications used to control blood sugar	89.9	10.1
3. Adhering to Insulin therapy is tiresome	30.2	69.8
4. Insulin therapy brings stigma	15.4	84.6
5. Long term Insulin therapy is habit forming	28.5	71.5

Table 4 - Percentages and frequencies of knowledge and attitude score categories

Independent variable	Category	Percentage (%)	Frequency
Knowledge	Poor	3	9
	Moderate	26.8	80
	Good	70.1	209
Attitude	Favourable	74.2	221
	Unfavourable	25.8	77

83.1%). Thus, the mean knowledge and attitude scores lied in the 'Good' and 'Favourable' ranges, respectively.

Being retired (p= .012) and being on insulin for more than 5 years (p = .028) were associated with a 'Good' knowledge score. Only 'the duration of insulin use' was found to be significantly associated with a favourable attitude score where having been on insulin for less than 5 years was significantly associated with a 'favourable' attitude (insulin therapy for less than a year; p = .017 and 1-5 years; p = .005).

Discussion

The main aim of the study was to assess the knowledge and attitude towards insulin therapy among patients treated with insulin for diabetes who are attending medical units of National Hospital, Kandy. In contrast to the findings of multiple studies across developing nations including Sri Lanka (5, 7-9), interestingly, the results of this study showed that most of the study subjects do have a good knowledge and a favourable attitude towards insulin therapy. The average knowledge and attitude scores of subjects were considerably high compared to most of the similar studies performed in some of the other developing nations. Nevertheless, it should be noted that not all studies performed in developing nations have shown suboptimal knowledge or attitude levels regarding insulin therapy. Good knowledge scores have been elicited in two studies carried out in tertiary care hospitals in Kolkata, India(4) and Galle, Sri Lanka.(8) In fact, a study performed in Bangalore, India has shown that 86.7% of the subjects had a good knowledge regarding self-administration of insulin, which is even greater than the figure found in this study.(12) Similar results with most of the subjects showing good knowledge and favourable attitude towards insulin therapy among patients with type 1 diabetes has been reported from a study conducted in Mekele Tigray region in Ethiopia.(13)

The fact that our study was based in the setting of a tertiary care hospital where frequent awareness programmes are being carried out by the medical staff, would have been one of the significant reasons for the better knowledge and attitude scores of the study subjects. This shows that the educational and awareness programmes on diabetes carried out in the hospital setting have a significant impact on knowledge and attitudes of the patients regarding the disease and its treatment.

The probability of having a higher knowledge score was positively associated with the duration of insulin therapy. A similar association was elucidated in several studies carried out in India, Sri Lanka and Ethiopia.(4, 7, 11, 14) This association possibly reflects that longer duration of diabetes results in having a better insight on the disease and its treatment which results in improved receptiveness to treatment with insulin. Being retired was also associated with a good knowledge score which might signify that more free time the patient has is translated to more time spent on education regarding disease conditions and their treatment.

Interestingly, despite the level of education being found to be positively associated with a good knowledge score and favourable attitude in many other studies, it was not consistent with the findings of our study. It may imply that offering adequate and clear instructions can improve knowledge and attitude of the patients treated with insulin irrespective of their level of formal education.

Although good average knowledge and attitude scores on insulin therapy were elucidated in this study, the results may not be readily generalised as the study population was not a representative sample of the general population. The study was based in a tertiary care hospital situated in an urban setting and it is possible that the outcomes would have been different if the study was based in a more rural or a peripheral setting as the socio-economic profiles of such a population would be different to that of the population of this study.

Limitations

Relatively small sample size, utilisation of a questionnaire which has not been previously validated for the Sri Lankan population and restriction of the study population to a single site are acknowledged as limitations of this study. Although the knowledge and attitude regarding insulin therapy were assessed, actual practice of use of insulin therapy was not assessed in this study.

Conclusion and recommendations

In conclusion, this study revealed that a majority of patients treated with insulin for diabetes who attended the medical units of National Hospital, Kandy had a good knowledge and a favourable attitude towards insulin therapy. It is very important to maintain and reinforce the educational and training modalities already made vailable for patients with diabetes who are attending medical care facilities to maintain and improve the positive outcomes.

Further studies in the community and peripheral settings incorporating the assessment of the actual practice of insulin therapy in addition to knowledge and attitude assessments are encouraged as these would give more information on this study area.

Declarations

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

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Clinical reasoning in Internal Medicine: the crucial role of synthesis as a cognitive skill in an era of specialisation

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Introduction

The origins of General Physicians or Specialists in Internal Medicine or Specialists in General (Internal) Medicine date back to several decades and the roles of physicians have differed across different countries.(1,2) The argument to support training of more generalists has spanned for more than a quarter century! The recently developed curriculum of the MD in General (Internal) Medicine was based on the foundation of defining a role of a 'general physician' as "those with expertise in the diagnosis and management of acute and complex, chronic and multisystem disorders in adult patients".(3) The definition then includes several descriptions that are common to any specialty: "They undertake a comprehensive assessment of a patient's problems, both biomedical and psychosocial. They are competent to provide coordinated care with the assistance of multidisciplinary teams to optimise health outcomes while working in hospitals and clinics".(3)

A recent review described the stages in the development of the specialty of internal medicine, its key drivers, and its role in the health care system in resource poor settings such as Sri Lanka.(4) It was also proposed to base the clinical practice of internal medicine using a transdisciplinary approach, with two key goals related to clinical reasoning: to be master diagnosticians (by 'taking a global comprehensive approach…') and master the science of therapeutics to manage multimorbidity (ie., 'treatment of complex problems affecting different organs of the body').

Do Internal Medicine physicians need any special cognitive skills to achieve these two goals in clinical reasoning?

Patients seen by Internal Medicine physicians are presenting with an increasingly complex set of disorders and problems. This is related to a rapidly increasing proportion of elderly patients who are more vulnerable to dysfunction in multiple organs. For example, the declining renal function with ageing makes individuals more susceptible to acute kidney injury, even from the newer non-steroidal anti-inflammatory drugs.(5) Similarly, with the availability of more effective treatment, those having chronic illnesses (e.g., diabetes) survive longer, resulting in an increased risk of developing complications (e.g., coronary artery disease and chronic kidney disease).

Another factor contributing to the complexity of clinical diagnosis is the advances in knowledge and technologies that have led to the detection of novel syndromes and disorders.(6) This situation is further compounded by the emergence and discovery of novel infections such as COVID-19.

Synthesis as a cognitive skill in clinical reasoning

The diagnostic thinking process is often characterised by two main strategies: pattern recognition or hypothetico-deductive approach (HAD).(7,-9) These strategies are utilised to varying degrees depending on the expertise of the clinician and the type of

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clinical encounter. For example, novices tend to rely more on the HAD approach while experts in the field can arrive at diagnoses almost instantaneously through pattern recognition. These two strategies (i.e. pattern recognition and HAD) closely correspond to System 1 (intuitive, emotional and fast) and System 2 type thinking (logical reasoning out which is deliberative) respectively, as described in the field of behavioural economics.(10)

In a recent paper we proposed that the cognitive process of synthesis plays a key role in encounters with patients having multimorbidity, or complex clinical problems.(11) Synthesis is a higher-order level of a hierarchy of cognitive functioning in Bloom's Taxonomy of educational objectives.(12) It is described by a series of verbs: combine, compile, organise, explain, reorganise, and summarise. There is increasing recognition of the role of synthesis in psychology.(13,14)

In my view, specialists in internal medicine should invest time in developing the cognitive skill of synthesis in their clinical reasoning. This is necessary to address the emerging challenges faced by the specialty, including increased case complexity, advancing knowledge and increased specialisation. The role of synthesis can be illustrated in the following example and figure:

A 70-year-old man was admitted with exacerbation of back pain followed by oliguria, lower limb swelling and was found to have high serum creatinine due to acute kidney injury (AKI). He had COPD, type-2 diabetes mellitus (T2DM), ischaemic heart disease (IHD), and backache from osteoporotic fractures. In the past he was prescribed long-term corticosteroids for COPD, diclofenac for his backache due to osteoporotic fractures, and recently treated with celecoxib for exacerbation of back pain.

The multiple pathologies and disorders must be viewed as a coherent whole. This process involves cognitive synthesis, wherein the clinical picture is described as an 'organic whole' and the case history is reframed using specific phrases. For instance: "The 70-year-old has COPD treated with several courses of corticosteroids that led to the development of osteoporosis and T2DM. As a result of the former he developed microfractures and back ache. The corticosteroid induced T2DM progressed to nephropathy and declining renal function. He was prescribed celecoxib for an acute exacerbation of back pain which precipitated acute kidney injury (AKI)

Figure 1 presents a graphical representation of the links across different clinical features, with arrows indicating causative pathways, and three individual pathways of pathogenesis shown in dashed arrows. This is an application of systems science thinking to understand a complex clinical scenario in the form of a networked diagram known as a Clinical Reasoning Map.(15, 16)

Without understanding these interactions as shown in figure 1, a novice clinician may disregard the

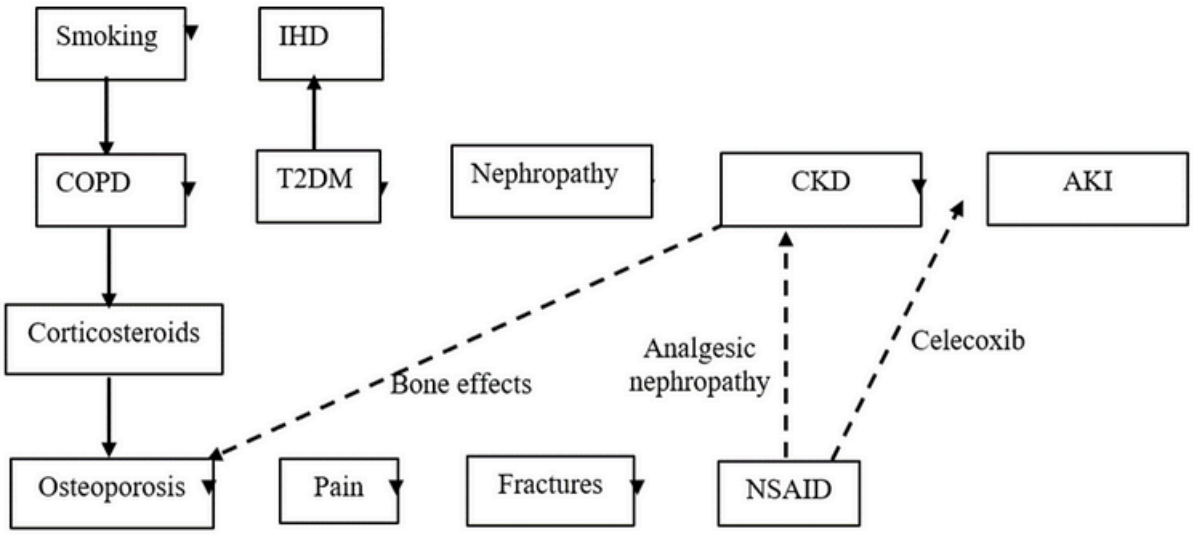

Figure 1 - The links between individual clinical features and their pathways in pathogenesis

opportunity to treat a holistic set of problems. Understanding these interactions is required of specialists in internal medicine to take 'a global comprehensive approach' and become master diagnosticians, experts in the 'treatment of complex problems affecting different organs of the body'.(4)

Figure 2 shows the contrast between cognitive synthesis of a specialist in internal medicine from the more limited domain of expertise found in specialties such as nephrology, rheumatology and cardiology. While the individual competencies of these specialists in their respective organ-systems are invaluable to the team managing the patient, it is the specialist in internal medicine who must detect and characterise the interactions and links among them. It is the specialist in internal medicine who then synthesises this specialist knowledge to develop a holistic picture and approach to the patient's set of problems. This holistic and comprehensive synthesis goes beyond addressing a mere bundle of individual problems.

This practice deviates from instances when a patient is referred to multiple specialists for their opinions on management, with less effort paid to synthesise the different viewpoints and produce a cohesive plan of management. Such an integrated, leadership role is essential for optimising care and preventing unnecessary drug interactions and medical errors (for example, in this instance act as a caution against future use of NSAIDs in the patient).

Implications

Accepting synthesis as a key cognitive skill carries several implications for professional training and practice of internal medicine. In clinical practice, synthesis requires a holistic approach that is enriched by a transdisciplinary approach, involving close collaboration with multiple disciplines. In most instances, such multidisciplinary teams should be led by a generalist who has the mindset and capacity to synthesise knowledge. Medical education and postgraduate training should promote synthesis, and give due emphasis to deliberative clinical reasoning. (17, 18) Another strategy is to use more graphical methods such as Clinical Reasoning Maps to promote synthesis.(15, 16)

The assessment of clinical skills [e.g.: OSCEs, Mini-Clinical Evaluation Exercise (mini-CEX), and Practical Assessment of Clinical Examination Skills – PACES- in the MRCP (UK)] must be revisited because these fragment cognitive competencies and work against synthesis. In contrast, traditional long case and case-based assessments provide more opportunities to assess synthesis and a comprehensive approach that reflects real-life clinical practice.

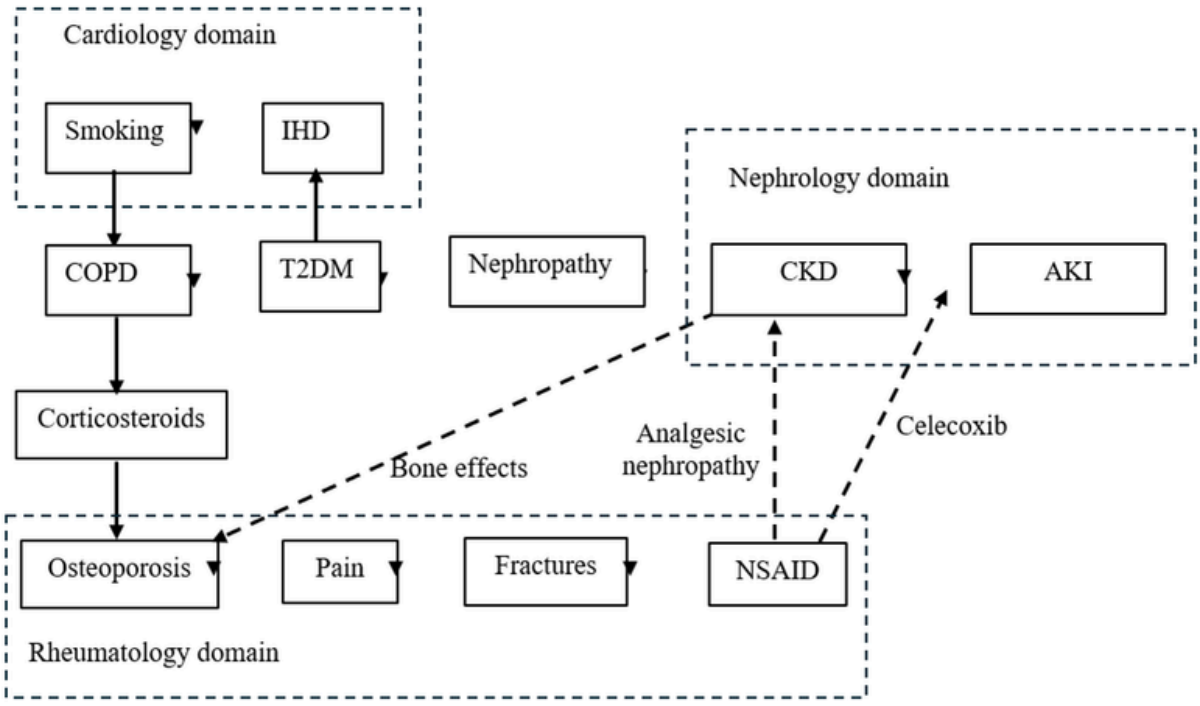

Figure 2 - Domains of expertise of other specialists in the clinical example

A role for the College of Internal Medicine

The establishment of the Sri Lanka College of Internal Medicine (SLCIM) was a significant step in Sri Lanka aimed at delineating and describing the clinical and other roles of a specialist in Internal Medicine. In fact, some would agree with the statement that the SLCIM was a response to concerns that specialties were 'taking over' some of the knowledge domains and clinical roles of a 'general physician'. Synthesis could therefore be considered a 'new' domain of expertise for the specialist in Internal Medicine. Recognising synthesis as a cognitive skill would be the first step in advancing a new field of thinking, research and evaluation.

It is opportune for the Sri Lankan College of Internal Medicine to build on this initiative and recognise and promote the cognitive skill of synthesis in clinical practice, education, and training. The challenge is for the College to take global leadership and rescue internal medicine from the clutches of Evidence-Based-Medicine (EBM) that has colonised our minds. The latter is fragmenting and systematically destroying the 'holistic clinician', especially in internal medicine. We are ideally placed to lead a global revival of clinical reasoning as a core competency. This will also enable us to develop expertise as 'synthesisers of knowledge' and navigate through the next wave of challenges, including the emerging era of artificial intelligence (AI), machine learning and its algorithms. This will be an epic battle, a clash between a natural synthesiser honed by millions of years of evolution, and an artificial system created by human ingenuity. More on that later!

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Decline in empathy among healthcare workers ; where have all the flowers gone?

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Abstract

Studies from around the world are reporting a decline in the empathy of healthcare workers (HCWs) in recent years. This review article explores the implications of this decline of empathy on patient care and provider well-being, and possible ways to promote empathy among HCWs. Empathy plays a crucial role in fostering therapeutic alliances and enhancing patient outcomes. However, practising clinical empathy poses significant challenges, including emotional exhaustion and burnout, time constraints, professional boundaries, and cultural differences. These challenges contribute to a substantial decline in empathy among HCWs, which is further exacerbated by high-stress environments, heavy workload, and drawbacks in the healthcare system. Junior doctors and medical students are particularly vulnerable to a decline in empathy due to the demands posed by medical education and demanding training periods. Structured programmes promoting self-care practices, fostering supportive work environments, and integrating empathy-focused training into education and practice can be used to teach clinical empathy. However, a conducive atmosphere and a culture of empathy in the clinical setting are also crucial. Furthermore, sustained effort and institutional support are essential to sustain the skills thus taught. Such endeavours would contribute to cultivating compassionate healthcare professionals who prioritise patient-centred care and well-being.

Key words: empathy, burnout, healthcare workers

Empathy versus sympathy

Empathy, sympathy, and compassion are related yet distinct concepts in emotional responses. Empathy involves understanding and sharing another person's emotions and perspectives(1); it encompasses cognitive empathy (understanding another's thoughts and feelings), emotional empathy (feeling what another person feels), and compassionate empathy (a combination of understanding and feeling, coupled with a desire to help).(2) Sympathy, on the other hand, involves feeling pity or sorrow for someone else's misfortune without necessarily sharing their emotional state.(2) It is more about acknowledging the suffering from an outside perspective rather than fully engaging with it. Compassion goes a step further: in addition to recognising and empathising with another's suffering, it includes a proactive component with a strong desire to alleviate that suffering.(3) These distinctions are crucial in healthcare. Where empathy helps build patient rapport and understanding, sympathy can sometimes distance the caregiver, and compassion drives the action to provide comfort and care.

Role of empathy in therapeutic alliance

Empathy plays a key role in clinical medicine and doctor-patient relationship by fostering understanding, trust, and mutual respect. In clinical practice, empathy allows healthcare providers to connect with patients on a deeper level, significantly enhancing patient care and outcomes.(4) By understanding the perspectives, emotions, and

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concerns of each patient, healthcare providers can tailor their approach to meet individual needs, leading to more effective diagnosis, treatment, and care planning.(5) Moreover, empathetic interactions help to empower patients to actively participate in their healthcare decisions(6), and make patients more likely to share vital information.(7) It also enhances patient compliance and adherence to treatment regimens, leading to better health outcomes.(8) Empathetic communication also alleviates the patient's anxiety, fear, and feelings of isolation, nurturing a healing environment and promoting a sense of support and emotional well-being.(5) When patients feel understood and valued, their satisfaction with care increases, leading to better psychological and emotional well-being.(7) It is also worth noting that empathy enhances the overall satisfaction and well-being of not only the patients but also the healthcare providers.(9)

Limitations of clinical empathy

Practising clinical empathy, though essential for improving patient care, has its limitations. Healthcare professionals often encounter emotional exhaustion and burnout due to the intense emotional demands of empathising with patients, which can impact their well-being and performance.(10) Time constraints in busy clinical settings further restrict the opportunity for deep, empathetic interactions, potentially compromising the quality of communication with the patient.(11)

Additionally, over-identifying with patients' emotions can blur professional boundaries, affecting clinical objectivity and decision-making.(12) The variability in empathetic skills among healthcare providers leads to inconsistencies in patient care, while cultural differences and communication barriers can hinder the practical expression and reception of empathy.(12) Lastly, there is a risk of misinterpretation, where empathetic responses might be misunderstood, confusing the seriousness of a condition or the nature of treatment.(13) Addressing these limitations requires a balanced approach that incorporates training, systematic support, and maintaining professional boundaries.(13)

Decline in empathy in HCWs

A significant decrease in empathy is being reported among healthcare workers in many parts of the world.(2,3,14,15) This decline in empathy is often due to a combination of high-stress working environments, heavy workloads, and emotional exhaustion.(16) Constant exposure to patients' suffering and the demanding nature of medical practice can lead to burnout, which is characterised by physical, emotional, and mental fatigue.(9) The pressure to perform efficiently in time-constrained settings often forces healthcare providers to prioritise tasks over patient interactions, reducing opportunities for empathetic engagement.(17) These challenges are further compounded by issues in the system such as understaffing, administrative burdens, and lack of support for mental well-being, making it difficult for healthcare workers to sustain the emotional and cognitive resources required for empathy.(17) This decline in empathy impacts the quality of patient care and contributes to job dissatisfaction and turnover among healthcare professionals, creating a vicious cycle that further strains the healthcare system.(9)

Empathy drop in junior students

The decline in enthusiasm and empathy among junior doctors and medical students can be attributed to several inherent factors of the medical education and training process.(12) The intense demands of medical school and residency training, including long hours, high-pressure environments, and exposure to human suffering, can lead to emotional exhaustion and burnout early in the career.(12) Additionally, the emphasis on clinical skills and academic achievement may overshadow the importance of empathy and compassionate patient care.(18) The hierarchical culture of medicine, where seniority often dictates interactions and decision-making, may discourage junior doctors, medical students and nursing students from expressing empathy or questioning established norms.(18) Moreover, navigating complex healthcare systems and various competing responsibilities can further compromise emotional reserves, leading to a gradual erosion of enthusiasm and empathy over time.(10) Addressing these challenges requires changes in the structure of medical education and healthcare delivery that prioritise holistic well-being, promote empathetic communication skills, and foster supportive learning environments that nurture the humanistic values of medicine.(19)

Empathy and burnout

The connection between a drop in empathy and burnout in healthcare professionals is well-documented, highlighting a bidirectional and

mutually reinforcing relationship.(17) While essential for effective patient care, empathy can lead to emotional exhaustion when healthcare providers constantly engage with patients' suffering.(7) This emotional toll, particularly in high-stress environments with heavy workload and time constraints , can contribute to burnout—a state of physical, emotional, and mental exhaustion.(9) Burnout, in turn, diminishes a provider's capacity for empathy as the emotional and cognitive resources required to connect deeply with patients become depleted. This reduction in empathy can lead to decreased patient satisfaction and poorer care outcomes, exacerbating the stress and dissatisfaction experienced by healthcare providers and perpetuating the cycle of burnout.(20) Addressing this issue requires changes in the system, such as manageable workload, emotional support resources, and training in resilience and self-care strategies to support the well-being of healthcare workers.(10)

Scales and measurements of empathy

Various scales and measurements have been developed to assess empathy in individuals within scientific research and clinical settings.(21) These scales often utilise self-report questionnaires or observer ratings to quantify different dimensions of empathy, including cognitive, emotional, and compassionate empathy.(21) Examples of commonly used scales include the Jefferson Scale of Physician Empathy (JSPE), Interpersonal Reactivity Index (IRI), and Toronto Empathy Questionnaire (TEQ), among others(22–24). These scales assess respondents' ability to understand and share others' emotions, perspectives, and experiences. Psychometric properties of these scales, such as reliability and validity, are rigorously evaluated to ensure the accuracy and consistency of measurement. While these scales provide valuable insights into individuals' empathetic tendencies, it is essential to acknowledge the limitations inherent in self-report measures, including social desirability bias and the subjective nature of empathy assessment. An additional limitation of these scales is that they cannot be used universally due to cultural and ethnic differences that they do not capture. Combining multiple measurement approaches, such as self-report scales and behavioural or physiological measures, can enhance the comprehensiveness and reliability of empathy assessment in scientific research and clinical practice.(21,25–27)

Can empathy be taught?

Whether clinical empathy can be taught has been widely explored. Evidence stemming from these explorations suggest that clinical empathy can be cultivated through targeted education and training that focus on developing cognitive empathy (understanding patients' perspectives) and affective empathy (emotionally resonating with patients' experiences).(28) However, the effectiveness of such training can vary based on the individual's baseline empathy levels, openness to learning, and the healthcare environment's supportiveness.(29) It can also vary according to certain personal attributes of the healthcare providers. Positive life experiences, and strong religious and spiritual beliefs, for example, can enhance the understanding of empathy and compassion.(29) As empathy can diminish over time due to burnout or high-stress conditions, continuous practice and reinforcement are essential to maintain it.(17) Thus, while clinical empathy can be taught, it requires sustained effort and institutional commitment to nurture and maintain these skills in healthcare settings.(17)

Strategies to improve empathy among healthcare workers

Integrating empathy-focused training into education, promoting self-care practices, fostering supportive work environments, providing regular supervision and feedback, encouraging team collaboration, incorporating patient perspectives, offering continuous professional development, and implementing organisational support measures are possible solutions to overcome the decline in empathy among healthcare workers.(10) These strategies aim to reinforce empathy skills, prevent burnout, and cultivate a culture of compassion and patient-centred care within healthcare organisations.(7)

Promoting empathy in medical clerkship

Promoting empathy among students in clinical clerkships involves integrating structured educational interventions and fostering a supportive learning environment emphasising the importance of empathetic patient care.(12) Educational interventions may include interactive workshops, role-playing exercises, and reflective activities that teach communication skills, perspective-taking, and emotional intelligence.(12) Encouraging students to actively engage with patients, listen attentively to

their concerns, and validate their experiences fosters empathy and understanding.(1) Providing opportunities for supervised patient interactions, feedback from preceptors, and debriefing sessions allows students to reflect on their experiences, identify areas for improvement, and develop empathy-enhancing strategies.(11) Additionally, incorporating narrative medicine, literature, and arts-based approaches into the curriculum encourages students to explore the humanistic aspects of medicine and develop a deeper appreciation for patients' lived experiences.(10) Creating a culture of empathy within the clinical environment, where empathy is valued, modelled by the faculty, and positively reinforced, can promote empathetic behaviour among students and contribute to the development of compassionate healthcare professionals.(12)

Mentorship and empathy

Mentorship is another important avenue that provides opportunities for healthcare professionals to learn and develop empathetic skills through guidance, observation, and feedback from experienced mentors.(12) Mentors are role models who demonstrate empathetic communication, compassionate care, and effective patient interactions, allowing mentees to observe and learn from their examples.(8) Through mentorship, mentees can gain insights into the nuances of empathetic patient care, learn how to navigate challenging situations, and develop strategies for connecting with patients on a deeper level.(5) Moreover, mentors can provide constructive feedback, encouragement, and support, helping mentees reflect on their experiences, identify areas for growth, and build confidence in their empathic abilities.(12) By fostering a culture of mentorship that prioritises empathy, healthcare organisations can nurture a new generation of compassionate healthcare professionals equipped to provide high-quality, patient-centred care.(11)

Conclusion

Addressing the decline in empathy among healthcare workers is crucial for improving patient care and provider well-being. Promoting self-care, fostering supportive environments, and integrating empathy-focused training is critical. By prioritising empathy in education and practice, we can enhance patient outcomes and cultivate compassionate healthcare professionals who prioritise patient-centred care.

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Hyponatraemia in oncology patients- what physicians should know?

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Case vignette

A 65-year-old patient with hyponatremia is referred to a physician from the oncology unit. She has a history of endometrial carcinoma which has recently been treated with adjuvant chemotherapy (cisplatin). Currently she is being managed for a right sided pneumonia. Patient is drowsy and dehydrated. She is in a 1500 ml negative fluid balance with a urine output of over 3L per day. Her blood pressure is 105/90 mmHg while pulse rate is 110 bpm.
Her serum electrolytes are as follows:
Serum sodium – 122 mEq/L
Serum Potassium - 3.8 mEq/L

What is the likely cause for the hyponatraemia in this patient?
How do you evaluate this patient?

Overview

Hyponatraemia is a common occurrence in patients with malignancies. Although aetiopathogenesis is most often similar to that in non-cancer patients, it can occur as a result of the cancer itself or its treatment.(1) Hyponatraemia has also shown to be a potential negative prognostic factor associated with both solid and haematological malignancies.(2,3) Patients may present with symptoms or may be detected on laboratory testing before, during or after treatment. Treatment has to be decided based upon multiple factors including aetiology, symptom severity and timing of onset. Under the circumstances where cancer incidence is rising globally, general physicians frequently encounter and are involved in multidisciplinary team management of such patients. Further, there are no published guidelines on management of hyponatraemia in oncological patients. Therefore, it is a timely need that physicians are updated and are well conversant with aetiology, diagnostic approach, and principles of management of these complicated patients.

Causes of hyponatraemia

Although the aetiology is broad in hyponatraemia, one must bear in mind the following important causes in oncological patients.

Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Hyponatraemia in cancer patients is most frequently caused by SIADH.(4,5) In this context, ectopic antidiuretic hormone secretion by tumour cells is a recognised cause. While SIADH is most commonly described in patients with small cell lung cancer (SCLC)(6,7), it is also reported in other multiple solid and haematological malignancies.(4,5) SIADH may also be caused by multiple anticancer or palliative drugs either through increased hypothalamic vasopressin production or potentiating its' action.(8) Refer to table 1.

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Table 1 - Anticancer agents and palliative medicines causing Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Anticancer agents
Vinca alkaloids (vincristine, vinblastine)
Platinum compounds (cisplatin, carboplatin)
Alkylating agents (cyclophosphamide, ifosfamide, melphalan)
Others (methotrexate, interferons)
Palliative care medicines
Analgesics (opioid analgesics, non-steroidal anti-inflammatory drugs)
Other supportive care medicines (antidepressants, antipsychotics, antiepileptics)
**Cisplatin may also cause hyponatraemia by damaging renal tubules and interfering with sodium reabsorption

Renal Salt wasting syndrome

Renal salt wasting syndrome is characterised by polyuria, hyponatraemia and extracellular fluid depletion and often mistaken for SIADH due to their basic clinical and laboratory similarities. It occurs due to a tubular defect in sodium transport and some anticancer agents, particularly platinum compounds can cause direct nephrotoxicity with renal tubular damage leading to interference with sodium reabsorption.(9)

Cerebral salt wasting syndrome

Cerebral salt wasting causes hyponatremia in the setting of central nervous system (CNS) diseases and can occur due to brain metastases, CNS surgery head trauma, or CNS infections in oncology patients.(10)
The exact mechanism of salt wasting with brain disease is still unclear. Postulated mechanisms are the release of brain natriuretic peptide (BNP) or injury to the sympathetic nervous system interfering with sodium reabsorption.

Diagnostic approach

The diagnostic approach is basically similar to that of a non-cancer patient, but the physician must be familiar with the aetiologies and clinical context specific to the individual patient.

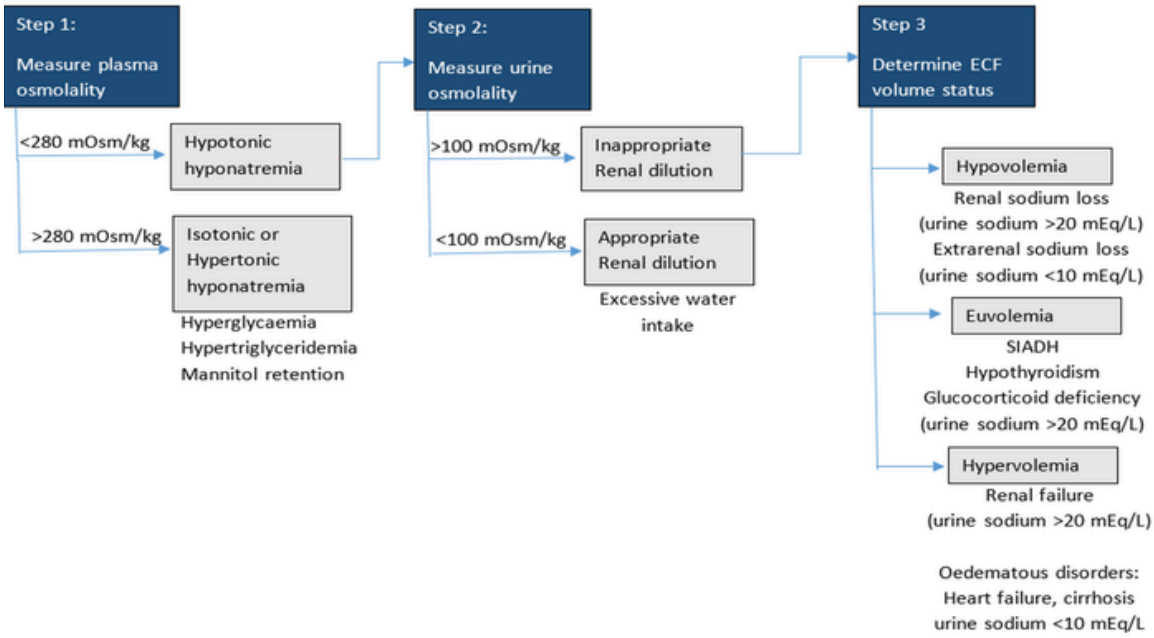
The following three step approach (flow chart 1) provides a focused assessment of hyponatremia in oncological patients.(11)

Step 1
First step is to measure serum osmolality. A serum osmolality >280 mOsm/kg is suggestive of isotonic or hypertonic hyponatraemia where there are osmotically active particles in the plasma (like in hyperglycaemia, hypertriglyceridaemia) and if serum osmolality is <280 mOsm/kg, it is a hypotonic hyponatraemia where further evaluation is necessary to establish a diagnosis.

Step 2
Next, urine osmolality should be measured to assess if the renal dilution system is intact in the face of hyponatraemia. Normal kidneys will maximally dilute urine (<100 mOsm/L) in the presence of hyponatraemia. If urine osmolality is <100 mOsm/kg it indicates an appropriate renal dilution which occurs in the case of compulsive water intake. If urine sodium is >100 mOsm/Kg there is an inappropriate renal dilution which should be evaluated further.

Step 3
The final step is to determine the extracellular volume status. This can be done through clinical assessment combined with investigations. Presence of postural hypotension, tachycardia, dry mucous membranes, and poor skin turgor will indicate hypovolaemia which could be due to either renal (urine sodium > 20mEq/L) or extra renal (urine sodium < 10 mEq/L) sodium loss. Renal salt wasting syndromes and diuretics are causes for renal sodium loss. Presence of concomitant hypokalaemia is observed with thiazide and loop diuretics. Extra renal sodium loss can occur with vomiting/diarrhoea.

If the patient is in a fluid overloaded state (with



Flow chart 1 - Three step diagnostic approach to hyponatraemia in cancer patients

oedema, ascites), in the presence of urine sodium urine sodium > 20 mEq/L, renal failure is the likely cause for hyponatraemia and when urine sodium is < 10 mEq/L, heart failure or liver failure is likely.

Patients without volume depletion or overload are considered euvolemic. In the presence of urine sodium > 20 mEq/L, the most likely cause for hyponatraemia is SIADH. However, thyroid and adrenal insufficiency must be ruled out before confirming SIADH and where there is clinical suspicion of such, thyroid stimulating hormone (TSH) and 9 AM cortisol can be performed for initial evaluation.

Blood urea nitrogen (BUN) and serum uric acid can aid determination of the volume status. High BUN and serum uric acid indicates hypovolaemia. Therefore, clinical assessment combined with osmolality studies (serum and urine osmolality, serum and urine sodium), renal functions and in selected cases TSH and 9 AM cortisol levels are sufficient to unravel the underlying cause for hyponatraemia in these patients.

The main diagnostic challenge is differentiating salt wasting syndromes from SIADH because both are characterised by low plasma osmolality, high urine sodium concentration and high urine osmolality.(4) The cardinal feature differentiating these two entities are the volume status of the patient where in the case of salt wasting syndromes, the patients are polyureic and dehydrated with elevated blood urea and serum uric acid levels. Although there is emerging evidence that fractional excretion of urate (FEurate) provides a better differentiation of these two entities, it is not practical to measure, especially in low resource settings.(12) However, this differentiation is mandatory in selecting the correct approach for management.

Management

There are no published guidelines on management of hyponatraemia in oncological patients. The following management approach and options are derived based on available current literature.(13-17) The treatment should be guided by considering following patient factors:

1. Presence of symptoms
2. Severity of symptoms
3. Extracellular volume status

While symptomatic patients require prompt attention to prevent complications, the serum sodium levels should be raised at a controlled rate at <12 mEq/L in 24 hours and <18 mEq/L in 48 hours to prevent osmotic demyelination syndrome. The available treatment options are hypertonic or isotonic saline, fluid restriction, oral salt replacement and pharmacological agents which can be used based on the principles outlined.

Management of SIADH (euvolemic) and hypervolaemic patients

The correction of symptomatic hyponatraemia in euvolemic (acute/chronic) or hypervolaemic patients is achieved by administering hypertonic (3%) saline via continuous infusion or bolus with aim of rapid increase in serum sodium by 4-6 mmol/L.

- 100 mL bolus infused over 10 minutes – May repeat 3 times as needed
- 150 mL over 20 minutes – May repeat twice or until target increase is achieved

Treatment with hypertonic saline should be stopped once symptoms resolve and either when a safe or maximum serum sodium concentration is reached. Asymptomatic SIADH (euvolemic) or hypervolaemic patients are managed with initial fluid restriction to achieve a negative water balance. This may take several days to cause a significant rise in sodium levels. However, for patients on chemotherapy requiring adequate hydration with fluids, the same approach for symptomatic patients can be followed in order to correct sodium levels while continuing anticancer treatment.

Management of salt wasting syndromes

In salt wasting syndromes, patients' volume status and sodium should be restored with isotonic (0.9%) saline and fluid replacement should be guided by the volume status and sodium concentration of the patient. However, in symptomatic patients, hypertonic (3%) saline and/or oral salt replacement (1-2 g per day up to three times a day) should be considered. Free water intake must be restricted.

Pharmacological agents

Since compliance to fluid restriction is often suboptimal pharmacological interventions may be required. Many of the older medications like lithium and demeclocycline are limited by toxicity, poor efficacy and tolerability. Vasopressin V2 receptor antagonists (e.g.: tolvaptan) which are used in medical patients to manage euvolemic and hypervolaemic hyponatraemia can successfully be used in cancer patients with the added benefit of being able to continue chemotherapy with platinum-based regimens without worsening hyponatraemia. Tolvaptan can be used in euvolemic and hypervolaemic patients but contraindicated in hypovolaemic patients and also during pregnancy and breastfeeding. Further, it is not useful when urgent correction is needed. Starting dose is 15m g once daily which can be increased to 30 mg once daily with a maximum daily dose of 60 mg. Treatment is preferably started while the patient is in the hospital allowing for therapeutic response monitoring and controlled correction.

Back to the case vignette...

With the underlying pneumonia and treatment with cisplatin, the main differential diagnosis is SIADH and renal salt wasting. Presence of polyuria and dehydration favours cisplatin induced renal salt wasting which was the ultimate diagnosis of the patient. She was successfully managed with initial hypertonic saline followed by fluid and salt replacement.

Conclusion

Aetiopathogenesis of hyponatraemia is somewhat different and is a negative prognostic indicator in oncological patients. Differentiating SIADH from salt wasting syndromes and other hypovolaemic states is crucial for selecting appropriate treatment schedules. General physicians are increasingly involved in medical management of these patients owing to rising cancer incidence and multidisciplinary approach of management. Therefore, physicians should be empowered with the necessary knowledge to assess and manage these patients in order to optimise patient care.

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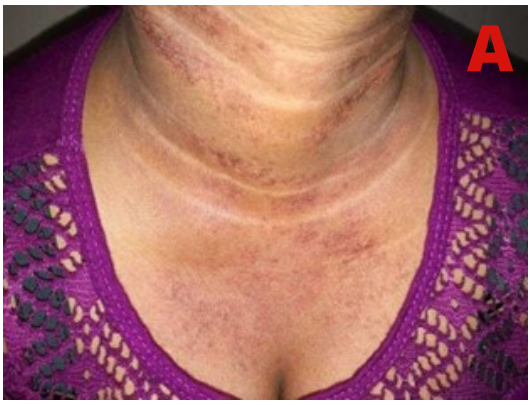
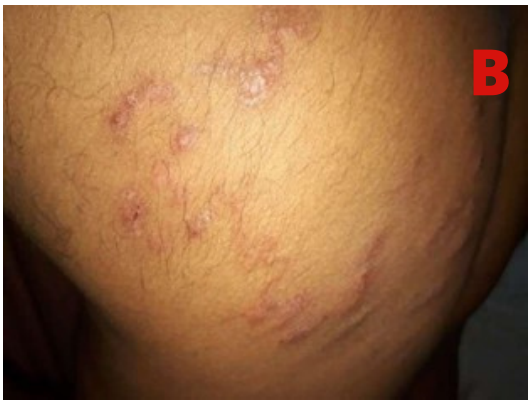
(1) A 62-year-old woman presented with progressive difficulty in climbing stairs and had a rash over her chest (A). Her serology was positive for anti-TIF-1 antibody. What is the most likely diagnosis?

(A) Mixed connective tissue disorder
(B) Antisynthetase syndrome
(C) Subacute cutaneous lupus erythematosus
(D) Rosacea
(E) Malignancy associated dermatomyositis



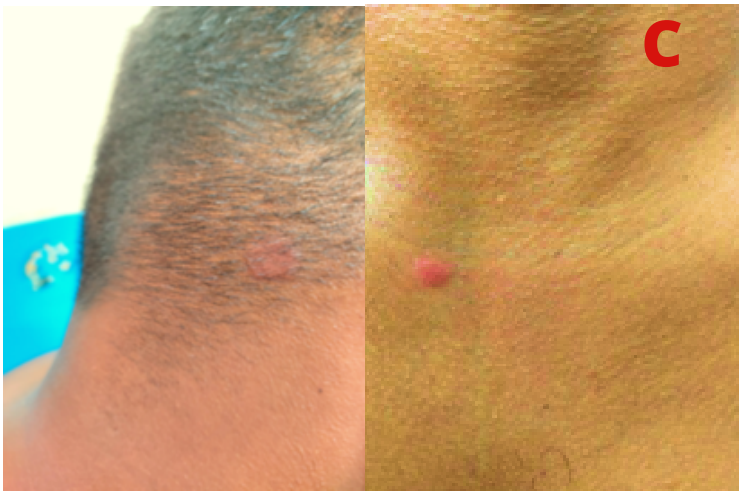
(2) A 28-year-old man presented with a pruritic rash (B) limited to the back of his chest. What is the diagnosis?

(A) Papular urticaria
(B) Scabies
(C) Cutaneous larva migrans
(D) Erythema gyratum repens
(E) Tinea corporis



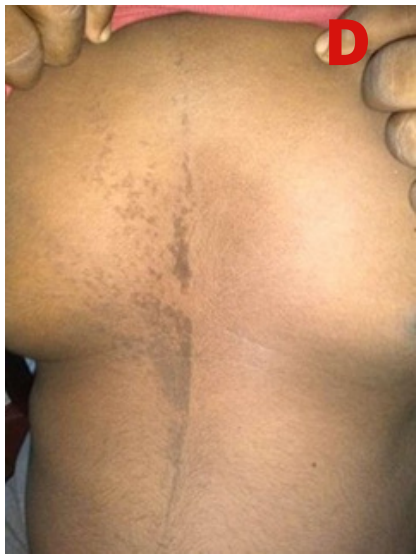
(3) A 30-year-old man presented with high grade fever and a painful rash over his anterior chest and posterior neck (C) with neutrophil leucocytosis on full blood count. The fever and the rash demonstrated prompt response to treatment. What is the most likely diagnosis?

(A) Sweet syndrome
(B) Guttate psoriasis
(C) Leukaemia cutis
(D) Rickettsial infection
(E) Idiopathic urticaria



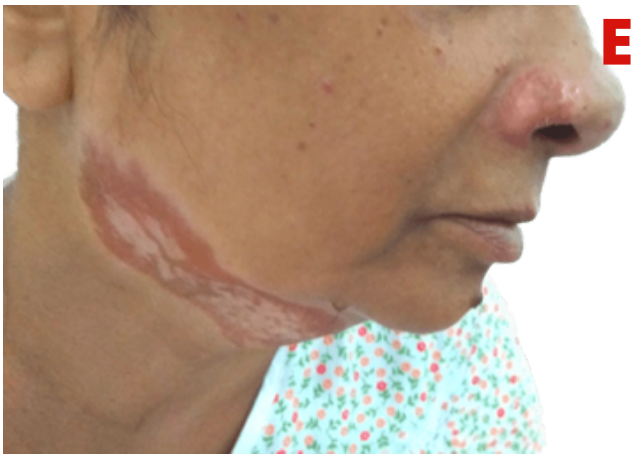
(4) A 17-year-old boy who was diagnosed to have thyrotoxicosis had a rash on his chest and upper abdomen (D). What is the most likely underlying condition?

(A) Neurofibromatosis
(B) McCune-Albright syndrome
(C) Carney complex
(D) Cowden syndrome
(E) Tuberous sclerosis



(5) A 55-year-old woman who presented with an unresolving non-productive cough for 2 months had a rash on her face and neck (E). What is the most likely diagnosis?

(A) Discoid Lupus Erythematosus (DLE)
(B) Plaque psoriasis
(C) Cutaneous Leishmaniasis
(D) Lupus vulgaris
(E) Cutaneous sarcoidosis



N.B.: The above photographs were published with consent from the respective patients.
**Refer the PICTURE QUIZ-KEY on page 128 for answers and explanations.*

CASE REPORT

Ischaemic stroke as the initial presentation of a pheochromocytoma associated with neurofibromatosis type 1

Gnanathayalan SW1[1]*, Fernando BMS[1], Bulugahapitiya U[1]

Abstract

Pheochromocytoma is a rare but well-recognised manifestation of neurofibromatosis type 1 (NF1). Ischaemic stroke has been rarely reported in patients with pheochromocytoma. It can be due to either hypertension or vasospasm. A 33-year-old woman presented with ischaemic stroke and was evaluated for young stroke. Examination revealed clinical diagnosis of NF 1. She had persistent regular tachycardia and mild hypertension. But she denied features suggestive of pheochromocytoma spells. 24-hour urinary metanephrine level was elevated and there was large left adrenal mass lesion. She underwent left sided adrenalectomy. Histology further confirmed the diagnosis of pheochromocytoma. There should be a lower threshold to suspect pheochromocytoma in patients with NF 1.

Keywords: pheochromocytoma, neurofibromatosis type 1, Ischaemic stroke

Introduction

Pheochromocytomas are rare neuroendocrine tumours arising from the adrenal medulla. It is considered as "the great masquerader" because these tumours secrete catecholamines and patients present with a wide spectrum of symptoms. Pheochromocytomas have the highest heritability among all the tumours. The well-known genetic syndromes associated with pheochromocytomas are multiple endocrine neoplasia syndrome 2 (MEN 2), Von Hippel Lindau syndrome(VHL) and neurofibromatosis type 1 (NF 1).

Around 3% of patients with NF 1 develop pheochromocytomas.(1) Ischaemic stroke has been rarely reported with pheochromocytoma.(2) It can be hypertension mediated, due to catecholamine induced vasospasm or due to dilated cardiomyopathy leading to thrombus formation and embolic stroke.(2) Few cases of catecholamine induced vasospasm leading to multifocal infarcts have been reported.(3) Here we discuss a patient presenting with ischaemic stroke as the initial presentation of underlying pheochromocytoma in the background of NF 1.

Case presentation

A 33-year-old woman presented with a sudden onset of headache, dizziness, vomiting and difficulty in swallowing. Examination revealed left sided facial and palatal weakness. Other components of neurological examination were normal. Clinical diagnosis of posterior circulation pathology was made. MRI brain confirmed the diagnosis of posterior circulation ischaemic stroke. Further examination showed persistent regular tachycardia (110-130 beats per minute) with mild hypertension. Abdominal examination identified a palpable left hypochondrial mass. She had cutaneous manifestations such as multiple café au lait spots, neurofibromas and axillary

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and inguinal freckling suggestive of NF 1 which was later confirmed (figure 1). Bilateral lisch nodules were identified during the ophthalmological assessment. She denied family history of similar cutaneous manifestations, young onset hypertension or stroke or any abdominal surgeries. Considering the features of tachycardia and hypertension in the background of NF 1, possibility of pheochromocytoma was considered. But she denied having palpitations, sweating, headache or features suggestive of pheochromocytoma spells.

Initial basic investigations were normal. ECG revealed sinus tachycardia without evidence of atrial fibrillation or left ventricular hypertrophy. 2D Echocardiogram was normal. There was a large para-aortic mass detected on the ultrasound scan abdomen. CECT abdomen was done to further characterise the lesion. It showed an intensely enhancing well defined adrenal tumour with non-enhancing cystic areas measuring 9 cm (AP)×9 cm (T)×13 cm (C) in size with few calcifications (figure 1). Non contrast radio density was 48HU. There was compression in the lower pole of the left kidney but there was no hydronephrosis or hydroureter. Further biochemical investigations were done to assess the secretory nature of the tumour. 24-hour urinary metanephrines were elevated to 6.39 mg/24 hours (Normal <1 mg/24 h). Other adrenal hormone profile including overnight dexamethasone suppression test , testosterone and DHEAS level were normal. The diagnosis of pheochromocytoma was made.

The diagnosis of pheochromocytoma was made approximately six weeks after the presentation with ischaemic stroke. During this period blood pressure values fluctuated between 100/70 mmHg to 150/90 mmHg. A left open adrenalectomy was planned. Prazosin was initiated 2 weeks prior to the surgery for the alpha blockade and the dose was titrated to maintain blood pressure < 130/80 mmHg with upright systolic blood pressure more than 90 mmHg. After adequate alpha blockade, oral propranolol was started to control tachycardia and to keep the heart rate 60-70 bpm in seated position and 70-80 bpm on standing. Both the BP and heart rate targets were achieved.

Left open adrenalectomy was performed. There was an abrupt rise in blood pressure during the surgery, to 240/130 mmHg. It was controlled with intravenous magnesium sulphate and glyceryl trinitrate (GTN). She was discharged on 10th postoperative day when blood pressure and heart rate were normal. Repeat biochemical assessment with urinary metanephrines revealed cure. Histology further confirmed the diagnosis of pheochromocytoma (figure 2). Further follow up with annual metanephrine assessment and imaging was planned if metanephrines are elevated.

Discussion

The symptoms of pheochromocytomas and paragangliomas (PPGLs) are well known to be non – specific and mimic many other clinical conditions leading to an exhausting evaluation process before the diagnosis is made. The typical presentation is with episodic headache, sweating and palpitations due to abrupt excessive release of catecholamines. These are the more frequent symptoms and hypertension is present in 80% of patients. Less commonly reported symptoms are fatigue, nausea, weight loss, constipation, flushing, anxiety, chest

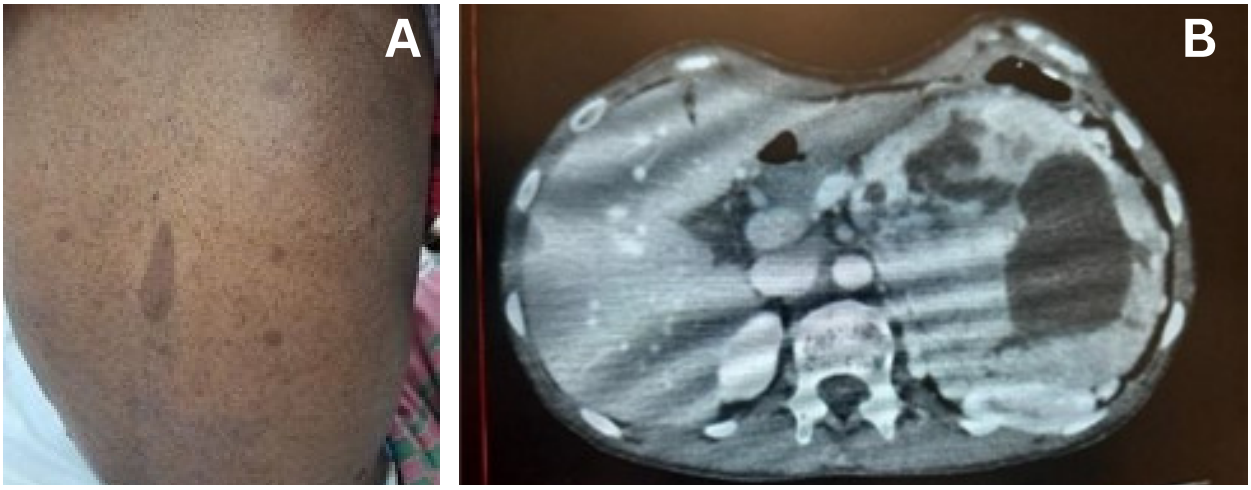

Figure 1 - Café au lait patches and neurofibroma on the back of the chest **A**. CT abdomen showing large left adrenal tumour with cystic areas and causing compression of the lower pole of left kidney **B**

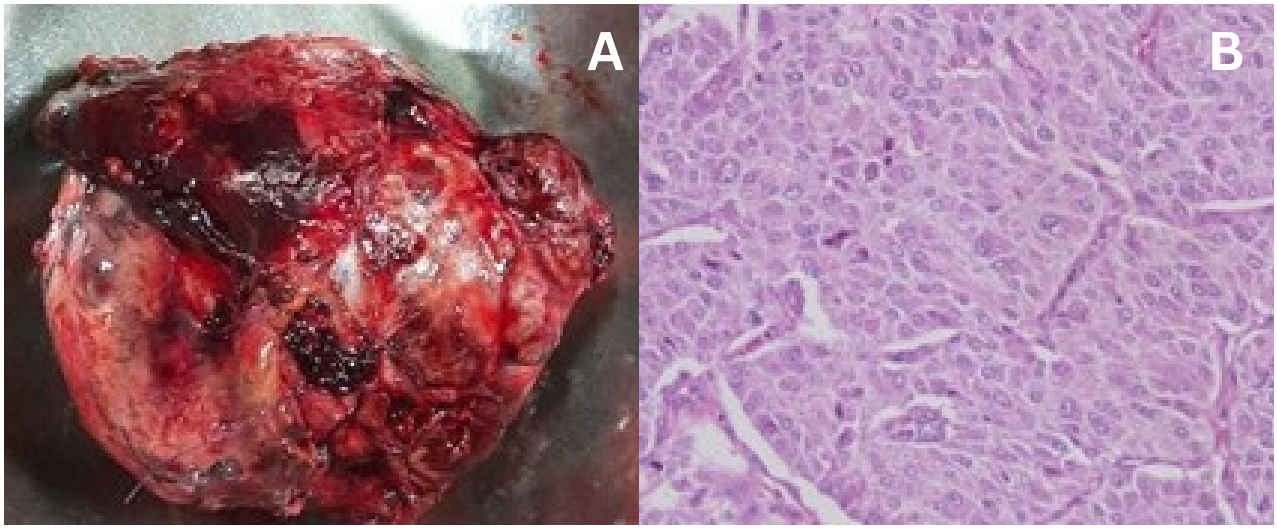

Figure 2 - Excised large adrenal tumour **A**; Tumour cells with large prominent vesicular nuclei arranged in a prominent cell-nesting pattern called zellballen, characteristic of pheochromocytomas and paragangliomas (PPGLs) **B**

pain, pallor, tremulousness and abdominal pain. Ischaemic stroke has been rarely reported with pheochromocytoma.

NF 1 is an autosomal dominant disease. The prevalence of PHEO/PGL in patients with NF 1 is 2·9%. (1) Patients with NF 1 develop pheochromocytoma usually in the fourth or fifth decade after some typical cutaneous manifestations of NF 1 have become evident. Therefore, the diagnosis of NF 1 can be made clinically without the need for genetic testing. Most pheochromocytomas in NF1 are benign and unilateral. Though the metastatic risk in NF 1 associated pheochromocytomas are very low, recent guidelines for screening of patients with high risk for endocrine cancers recommend initiation of biochemical screening of asymptomatic NF 1 mutation carriers every 3 years from the age of 10-14 years.(4). Imaging is recommended only if biochemical screening is positive. Emerging literature also suggests screening in people with NF 1 undergoing surgical procedures, pregnancy and delivery since these procedures can trigger cardiovascular crises.(5)

Diagnosis of Pheochromocytoma is made biochemically with elevated plasma or 24-hour urinary metanephrines. Once the biochemical diagnosis is made, imaging should be done to localise the lesion. The first line imaging modality used to investigate and localise the tumours is computed tomography.

Laparoscopic adrenalectomy is the procedure of choice for solitary, intra-abdominal pheochromocytomas. But in large tumours more than 6-8 cm, open adrenalectomy is needed . Adequate preoperative preparation is deemed necessary to avoid paroxysmal crisis pre or intraoperatively and to reduce intraoperative haemodynamic instability. Cardiac risk assessment, blood pressure and heart rate control and hypovolaemia correction are the essential components of pre-operative preparation. Hypertensive crisis during the surgery, quickly after induction of anaesthesia or with the handling of tumour needs to be treated with prompt initiation of the first-line parenteral vasodilators such as sodium nitroprusside (SPN), phentolamine, or magnesium sulphate. Intravenous glyceryl trinitrate (GTN) can be used when the first-line options are not available or as an add-on medication if blood pressure is not adequately controlled. GTN is less potent than SPN in blood pressure reduction as it is a venodilator in comparison to SPN which predominantly causes arteriolar dilatation.(6)

Post surgical surveillance is an essential part of the management of pheochromocytomas due to the risk of recurrent, multifocal, or metastatic disease. Biochemical assessment should be done 2-6 weeks after surgery to confirm biochemical remission. How long these patients need to be followed up with biochemistry and imaging is questionable but lifelong monitoring is preferred because the metastasis has been reported even after 50 years of initial diagnosis. (7) Patients with syndromic disease with pheochromocytomas require an individualised

approach according to affected genes and other associated tumours or comorbidities. Genetic counselling is also an important aspect to be considered.

Conclusion

The possibility of pheochromocytoma should be considered in patients with ischaemic stroke associated with hypertension when there are clinical features of pheochromocytoma or the features suggestive of genetic syndromes known to cause pheochromocytoma. Though regular screening for pheochromocytoma in all patients with NF 1 is not cost-effective, there should be a lower threshold to screen them. It is advised to exclude pheochromocytoma in NF 1 patients who are about to undergo major surgeries.

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest to be addressed regarding this case report.

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Multiple pathological fractures with a hidden aetiology

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Abstract

Bone disease is a well-recognised complication of primary hyperparathyroidism (PHPT). With early diagnosis of PHPT, florid bony changes such as brown tumours, lytic lesions and pathological fractures are rarely seen now. Here, we report an unusual presentation of PHPT in the current era. A 47-year-old lady was evaluated for multiple fragility fractures. Biochemical assessment confirmed primary hyperparathyroidism. DEXA scan showed severe osteoporosis. Left parathyroid adenoma was localised with imaging. She had multiple brown tumours. She underwent parathyroid adenoma excision and recovered after surgery with improved quality of life. Proper evaluation for secondary causes of osteoporosis is vital especially in premenopausal women. Early diagnosis and treatment of PHPT prevent disastrous complications.

Keywords: primary hyperparathyroidism, brown tumour, parathyroid adenoma, osteoporosis

Introduction

Primary Hyperparathyroidism (PHPT) is a common disorder of calcium characterised by hypercalcaemia and inappropriately normal or elevated parathyroid hormone (PTH) concentration. It is due to excessive secretion of PTH from one or more of the parathyroid glands. Early detection of PHPT during the asymptomatic phase has become very common especially in developed countries where biochemical screening is routinely recommended. Therefore, hypercalcaemia is usually mild, overt kidney stone disease occurs in less than 20% of patients and radiologically evident bone disease has become even less common. Fractures as the presentation of PHPT has become an unusual presentation. Unfortunately, target organ damage at presentation predominates in countries like China and India where the routine screening is not being practised.(1) In Asia, PHPT is more likely to present with overt hypercalcaemia and target organ damage compared to other parts of the world.(2) With the practice of routine screening, another variant of asymptomatic PHPT has been described; it is “normocalcemic PHPT”. Patients with symptomatic PHPT should undergo surgery unless contraindicated.

More than half of the premenopausal women with osteoporosis have a secondary cause.(3) So, it is critical to exclude the secondary causes of osteoporosis in patients with fragility fractures in the absence of traditional risk factors for osteoporosis, especially in premenopausal women, men younger than 50 years and in all patients with low bone density for age and sex (Z-score ≤ -2). With prompt identification of the cause and treatment, secondary osteoporosis is often reversible.

Case presentation

A 47-year-old, previously healthy premenopausal woman was evaluated for multiple fragility fractures over 2 months. She developed right sided tibia-fibula fracture followed by left sided femur shaft fracture. She had polyuria and polydipsia associated with

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constipation. She denied any bone pain. She was not on any medications, specially steroids. Family history was not significant for recurrent young onset fractures, hypercalcaemia, neck surgeries or other features suggestive of MEN syndrome. She had a palpable neck mass.

Initial biochemical assessment revealed moderate hypercalcaemia (13 mg/dL) with low phosphate and elevated ALP (415 U/L). PTH dependent hypercalcaemia was confirmed with an intact PTH level of 2513.9 pg/mL. She had vitamin D deficiency as well. "Symptomatic primary hyperparathyroidism with vitamin D deficiency" was diagnosed. Renal function was normal and there was no ultrasonic evidence of nephrolithiasis or nephrocalcinosis. DEXA scan revealed severe osteoporosis with a T-score of -4.3 for total lumbar spine and a Z – score of -3.2 suggestive of probable secondary osteoporosis.

Hypercalcaemia was managed with adequate hydration. Vitamin D replacement was started with careful monitoring of calcium levels. Parallelly, imaging studies for localisation were arranged. USS scan of the neck showed a nodule of the left lobe of the thyroid gland. No separate parathyroid lesion was reported. Thyroid function test was normal. 99M Tc – Sestamibi scan revealed an active left parathyroid adenoma. For further anatomic characterisation, 4D CT scan was arranged, it showed left parathyroid neoplasm measuring 4.4 cm (CC) × 2.7 cm (Tr) × 2.6 cm (AP). Bony changes such as brown tumours at left clavicle, mandible and bilateral maxillary sinuses and lytic lesions at cervical vertebrae were also noted in the CT scan (see figure 1). Though she had PTH dependent hypercalcaemia, in the presence of lytic lesions, the possibility of multiple myeloma was evaluated and excluded. Taking into account the very high PTH level with significant target organ damage and the large parathyroid tumour, the possibility of parathyroid carcinoma was considered.

She underwent parathyroid adenoma excision with intraoperative PTH monitoring. Intraoperative PTH dropped more than 50% from the baseline within 10 minutes. Being large tumour, severe hypercalcaemia, high PTH level, vitamin D deficiency and presence of skeletal abnormalities are predictors of hungry bone syndrome. However, she didn't develop it postoperatively. Post op period was uneventful. She

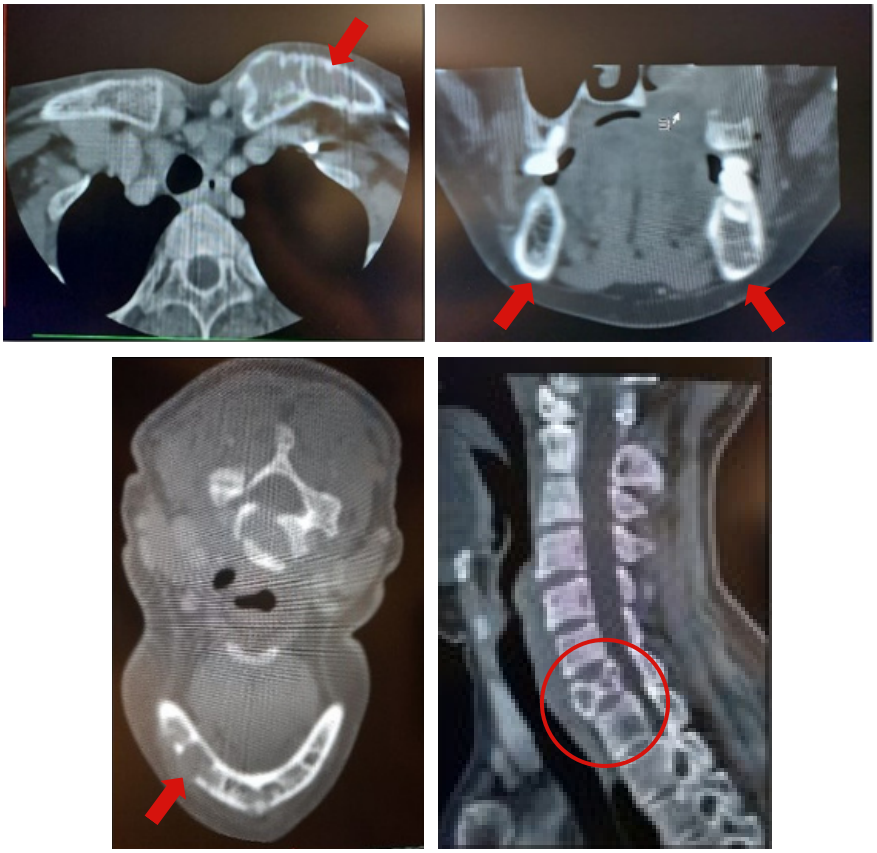

Figure 1 - 4D – CT images showing Brown tumours at left clavicle **A**; bilateral maxillary sinuses **B**; mandible **C**; lytic lesions at cervical vertebra **D**

was discharged on post op day 2 with calcium, vitamin D3 and active vitamin D supplements. Histology was compatible with parathyroid adenoma. Calcium supplements were tailed off gradually. She is awaiting a repeat assessment of bone mineral density with DEXA scan. She is free of symptoms with improved quality of life and has started to mobilise independently. Though a thyroid nodule was detected in the USS neck, a separate thyroid nodule was not identified in CT scan or during the surgery. It is likely that the USS neck detected the parathyroid lesion.

Discussion

Primary Hyperparathyroidism can present with three distinct clinical phenotypes: Overt target organ involvement, mild asymptomatic hypercalcaemia and normocalcaemic hyperparathyroidism. The important factors determining the predominant phenotype of presentation in a particular country are the extent of routine biochemical screening, prevalence of vitamin D deficiency and whether patients diagnosed with osteopenia or osteoporosis are screened for PHPT. Overall, the incidence of presentation with target organ damage has considerably reduced and it has become very rare in developed countries. In Sri Lanka routine screening for calcium or PTH level is not done. Vitamin D deficiency has been identified as a common under diagnosed entity.(4) Even though it is recommended to screen for secondary causes including PHPT after the diagnosis of osteoporosis is made, it is less widely practised. Screening for osteoporosis and evaluation of secondary causes don't occur in most settings where patients present with fractures. It indicates a wide care gap in the management of osteoporosis. Fortunately, our patient was evaluated for the secondary causes and the hidden aetiology was identified.

Bone is a major target organ affected in PHPT. Patients can present with bone pain; fragility fractures or skeletal deformities and various characteristic radiographic changes have been described. The classic imaging appearance is osteitis fibrosa cystica (OFC) in which brown tumours, lytic lesions, subperiosteal resorption of phalanges and bony cysts are seen. Brown tumours are identified in around 3% of patients.(5) Parathyroid surgical management results in complete regression of brown tumours in most of the patients.(6)

Osteopenia and osteoporosis are well – recognised skeletal manifestations of PHPT. PHPT preferentially affects the peripheral skeleton rather than axial skeleton in comparison to postmenopausal osteoporosis where the opposite happens. Early diagnosis of PHPT can prevent progression into osteoporosis and incidence of pathological fractures which increase mortality and impair quality of life. Thus, evaluation of patients with PHPT includes assessment with DEXA scans (lumbar spine, hip and distal radius) and vertebral spine assessment.

After the biochemical diagnosis of PHPT is made, preoperative localisation is important to allow more accurate and potentially curative minimally invasive treatment for the patients with single gland disease. Approximately 80% of patients have single parathyroid adenoma.

Conclusion

It is crucial to evaluate secondary causes of osteoporosis in all patients, especially in premenopausal women and young men less than 50 years old, when they are diagnosed with osteoporosis or present with fractures. Patients with PHPT manifesting severe skeletal and other end organ damage are still observed due to delayed diagnosis of severe disease. Prompt diagnosis and management can cure the disease with reversal of the skeletal damage and improvement in quality of life.

Declarations

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

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Comparing two different presentations of Takayasu arteritis

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Abstract

Reported here are two Asian patients with Takayasu arteritis (TA) with contrasting presentations and responses to treatment. The first patient was a 53-year-old man who presented with disabling abdominal pain. Imaging revealed thickening of the coeliac axis extending to common hepatic and splenic arteries causing external compression with luminal narrowing. There was uniform thickening of the aortic arch and the wall of the descending aorta along with retroperitoneal fibrosis. Early treatment resulted in almost complete remission in eight weeks. The second patient was a 48-year-old woman with pain down the left upper limb with eventual ischaemia of the fourth finger. Imaging revealed circumferential wall thickening at the origin of the left subclavian artery. Treatment started after 3 weeks of the initial presentation, and took up to 14 months for clinical improvement. The relative rarity of this disease and the heterogeneous nature of its clinical manifestations predispose to late diagnosis and delayed treatment. Clinical suspicion and relevant imaging are crucial for the early and accurate diagnosis and management of patients with TA.

Keywords: Takayasu arteritis, abdominal pain, retroperitoneal fibrosis

Introduction

Takayasu arteritis (TA) is a large vessel arteritis that mainly involves the aorta and its branches. In this relatively rare disease, the abdominal aorta and its branches tend to be affected in men, whereas in women involvement of the thoracic aorta and its branches is encountered more commonly.(1)

Depending on the vessel that presents the occlusive or stenotic lesions or aneurysmal dilatations, clinical manifestations vary. Interestingly, the involvement of the aortic arch is referred to as the Japanese form while the involvement of the descending thoracic or abdominal aorta and its branches is known as the Indian form. The subclavian and innominate arteries are by far the most common sites of stenosis. Involvement of coronary arteries is also recognised. Isolated pulmonary arterial stenosis(2) has been reported. Renovascular hypertension due to disease of the renal arteries(3) is seen in the paediatric age group.

In the adult TA patient, involvement of the renal arteries is common, explaining the elevated incidence of hypertension, which is encountered more frequently in the Asian patient. Heart failure and uncontrolled hypertension due to abdominal aortic thrombosis has been reported.(4)

The pathogenesis of TA is mainly due to abnormal cell-mediated immunity(5) CD4+ T cells, CD8+ T cells, Th17 cells, NK cells, γδ T lymphocytes and granulocytes have been recognised in the cellular infiltrate.(6) Involvement of the humoral immune response is also recognised in TA.(7)

It is recognised that TA coexists with inflammatory bowel disease (IBD). The two diseases may have common genetic backgrounds and molecular

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pathways. This may influence treatment decisions.(8) Eshed et al. suggest that IBD and sacroiliitis should be routinely screened for in the TA patient.

Large-artery biopsies cannot easily be done in patients with suspected TA. The non-specificity of clinical presentations, can vary from asymptomatic disease to severe cardiac failure, and casue delayed treatment.(9) Imaging tools such as computed tomography, magnetic resonance angiography, fludeoxyglucose positron emission tomography-computed tomography and more recently contrast-enhanced ultrasonography are frequently used in the diagnosis and to assess vascular inflammation.(1)

Accumulating evidence has shown that biological agents such as anti-tumor necrosis factor agents, tocilizumab and rituximab could be used effectively in refractory cases.(1) Loricera et al. have shown that tocilizumab appears to be effective in the management of patients with TA, particularly in patients refractory to corticosteroids and/or conventional immunosuppressive drugs.(10)

Case presentation 1

A 53-year-old Asian man, developed sudden onset severe abdominal pain. He had noticed episodes of mild abdominal pain in the preceding month, along with constitutional features. He also complained of dizziness. The pain was not postprandial. His bowel habits were normal. He did not give a history of back pain.

Examination did not reveal any murmurs or bruits. The abdomen was nontender. There were no features suggestive of systemic lupus erythematosus. Initially, he was treated with intravenous pantoprazole on the assumption that the pain was due to gastritis, to which there was no response. The ECG t and troponin T levels were both normal. A CT aortic angiogram was performed on the same day that he developed disabling pain. There was enhancing soft tissue thickening of a long sequence of the coeliac axis extending to common hepatic and splenic arteries causing external compression with luminal narrowing. There was uniform thickening of the aortic arch and the wall of the descending aorta. The right renal artery demonstrated mild thickening at the origin (figure 1A).

An MRI scan performed on the next day demonstrated inflammatory changes in the retroperitoneum at the origin of the coeliac axis. MRA of the brain demonstrated subtle wall thickening of the M2 segment of the left middle cerebral artery. His ESR was 82 mm/1st hour.

The patient was commenced on methotrexate and administered 1000 mg of intravenous methylprednisolone for three consecutive days. After 3 days, this 55 kg patient was commenced on 1 mg/kg of oral prednisolone and the dose was reduced by 5 mg every week while monitoring disease activity with the ESR. The abdominal pain improved significantly. The CT aortogram was repeated 8 weeks later, and showed almost complete resolution of arterial wall thickening of the coeliac axis and the proximal hepatic artery. Mild residual thickening of the splenic arterial wall was seen (figure 1B). The ESR had dropped to 14 mm/1st hour. The patient was completely asymptomatic by this time.

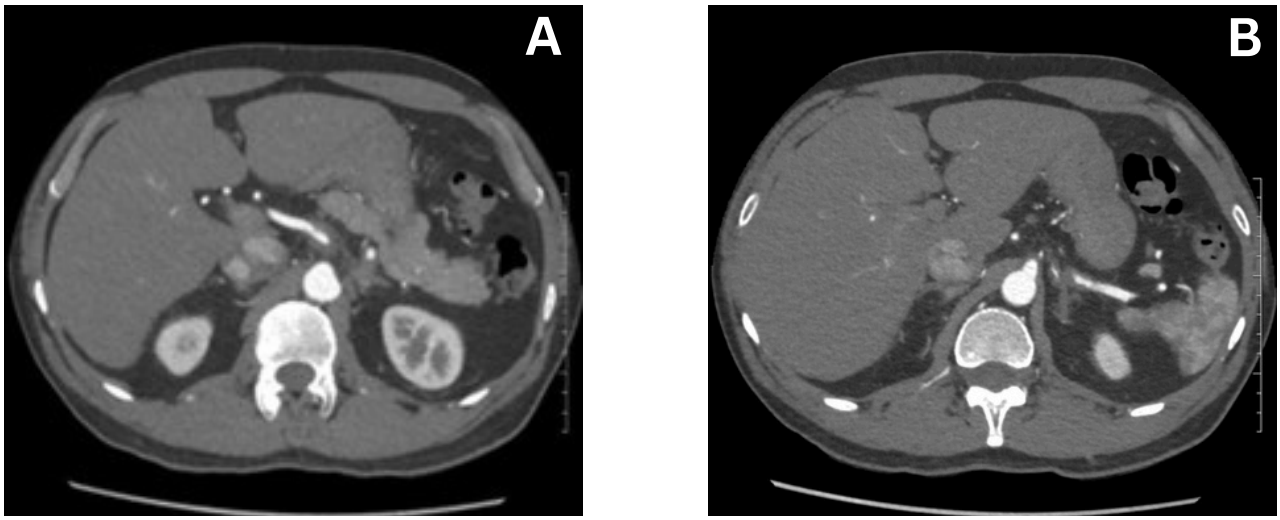

Figure 1 - CT aortogram; Before treatment **A,** After treatment **B**

Case presentation 2

A 48-year-old Asian woman presented with pain down the left arm. Her history dated back to 14 months, when she had presented with severe pain down the left arm with dysaesthesia. The patient was investigated for ischaemic heart disease. In two weeks she developed excruciating pain in the 4th finger of left hand which changed colour. There had been no evidence of vasculopathy or trauma. The patient was a non-smoker. The left radial pulse was absent, and the brachial pulse was of low volume. The CT angiography of the thoracic aorta and left upper limb revealed circumferential wall thickening of the origin of the left subclavian artery, with significant luminal narrowing of approximately 50% (figure 2).

The patient was commenced on methotrexate and 0.5 mg/kg of oral methylprednisolone about three weeks after the onset of pain. Despite increasing doses of methotrexate, there was no improvement of the symptoms. The patient decided to travel to India for medical treatment. In India, she was treated with two doses of tocilizumab. There was some improvement in the pain. The patient was asked to repeat a CT aortogram. Due to financial constraints, the next angiography was performed seven months later. This scan was almost identical to the first scan, but the luminal narrowing had increased up to 60%. In addition, mild eccentric atheromatous lesions were seen in the infra-renal abdominal aorta, causing no significant luminal narrowing. The patient was developing worsening upper limb pain. Due to the unavailability of tocilizumab and the recurrence of symptoms she was commenced on mycophenolate mofetil. Six weeks following mycophenolate mofetil therapy she improved clinically. Two months later the patient started developing the same symptoms again. She was commenced on tofacitinib 5 mg twice daily to which she has responded remarkably up to now.

Discussion

According to the 2022 American College of rheumatology/EULAR classification criteria for Takayasu arteritis(11) both patients fulfil the criteria for diagnosis of TA. When referring to the 2021 American College of rheumatology/vasculitis foundation guideline for the management of giant cell arteritis and Takayasu arteritis(12) both patients presented with features of both active and severe disease.

When considering the first patient, although involvement of the descending and abdominal aorta is more commonly seen in Asians, associated retroperitoneal fibrosis makes it a rare presentation of TA. Only five such cases have been reported in the literature so far.(13) Abdominal pain is rarely described as a clinical manifestation of Takayasu arteritis, although abdominal vascular involvement is common.(14)

The second patient had ischaemia of a digit which is rarely reported, which appeared after 2 weeks of the initial presentation. Ischaemic heart disease (IHD) was considered initially in this patient. While considering ischaemic heart disease in a patient with pain down the left arm is of paramount importance, other diagnoses also should be entertained,

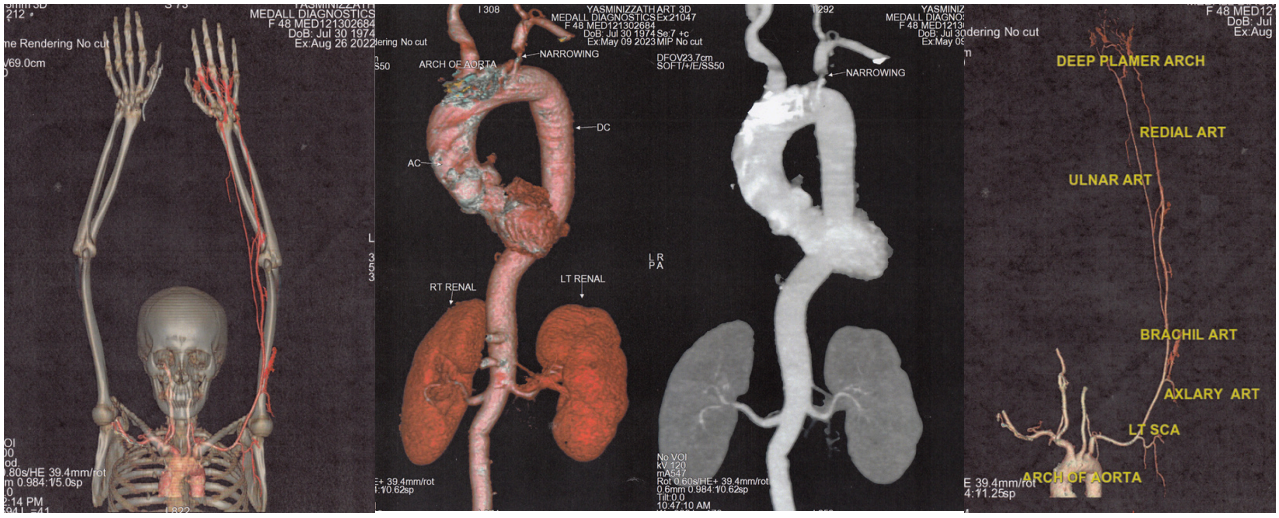

Figure 2 - Images depicting narrowing at the origin of the left subclavian artery

especially when the investigations supportive of IHD are negative and the symptoms are prolonged. This case reiterates this aspect.

Even though TA is 8-9 times commoner in the female(15) and the subclavian and innominate arteries are the most common sites of stenosis(4), there was a delay of over 3 weeks in commencing immunosuppression. Contrastingly, the patient discussed in the 1st case was fortunate to have the CT aortic angiogram conducted on the same day and have treatment commenced.

The patient in case number one responded almost completely to methotrexate and IV pulse methylprednisolone and subsequent high-dose oral steroids, in eight weeks. There is no evidence that IV pulse glucocorticoids are more effective than high-dose oral glucocorticoids.(12) IV pulse glucocorticoids may be considered for patients with life- or organ-threatening disease, as in patient 01 where there was impending bowel ischaemia.(12) The second patient commenced on treatment three weeks after the onset of symptoms, and was treated with high dose oral steroids and methotrexate initially. The response was poor.

The guidelines recommend the use of a non glucocorticoid immunosuppressive agent such as methotrexate plus glucocorticoids over glucocorticoids alone. Tocilizumab is not recommended as initial therapy. The guidelines recommend tapering off glucocorticoids in TA patients who achieved remission while receiving high-dose glucocorticoids for ≥6–12 months, for remission maintenance.(1) Patient 01 easily achieved remission in eight weeks, and was maintained on 5 mg of prednisolone which has now been taken off.

Patient 2 who had not achieved remission even at 14 months was continued on low-dose steroids. She was commenced on bisphosphonates to prevent glucocorticoid-induced osteoporosis (GOIP).(16) She was treated with two doses of tocilizumab, to which there was no improvement. Adding a TNF alpha inhibitor is better than tocilizumab at this point.(12) Due to the unavailability of biologics the patient was commenced on mycophenolate mofetil to which she clinically responded initially only to present with recurrent symptoms in eight weeks. She was commenced on tofacitinib 5 mg twice daily to which she responded.(17) This patient's treatment history depicts a refractory case of TA.

Conclusion

There is no literature available on the treatment delay and how it affects the response to treatment in the TA patient. Nonetheless the comparison of these two case reports calls for greater clinical suspicion in considering TA in a patient with ischaemic symptoms of an arterial territory.

Declarations

Conflicts of interest
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A case of self-limiting respiratory distress in a postpartum mother – transfusion related acute lung injury

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Abstract

A 37-year-old woman, treated for postpartum haemorrhage, developed sudden-onset acute respiratory distress characterised by tachypnoea, desaturation and widespread crepitations, on the first day postpartum. She had low partial pressure of oxygen to the fractional inspired oxygen concentration (PaO2/FiO2) ratio and bilateral patchy opacities in chest radiograph. Despite having a high oxygen requirement, her clinical and radiographic abnormalities spontaneously resolved in 30 hours, after a conservative treatment approach. This case report delves into the rare, yet serious entity of transfusion-related acute lung injury (TRALI) and underscores the importance of considering it among other potential causes of shortness of breath following blood transfusion in postpartum patients.

Keywords: transfusion related acute lung injury, postpartum dyspnoea, adverse blood transfusion reaction

Introduction

Transfusion-related acute lung injury (TRALI) is a relatively rare yet significant complication associated with blood transfusions, often culminating in severe acute adverse events and occasionally in fatalities. Defined by the Canadian Consensus Conference of 2004 as the development of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) within 6 hours following a blood transfusion, TRALI has been recognised as early as 1957.(1, 2) Incidence rates vary widely, ranging from 0.1% to 15% among transfused patients, with higher prevalence observed within intensive care unit cohorts.(3, 4) Despite often being self-limiting within 72 hours, severe cases can be fatal, with mortality rates ranging from 5% to 25%, and even higher rates, up to 47%, reported within intensive care unit settings.(5, 6) The prognosis remains generally unfavourable due to the lack of effective therapeutic interventions.

This case report presents a noteworthy instance involving a young postpartum woman who experienced severe respiratory distress within the first day postpartum, ultimately resolving within 30 hours. After excluding alternative aetiologies, the episode was attributed to TRALI, stemming from a blood transfusion administered to address minor postpartum haemorrhage. By elucidating the clinical trajectory of TRALI, this case report and subsequent review offer valuable insights into its rare yet potentially grave implications in the postpartum period.

Case presentation

A 37-year-old woman, with gravidity-3, parity-2, having a history of chronic essential hypertension and mild intermittent asthma, both well-controlled with medications, presented in her third pregnancy.

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She had previously delivered two children via vaginal delivery without complications. During this pregnancy, she was diagnosed with gestational diabetes at 28 weeks, which was effectively managed with dietary adjustments and Metformin. Her antenatal period was otherwise unremarkable. At 37 weeks and 3 days of gestation, she was admitted to the labour ward in early labour and received a slow infusion of oxytocin as a tocolytic. Due to slow progress, an emergency lower segment caesarean section was performed under spinal anaesthesia after ten hours of labour. Post-surgery, her recovery was uneventful.

Six hours after surgery, she received one pint of cross matched packed red blood cells due to a drop in haemoglobin levels by 1.5 g/dL from baseline, attributed to modest intraoperative and postpartum uterine bleeding. Approximately four hours into the transfusion, she reported sudden difficulty in breathing without associated symptoms such as fever, cough, or chest pain. She had been immobile since admission to the labour ward but denied painful asymmetric lower limb swelling. No significant family history or risk factors for thrombotic conditions were reported. Her COVID-19 vaccination status was up to date, and she had no known allergies. Physical examination revealed tachypnoea, increased work of breathing, and reduced chest movements with bilateral crackles and dullness on percussion at lung bases. There was no raised jugular venous pulsation or gallop rhythm. Cardio-haemodynamic parameters including pulse rate and blood pressure were within normal limits. Pulse oximetry showed an oxygen saturation of 85% on room air. Arterial blood gas analysis revealed respiratory alkalosis with a partial pressure of oxygen to the fractional inspired oxygen concentration (PaO_2/FiO_2) ratio of 158.0 with an FiO_2 of 36%. The other biochemical parameters are summarised in table 1. Chest radiography demonstrated bilateral lower zone consolidations (figure 1, panel A). Bedside ultrasound ruled out effusions. Blood, urine, and high vaginal swab cultures yielded no growth. An urgent echocardiogram revealed normal systolic diastolic biventricular function, ruling out cardiomyopathies, left atrial abnormalities or massive pulmonary embolism. CT pulmonary angiogram and doppler ultrasound of deep veins of the legs ruled out pulmonary thromboembolic causes. A high-resolution CT of the chest was not performed. The diagnosis of TRALI was considered based on clinical presentation and exclusion of other causes.

A tentative diagnosis of TRALI was considered, due to the occurrence of symptoms within 6 hours of transfusion, on-air saturation less than 90%, on-air PiO_2/FiO_2 ratio below 300, presence of bilateral lung infiltrates on chest radiograph, and absence of left atrial anomalies on echocardiogram or any features of circulatory overload.(7) Other postpartum-specific aetiologies such as venous thromboembolism, peripartum cardiomyopathy, amniotic fluid embolism, ARDS due to chorioamnionitis or placental abruption, tocolytic-induced pulmonary oedema and preeclampsia-related pulmonary oedema were unlikely. Acute asthma, respiratory tract infection, structural or functional heart disease, transfusion-related circulatory overload, post-transfusion anaphylaxis, and transfusion-related haemolysis too were unlikely. Gastric acid aspiration induced ARDS was also unlikely due to no suggestive history, though the occurrence of subclinical microaspirations cannot be ruled out completely.

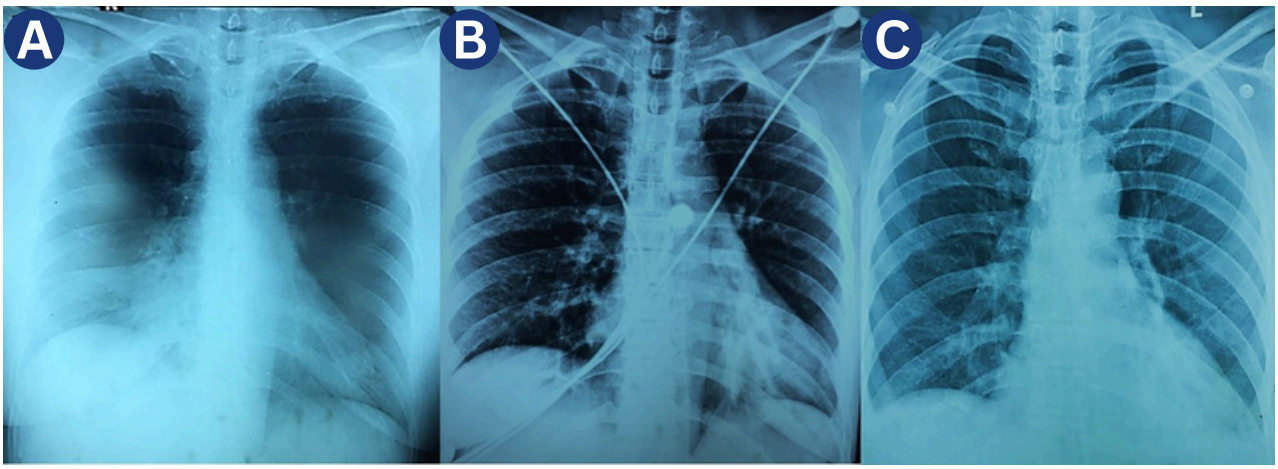

Figure 1 - Serial chest radiographs showing resolution of bilateral radiographic changes. Panel **A**: 1 hour, Panel **B**: 14 hours, Panel **C**: 35 hours since symptom onset

Table 1 - Summary of biochemical and arterial blood gas parameters

Biochemical parameter	Patient's value	Reference level
Total white blood cell ($x10^9$/L)	15	4 – 10
Absolute neutrophil count ($x10^9$/L)	13.8	2 – 7
Haemoglobin level pretransfusion (g/dL)	8.8	11 – 13
Haemoglobin level posttransfusion (g/dL)	10.1	11 – 13
Platelet count ($x10^{12}$/L)	184	150 – 450
CRP (mg/L)	8.8	<6
ESR (mm/h)	15	<20
Alanine transaminase (U/L)	23.4	5-35
Aspartate transaminase (U/L)	20.1	13-31
Total bilirubin (umol/L)	3.6	3 – 21
Blood urea (mmol/L)	6.3	2 – 7
Serum creatinine (umol/L)	52.31	45-85
Serum sodium (mmol/L)	144	135 – 145
Serum potassium (mmol/L)	3.4	3.5 – 5.5
Troponin I (mg/L)	<0.01	<0.01
Random blood sugar (mg/dL)	156	110 – 200
Arterial pH	7.48	7.35 – 7.45
Arterial oxygen pressure (mmHg)	79	60 – 100
Arterial carbon dioxide pressure (mmHg)	28	40-45
Arterial bicarbonate (mmol/L)	20	22 - 26

The patient was managed with supplemental oxygen (15 L/min) via non-rebreather mask, nebulisation, and close monitoring in a high dependency unit, leading to resolution of symptoms within 30 hours. Follow-up chest radiographs showed improvement (figure 1, panel B and C).

Discussion

Diagnosing TRALI relies on clinical and radiographic assessments. Symptoms typically manifest within 6 hours of transfusion, and characteristic radiographic findings include bilateral infiltrates, which may present as patchy, homogeneous, diffuse, or asymmetric patterns suggestive of alveolar or interstitial disease. In our case, the patient exhibited bilateral patchy pulmonary infiltrates on chest radiography. Hypoxaemia, often quantified by a PaO2/FiO2 ratio of less than 300 mmHg or oxygen saturation below 90% on room air, is a hallmark of TRALI.(1,7) Our patient demonstrated an oxygen saturation of 84% on air and a PaO2/FiO2 ratio of 158 mmHg, despite receiving an FiO2 of 35%. Although fever, cyanosis, and hypotension are common manifestations of TRALI, our patient did not exhibit these symptoms. Recent advancements in diagnostic criteria, such as those introduced in 2019, have refined TRALI classification into Type I and II based on the presence or absence of ARDS risk factors.(7)

Pathophysiological mechanisms underlying TRALI include immune and non-immune theories. The immune theory posits that antibodies targeting human leukocyte antigen (HLA) class 2 and human neutrophil antigen (HNA) class 3a in the donor blood

interact with corresponding antigens on the recipient's leukocytes. The non-immune "two-hit" model involves priming events and subsequent endothelial injury.(8, 9) Notably, the exact relationship between the administered dose of implicated blood products and the severity of TRALI remains elusive. Despite this uncertainty, evidence suggests that even trace amounts of plasma exposure may suffice to instigate the onset of TRALI.(10) Notably, the risk of TRALI varies across different blood components, with whole blood, platelets, fresh frozen plasma, packed red cells, granulocyte, cryoprecipitate, and human immunoglobulins exhibiting decreasing orders of risk.

Diagnosing TRALI in the postpartum period poses distinct challenges. Symptoms of TRALI often overlap with those of other common conditions encountered during this phase. Physiological manifestations such as tachypnoea and mild hypoxaemia are also expected after normal childbirth. Distinguishing TRALI from other critical postpartum conditions, such as amniotic fluid embolism, pulmonary embolism, and peripartum cardiomyopathy, proves intricate due to shared clinical features among these disorders. Additionally, postpartum women may present with dyspnoea attributed to various aetiologies, including anaemia, fatigue, or the physiological stress of labour itself. It is reported that among patients transfused for postpartum haemorrhage, those with a history of gestational hypertension and preeclampsia, particularly if they have not received antihypertensive therapy, exhibit a heightened risk of developing TRALI.(11) Our patient did not have such risk factors. Cohort studies state that the risk of TRALI in postpartum women is further exacerbated in those who receive three or more units of packed red cells.(12)

The lack of specific diagnostic markers for TRALI exacerbates the diagnostic challenge, contributing to its frequent under-recognition and underreporting within clinical settings. In light of the absence of definitive diagnostic tests for TRALI, clinicians must employ a comprehensive assessment approach. This involves meticulous consideration of the patient's clinical presentation, radiological findings, and the systematic exclusion of alternative aetiologies.

To date, there are no established treatments for TRALI beyond supportive care. Essential steps in management should include immediately discontinuing transfusion, providing supplemental oxygen, administering intravenous fluids, conducting frequent monitoring of vital parameters, initiating empirical antibiotics, and notifying the blood bank to quarantine blood products from the same donor.(8) In severe cases, ventilation with a low-tidal volume strategy and extracorporeal membrane oxygenation (ECMO) may be necessary.(13,14) However, we managed our patient with supplemental oxygen alone. While high-dose steroids were utilised, partly due to the assumption of an immunological cause, there is no direct evidence of their benefit.(15) A randomised controlled trial demonstrated improved 7-day survival in critically ill patients with TRALI following intravenous administration of high-dose ascorbic acid.(16) Neither steroids nor ascorbic acid was utilised in our patient.

Prevention strategies for TRALI entail several measures including avoiding the procurement of blood donations from multiparous women, who may have developed sensitisation from multiple fetoplacental blood transmissions, as well as from donors whose blood has previously resulted in TRALI.(17) Given that anti-HLA production increases over time, minimising the shelf time of blood products also contributes to TRALI prevention. Furthermore, it is advisable to refrain from using whole blood, as it poses a higher risk of TRALI compared to packed red cells. In developed countries, the implementation of strategies such as the introduction of male-only donors, male-dominated plasma, exclusion of all-exposure donors, and antibody screening has significantly reduced the morbidity associated with antibody-dependent TRALI.(8) However, the routine implementation of anti-leukocyte antibody screening faces challenges due to financial complexities.(18) Nevertheless, retrospective analyses have demonstrated that leukoreduction of blood components can substantially reduce the occurrence of TRALI cases by up to 83%.(19)

Conclusion

TRALI represents a severe yet under-recognised complication of blood transfusions, particularly in the postpartum period. Heightened awareness among clinicians is crucial for early recognition and management. Adequate supportive care plays a key role in improving outcomes for affected patients. TRALI can be prevented by avoiding blood donated by selected donors, avoidance of longer storage, and minimising products that can increase the risk. Addressing gaps in awareness and recognition is essential to minimise the morbidity and mortality associated with TRALI.

Declarations

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

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None

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Encephalomyelitis as a rare presentation of melioidosis

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Abstract

Cerebral melioidosis is a rare entity which is minimally reported in literature, having multiple diagnostic challenges as it mimics most of the other diseases of the central nervous system (CNS). Spectrum of CNS melioidosis depends on the entry of the organism and immune status of the patient. Due to the delay in diagnosis, it has a high morbidity and mortality. It is thought to be a disease of the immunocompromised with risk of exposure to soil or surface water. We present a case of an immunocompetent patient without any known risk factors for significant exposure, who presented with fever and rapidly progressive multiple cranial nerve palsies followed by reduced level of consciousness and cerebellar signs. She was eventually diagnosed to have encephalomyelitis, a form of neuro melioidosis, with radiological evidence of acute demyelinating encephalomyelitis, and successfully treated with parenteral meropenem for intensive phase and cotrimoxazole for a long eradication phase. High index of suspicion and early initiation of treatment with suitable antibiotics for an optimal duration, evidenced complete recovery.

Keywords: CNS melioidosis, encephalomyelitis, cranial nerve palsies, acute demyelinating encephalomyelitis, ADEM

Introduction

Melioidosis is a multisystem infectious disease which mimics most of the other infectious, inflammatory, demyelinating and neoplastic illnesses, thus called the great mimicker.(1) There are various presentations of the disease which are associated with immunocompromised state of the host and risk factors for exposure.(1) Worldwide, the number of patients who present with rare manifestations of melioidosis such as central nervous system (CNS) infection are less in immunocompetent individuals.(1-3)

Case presentation

A 45-year-old previously unevaluated woman from Batticaloa, presented with headache, fever and upper respiratory tract symptoms for 4 days. There was no photophobia or focal neurological symptoms. On examination she was ill and afebrile. Sinus tenderness was present. There was no evidence of neck stiffness on admission. Cardiovascular examination showed a blood pressure of 120/80 mmHg, pulse rate of 120 beats per minute with good volume and normal precordium. Respiratory rate was 26 breaths per minute and no added sounds were audible in lungs. Abdominal and neurological examinations were unremarkable with normal fundoscopy. The patient was initially managed for sinusitis, with oral antibiotics.

On day 2, the patient developed neck stiffness, complex ophthalmoplegia with horizontal nystagmus and bilateral papilloedema, while her conscious level was preserved and limbs remained neurologically normal with stable haemodynamics. Urgent non

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contrast CT brain was unremarkable and the patient was managed for meningoencephalitis with intravenous ceftriaxone, acyclovir and dexamethasone. During the next 48 hours, the patient rapidly deteriorated with multiple cranial nerve palsies; left V, VII, X and XII, left side cerebellar involvement and hyperreflexia in all four limbs.

With the clinical diagnosis of basal meningitis along with laboratory evidence of lymphocytic predominant cerebrospinal fluid (CSF) with high protein and low sugar levels, the patient was commenced on empirical anti -tuberculosis drugs, suspecting CNS tuberculosis.

Despite treatment with steroids and anti tuberculosis therapy (ATT), her clinical condition continued to worsen. TB PCR and Adenosine deaminase of CSF reports were negative, as well as the cultures. The CECT brain was also inconclusive.

On day 4, her Glasgow coma scale dropped to 10/15 with significant airway compromise, necessitating elective intubation, and she was transferred to ICU for further care. Nonetheless, her neurological and physical state remained the same, warranting further evaluation for the diagnosis. Non-contrast CT of the brain (figure 1) was repeated following a drop in conscious level, which was reported as possible viral encephalitis with brainstem oedema and the EEG was suggestive of mild to moderate encephalopathy. An MRI was then taken (figure 2) which reported the condition to be acute demyelinating encephalomyelitis (ADEM), secondary to viral infection. Therefore, IV methylprednisolone and IV Immunoglobulins were started, with the plan to continue for 5 days.

As her clinical condition did not show any improvement, with suspicion of melioidosis, serum melioidosis antibody level was performed, which was positive with a high titre of 1:2560. Viral studies were negative. Investigations of the patient are summarised in table 1.

On day 8, oral cotrimoxazole was given twice daily with intravenous meropenem. The patient then started to show rapid improvement in GCS as well as in clinical status. The patient was discharged after completion of IV meropenem for 8 weeks, with oral cotrimoxazole for 6 months. On the follow up reviews her neurological symptoms improved and the patient became completely asymptomatic after 3 months of cotrimoxazole.

Discussion

Melioidosis is caused by a gram-negative saprophyte, *Burkholderia pseudomallei,* which lives in soil at 10 cm or more from the surface and surface water.(1) It enters the body via direct skin contact, ingestion or inhalation. Risk factors for the infection are occupations related to soil and water such as road workers and farmers and immunocompromised state of the host.(1) In our patient there was neither a history of immunocompromised state nor an identified risk of exposure. Incubation period varies

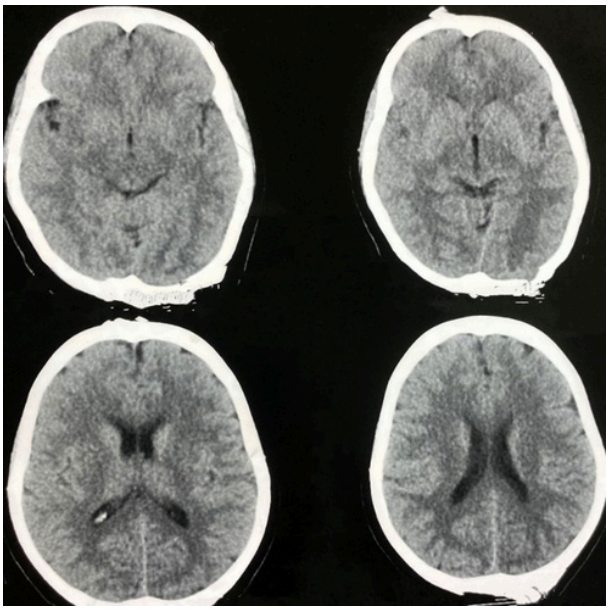

Figure 1 - Non contrast CT brain of the patient

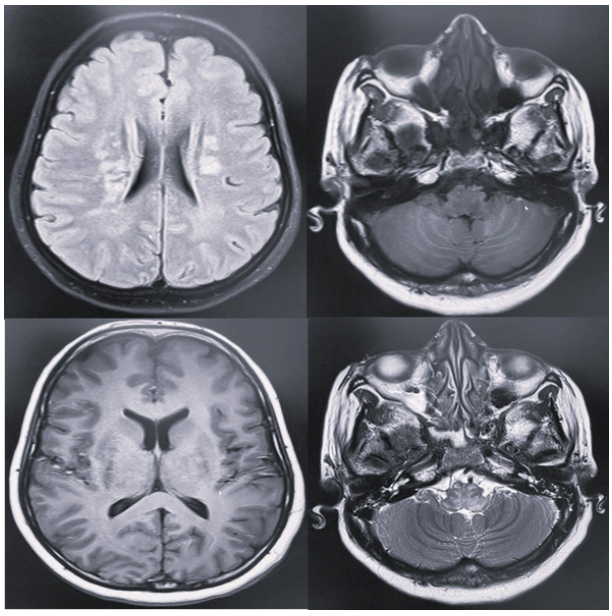

Figure 2 - MRI brain of the patient

Table 1 - Summary of investigations

Investigation	Patient's result
White cell count (x 10^3/uL)	10.81
Neutrophil (x 10^3/uL)	8.25
Lymphocyte (x 10^3/uL)	1.01
Haemoglobin (g/dL)	12.8
Platelet (x10^9/uL)	250
C reactive protein (mg/L)	16.2
Serum sodium (mmol/L)	136
Serum potassium (mmol/L)	3.9
Erythrocyte sedimentation rate (mm/1st hour)	62
Urine full report	Albumin nil, no cells or cast
Aspartate transaminase (U/L)	39
Alanine transaminase (U/L)	24
Serum albumin (g/L)	30
Serum globulin (g/L)	43
Gamma GT (U/L)	24
CSF	
Sugar (mmol/L)	3.4
Protein (mg/dL)	95
Polymorphs (/mm^3)	47
Lymphocytes (/mm^3)	1620
Red blood cells (/mm^3)	90
Random blood sugar (mmol/L)	8.6
CSF adenosine deaminase (U/L)	15
Blood culture	No growth
Urine culture	No growth
CSF culture	No growth
Melioidosis antibodies	1:2560
CSF gene xpert	Not detected
Toxoplasma IgG and IgM antibodies	Negative
HIV antibodies 1 & 2	Negative
Herpes simplex Type 1 and 2 DNA	Not detected
CSF cytology	No atypical cells seen

Table 1 - Summary of investigations continued...

Investigation	Patient's result
VDRL	Not reactive
Electroencephalogram	symmetrical background mainly consists of generalised theta rhythm that is intermittently interrupted by delta waves. There were no epileptiform discharges or focal slowing. EEG was suggestive of mild to moderate encephalopathy.

from days to years; therefore, it has a potency to have a long latency period of years, which is reported in several cases.(2) Spectrum of the clinical manifestations could be simply localised to the point of skin contact or to devastating, disseminated infection with life-threatening complications. This largely depends on the bacterial virulence factors, host's immune status, route of bacterial entry into the body and the bacterial load.(1) Even though it can affect the whole body, spleen, prostate, liver and kidneys are reported to be the common organs.

CNS involvement in melioidosis is rare, and can present as an acute infection, occurring within 2 months of onset or chronic infection.(2) Entry into the brain in CNS melioidosis occurs by three distinct mechanisms: 1) direct skin invasion through the scalp, trans-osseous invasion of the skull reaching the brain; 2) entry through nasal epithelium, to olfactory bulb and cranial nerve, reaching the brainstem; 3) haematogenous spread of the organism from the site of entry through any part of the body, crossing the blood-brain and blood-CSF barrier entering the brain. (2) There are various presentations of CNS melioidosis reported in several articles, such as encephalitic syndrome with or without myelitis, cerebral abscess, isolated meningitis, isolated extra axial collections, isolated nerve palsies and osteomyelitis of the skull.(2-5) The clinical features vary according to the underlying spectrum of above, which includes fever, headache, altered level of consciousness, neck stiffness, seizure, limb weakness and cranial nerve palsies.(2-4) Interestingly our patient had most of the above clinical manifestations in a rapid progressive manner, beginning with upper respiratory infection, fever and headache, progressing to multiple cranial nerve palsies and reduced level of consciousness, ultimately resulting in the need for intubation and ventilation.

As CNS melioidosis is a great mimicker of most other illnesses like CNS tuberculosis, diagnosis is a challenge, especially when a known risk factor is not encountered in the history. Hence, most of the time diagnosis is delayed, eventually increasing the morbidity and mortality. Imaging and CSF analysis, the two first line investigations, though nonspecific, give a diagnostic value in the suspicion of CNS melioidosis, while the definitive diagnosis must be made microbiologically, either by isolation of the organism from blood, pus or CSF, or serologically by melioidosis antibodies.(2) Pleocytosis with lymphocytic predominance is the commonest finding in the CSF, which mostly resembles tuberculous and viral meningitis.(2,3) Additionally, in our patient, high protein with low sugar was also present, which is known to occur in tuberculosis, considering the diagnosis of CNS tuberculosis. Contrast enhanced MRI, having high sensitivity, would be the neuroimaging of choice, but is nonspecific.(2) Involvement of the area of the brain depends on the spectrum of disease. For example, prominent brainstem involvement is seen in encephalomyelitis type.(2) In addition to the proven findings, our patient had features of ADEM, which was not documented previously as a recognised manifestation of CNS melioidosis.

Successful treatment could be achieved by early initiation of antibiotics, correct choice of antibiotics and optimal duration of therapy. In accordance with the CDC recommendations following 2010 expert workshop, the drugs of choice for intensive and eradication phase therapy are ceftazidime or meropenem, and trimethoprim/sulfamethoxazole (Cotrimoxazole), respectively.(11) In case of CNS involvement, the duration should be eight weeks for intensive phase with intravenous antibiotics where meropenem is preferred over ceftazidime and minimum of six months for eradication phase.(1,2) Similar to the successful recovery of our patient, most of the patients are completely or partially recovered from the disease.

In this article we would like to highlight that melioidosis can occur in a patient without risk factors,

and the disease can resemble many other neurological conditions. Melioidosis should be suspected in any patient, who has clinical features suggestive of CNS tuberculosis with negative microbiological evidence. It is worthy to note that the drastic improvement was noticed following addition of cotrimoxazole to the regime. ADEM, which was not previously reported as a manifestation of CNS melioidosis, was present in our patient raising the possibility of an unrecognised presentation of the disease. Also the poor response for steroid therapy could not be explained. Possibilities are that the disease itself could be misdiagnosed as ADEM or in this particular association the response to steroids might be poor. However, ADEM in melioidosis needs to be studied further in view of pathogenesis and response to steroids in the particular concurrence.

Conclusion

CNS melioidosis is a rare entity with multiple diagnostic challenges, as it mimics most of the neurological diseases. High index of suspicion is needed in a patient coming from an endemic area, even in the absence of traditional risk factors. Early empirical treatment on suspicion should be started with appropriate antibiotics which can lead to complete recovery of the patient. Addition of cotrimoxazole to meropenem, in the intensive phase followed by cotrimoxazole alone for an extensive period of 6 months in the eradication phase would be helpful in successful recovery from CNS melioidosis.

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Ectatic coronary arteries, a cause for myocardial infarction with non-obstructive coronary arteries

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Abstract

Ectatic coronary arteries are an abnormal dilation of the coronary arteries and can contribute to the development of myocardial infarction with non-obstructive coronary arteries (MINOCA). We present a case of a previously unscreened 27-year-old man who presented with ischaemic type chest pain and was found to have ectatic coronary arteries on coronary angiogram. Despite the absence of significant stenosis, the patient experienced an acute myocardial infarction. The patient was treated with dual antiplatelet therapy and statins, and subsequent assessments showed normal echocardiography findings. Coronary artery ectasia (CAE) is a relatively uncommon condition often associated with coronary artery disease (CAD) and atherosclerosis. While antiplatelet therapy is indicated in CAE patients, the use of anticoagulation remains uncertain. Further research and clinical guidelines are needed to establish standardised management approaches for patients with CAE and MINOCA.

Keywords: ectatic coronary arteries, MINOCA, coronary artery ectasia

Introduction

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a distinct clinical entity characterised by evidence of myocardial infarction with either normal coronary arteries or coronary arteries with less than 50% stenosis.(1) Ectatic coronary arteries represent an uncommon coronary artery abnormality, characterised by the abnormal dilation of the arteries. Coronary artery ectasia is seldom inherited. It typically occurs due to acquired factors such as atherosclerosis, Kawasaki disease, certain infections, genetic disorders like Marfan syndrome, or inflammatory conditions like polyarteritis nodosa, Takayasu disease, or lupus. Iatrogenic causes, such as angioplasty, stent placement, or coronary atherectomy, can also lead to coronary artery ectasia. This condition can lead to the development of acute myocardial infarction (AMI), even in the absence of complete occlusion of the affected artery, due to sluggish blood flow and increased thrombotic risk.(2)

This case report presents a previously unscreened 27-year-old man with MINOCA, attributed to ectatic coronary arteries. The patient experienced ischaemic chest pain and was found to have ectatic coronary arteries during coronary angiography. Despite the absence of significant stenosis, the patient suffered an acute myocardial infarction. This case highlights the clinical significance of ectatic coronary arteries as a potential cause of MINOCA. While coronary artery ectasia (CAE) is relatively uncommon, it is important to recognize its association with AMI, and to develop standardised management approaches for patients presenting with this unique combination.

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Case presentation

Our patient was a 27-year-old, previously unscreened man who presented with ischaemic type chest pain associated with sweating and radiation to the neck for 45 minutes. He was a non-smoker and his father had a myocardial infarction at the age of 45.

On examination, his BMI was 24.5 kg/m^2, blood pressure 117/77 mmHg, pulse rate 88 beats per minute. Other system examination findings were normal. At the emergency treatment unit, the ECG showed partial right bundle branch block and high sensitivity troponin I was 9.84 ng/mL(<0.034). The patient was given aspirin 300 mg, clopidogrel 300 mg, atorvastatin 40 mg as stat doses with subcutaneous enoxaparin 60 mg. The patient subsequently underwent an urgent coronary angiogram (CA). In the coronary angiogram, the left main coronary artery (LMCA), left anterior descending artery(LAD) and left circumflex artery(LCX) were normal. The right coronary artery (RCA) was ectatic and non obstructive (figure 1). His troponins dropped from 9.87 to 4.53 on the following day and echocardiography was normal with no regional wall motion abnormalities and an ejection fraction of >60%. On the lipid profile, total cholesterol was 223 mg/dL(<200), Triglycerides 70 mg/dL(<150), HDL 45 mg/dL(>50) and LDL 163 mg/dL(<100). His full blood count, liver profile and renal functions were normal.

Following the CA he was started on aspirin 75 mg, clopidogrel 75 mg, atorvastatin 40 mg and subcutaneous enoxaparin 60 mg twice daily for 3 days. He was discharged on day 4 with dual antiplatelets, a statin and cardiology follow up.

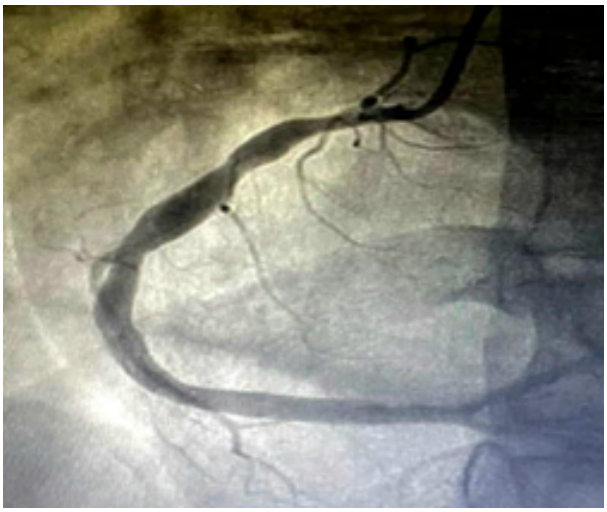

Figure 1 - Ectatic and non-obstructive right coronary artery

Discussion

Coronary artery ectasia (CAE) is a relatively uncommon coronary artery abnormality which is characterised by localised or diffuse dilatation of the coronary artery diameter exceeding the diameter of adjacent normal artery (reference vessel) segments by 1.5 times.(3,4) Clinical presentation can vary widely. They can be asymptomatic or present with atypical chest pain or typical ischaemic chest pain which can be either stable angina or acute coronary syndrome.(4) Coronary angiography is the main diagnostic tool used to diagnose CAE.(5), and an incidence of 1% to 5% of CAE has been identified in patients who undergo coronary angiograms.(3)

The pathogenesis and aetiology of CAE is not fully understood, but CAE is commonly associated with conditions like Kawasaki disease or familial hypercholesterolaemia.(6) The most common disease association is coronary artery disease (CAD) and about 85% of CAE patients are also found to have coronary atherosclerosis.(4) In fact, most studies have established a significant incidence of myocardial infarctions in CAE patients. Hence aspirin is indicated in all.(3-5) CAE with associated atherosclerosis has similar morbidity, mortality rates and risks to atherosclerotic coronary artery disease.(7) Hence, atherosclerotic CAE management consists of regular antiplatelet therapy(3) and aggressive risk factor management such as lipid control.(7) Drug groups such as statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and dihydropyridine calcium channel blockers have shown a beneficial effect in the management of CAE but most of the treatment options are based on expert opinion as there are no clinical guidelines to follow.(7)

Our patient was discharged with dual antiplatelets, a statin and routine cardiology follow up assessments. The decision to start him on anticoagulation was a dilemma since literature was unclear about it. Coronary blood flow disturbances have been observed in ectatic segments of coronary arteries, hence, some experts suggest that there's a place for anticoagulation.(3) Since data is insufficient to support this treatment, it should be individualised until further evidence is available.(3)

In a case where CAE presents as a STEMI the treatment options include medical thrombolysis, percutaneous stenting or surgical revascularization. (3) It is very important to note that both stenting and aspiration thrombectomy can result in distal thromboembolism.(7) Although CAE is a strong

independent risk factor for failure to achieve reflow after PCI for STEMI, and alternative management options may be needed, revascularization and mortality rates are comparable to those in patients without CAE.(8,9)

Conclusion

This case presentation underscores the importance of recognising and managing coronary artery ectasia (CAE) in patients presenting with chest pain. Although the aetiology and pathogenesis of CAE remain unclear, associations with conditions such as coronary artery disease (CAD) have been observed. Antiplatelet therapy, particularly aspirin, is indicated in CAE patients, and aggressive risk factor control is essential.

While there is no clear consensus on the use of anticoagulation in CAE, individualised treatment decisions should be made based on available evidence. Further research and clinical guidelines are needed to establish standardised management approaches for CAE patients.

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Unilateral basal ganglia infarction presenting as sudden onset daytime sleepiness

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Abstract

Basal ganglia (BG) are involved in motor coordination. BG strokes usually present with problems controlling speech, movements, mood and posture leading to abulia which is a prominent feature. BG stroke presenting with daytime sleepiness is not well reported. We report a 63-year- old Asian woman with hypertension presenting with sudden onset daytime sleepiness due to basal ganglia infarction. This case highlights the importance of considering BG infarction as a differential diagnosis for sudden onset daytime sleepiness.

Keywords: basal ganglia infarction, apathy, lacunar infarcts, excessive daytime sleepiness, stroke

Introduction

Basal ganglia are a group of subcortical nuclei responsible primarily for motor control as well as motor learning, executive functions, behaviour, and emotions. It is the key part of the network of the brain that controls your voluntary movements.(1) BG lesions lead to abulia, which is a syndrome of "hypofunction," with lack of initiative, spontaneity, drive, apathy, slowness of thought (bradyphrenia), blunting of emotional responses and response to external stimuli.(2) The commonest cause of BG strokes is lacunar infarcts due to lenticulostriate artery ischaemia.(3) Damage to the basal ganglia causes problems in controlling speech, movement, and posture similar to the symptoms of parkinsonism. Sudden changes in behaviour and apathy have been reported as signs of basal ganglia stroke.(4,5) However, basal ganglia stroke, which presents as excessive sleepiness is not reported.

Case presentation

A 63-year-old active woman complained of excessive sleepiness for a day. She was otherwise well. She was on losartan 50 mg twice a day and atorvastatin 20 mg at night for the past 3 years. The sleepiness persisted for the next day as well and she accidentally dropped a glass bottle held in her left hand. She cut her left index finger while chopping vegetables, which was unusual for her. Her family noted some subtle changes in her behaviour with unusual lethargy and she was taken for medical advice.

On examination, her GCS was 15/15, and there were no focal neurological signs, including sensory disturbance or incoordination. Her blood pressure was 150/90 mmHg and the pulse was 88 beats per minute. All her basic haematological and biochemical studies, including serum electrolytes, random blood sugars and other investigations, were normal.

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Because of the sudden onset of symptoms, she had a magnetic resonance imaging (MRI) scan of the brain done following 48 hours of the index event. The MRI of the brain showed an acute infarction of the right-side basal ganglia region (figure 1).

She was managed for an acute infarction of the brain with Aspirin 300 mg stat and Clopidogrel 300 mg stat, followed by Aspirin 75mg and Clopidogrel 75 mg at night for 3 weeks. Furthermore, her blood pressure control was optimised by adding hydrochlorothiazide 25 mg in the morning to losartan 50 mg twice daily while the atorvastatin dose was increased to 40 mg a day. Her sleepiness improved over a month and her apathy improved gradually over one year, but she's still not as active as she was before, after two years from the event.

Discussion

This previously active woman with sudden onset sleepiness, apathy and incoordination was diagnosed to have a BG infarction based on MRI findings. She did not have prominent weakness of muscles but had bradykinesia and incoordination confirming basal ganglia involvement. She was treated for a cerebral infarction but was not thrombolysed, as she presented after 6 hours of the onset of symptoms and because she did not have an objective weakness or impairment.

BG are a group of subcortical nuclei primarily responsible for motor control, motor learning, executive functions like paying attention and staying focused, self-monitoring, organising, planning, behaviour, and emotions.(1,6,7) Our patient had an impairment of most of these functions which were difficult to be identified by an external person or the clinician, as they are difficult to assess objectively. However, her family who knew her usual behaviour, had noted some abnormality.

Basal ganglia infarction, presenting with impairment in speech, movement, and posture leading to abulia, akinesia, amnesia, dis-inhibition and hemi-neglect is reported in the literature.(8,9,10) Abulia is the commonest behavioural symptom that is observed in BG infarcts, with a prevalence of 13%.(8,11) Abulia and confusion have been noted in patients with right side anterior lenticulostriate artery infarcts, which were also present in our patient. Prominent motor deficits, neglect, frontal system dysfunctions and visual amnesia have been noted in relation to right side lateral lenticulostriate artery infarcts.(9) Daytime somnolence is not reported as a presenting symptom of BG strokes.

BG receives input from the suprachiasmatic nucleus (SCN), which is the master pacemaker of the circadian rhythm located in the hypothalamus. BG has a reciprocal connection with the SCN, which allows BG to influence the circadian rhythm. In addition, BG receives input from other sleep-regulating areas of the brain like the thalamus and brainstem. All these signals play a role in the regulation of sleep and wakefulness during higher level cognitive processes. Damage to the BG nucleus in an infarct can disrupt these actions.(14) BG are responsible for choosing actions that will lead to a positive consequence and facilitate desired movement while inhibiting unwanted movements that contradict the said action

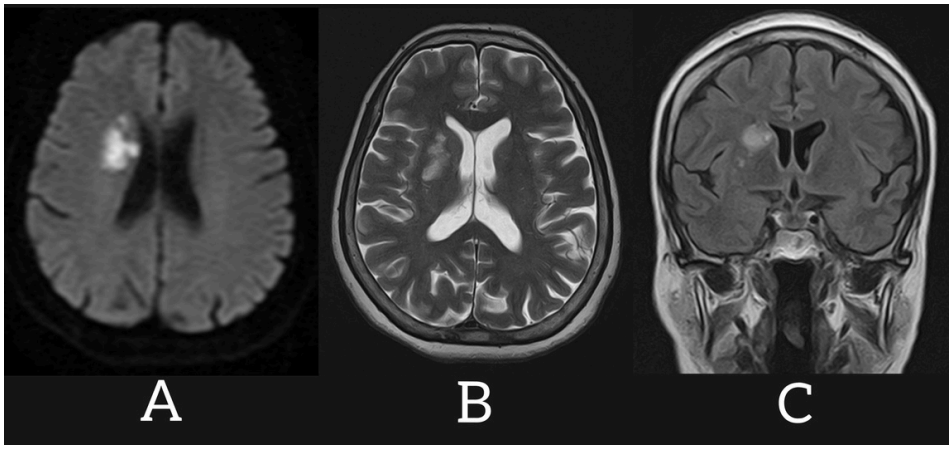

Figure 1 - Non-contract magnetic resonance image of the brain after 48 hours of the index event showing acute infarction of the right-side basal ganglia, **A;** Diffusion weighted image, **B;** Apparent diffusion coefficient image, **C;** T2 Flair imagest x-ray taken on admission(left) and after treatment(right) showed remarkable improvement

simultaneously.(8,11-13) "Rate model of basal ganglia" explains this by modulating firing rates of neurons in the BG by the balance of excitatory and inhibitory inputs received(15), explaining the maintenance of awake status.

Conclusion

This case highlights the importance of considering basal ganglia stroke as a differential diagnosis of acute onset daytime sleepiness. It also highlights the importance of taking a good history from the patient as well as from close family or eyewitnesses.

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A fatal case of diphtheria endocarditis complicated with microangiopathic haemolytic anaemia and multiple septic emboli causing brain infarctions in a patient with smear-positive pulmonary tuberculosis

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Abstract

Endocarditis due to non-toxigenic Corynebacterium diphtheriae is emerging as a rare subtype of endocarditis, with limited case reports available. It has been related to the presence of prosthetic valves, underlying cardiac disease, or the use of injectable drugs. We present a fatal case of endocarditis due to non-toxigenic Corynebacterium diphtheriae in a native aortic valve complicated with microangiopathic haemolytic anaemia and multiple septic emboli in the brain causing infarctions in a patient with smear-positive pulmonary tuberculosis who was on anti-tuberculosis therapy (ATT). Following blood culture positivity and suggestive evidence from the echocardiogram, the patient was initially treated with intravenous ceftriaxone and vancomycin along with ATT. Evolution was assessed by sterile blood cultures post therapy and follow-up transthoracic echocardiograms (TTE) and transesophageal echocardiograms (TOE). Even though the patient's condition improved with intravenous antibiotic therapy, it later deteriorated with disseminated intravascular coagulation and liver injury followed by prerenal acute kidney injury and multiple septic emboli causing the patient's demise, which may have necessitated surgical interventions.

Keywords: *Corynebacterium diphtheriae*, infective endocarditis, septic emboli, pulmonary tuberculosis, microangiopathic haemolytic anaemia, disseminated intravascular coagulation

Introduction

Corynebacterium diphtheriae, a Gram-positive bacillus, was originally identified by Loeffler in 1884. In 1893, the first case of infective endocarditis caused by the organism was documented. It has been associated with factors such as the use of injectable medications, the presence of prosthetic heart valves, and underlying cardiac conditions.(1–3) After the introduction of the EPI immunisation program in 1978, the disease caused by Corynebacterium diphtheriae has declined and achieved elimination status in the late nineties. There have been isolated reports of adult Corynebacterium diphtheriae infections in the non-immunized adult population.(4) In patients with prosthetic heart valves, non-toxigenic

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Corynebacterium diphtheriae, a Gram-positive bacillus, was originally identified by Loeffler in 1884. In 1893, the first case of infective endocarditis caused by the organism was documented. It has been associated with factors such as the use of injectable medications, the presence of prosthetic heart valves, and underlying cardiac conditions.(1–3) After the introduction of the EPI immunisation program in 1978, the disease caused by *Corynebacterium diphtheriae* has declined and achieved elimination status in the late nineties. There have been isolated reports of adult *Corynebacterium diphtheriae* infections in the non-immunized adult population.(4) In patients with prosthetic heart valves, non-toxigenic strains cause an invasive disease that more frequently requires surgical interventions owing to its aggressive nature. However, it is an uncommon cause of infective endocarditis in native valves. Current evidence suggests that endocarditis of either native or prosthetic valves, caused by *C. diphtheriae*, demonstrates a favourable outcome when treated with either beta-lactamase monotherapy or combined therapy with an aminoglycoside.(2)

Case presentation

A 56-year-old man with a history of diabetes mellitus for 18 years and poor compliance with medications was recently diagnosed with smear-positive pulmonary tuberculosis. By the time of presentation, he was on day 13 of anti-tuberculosis therapy (ATT) and presented with a fever associated with loss of appetite, malaise, and generalised ill health. He was unaware of his vaccination status, denied the use of intravenous drugs other than a history of frequent cannulation during the period of evaluation for pulmonary tuberculosis, and had no history of cardiac surgeries.

Examination revealed a febrile (101^{0}C), ill, toxic-looking, thin-built male with a blood pressure of 100/70 mmHg and tachycardia at 112 beats per minute. There was a grade III mitral regurgitation (MR) murmur and a grade IV aortic regurgitation (AR) murmur with bilateral fine crepitations. There was no splenomegaly or peripheral stigmata of infective endocarditis. No neck stiffness or focal neurological signs were observed.

Baseline investigations including full blood count (FBC), inflammatory markers, and blood picture showed severe infection with ongoing microangiopathic hemolytic anaemia. Renal and liver function tests were initially normal (table 1). The *Corynebacterium diphtheriae* organism was isolated in two of three blood cultures that were taken before intravenous antibiotic therapy and a transthoracic echocardiogram demonstrated a moderate to severe AR, moderate MR, and a hyperechoic mass attached to the ventricular side of the non-coronary cusp of the aortic valve (1*0.3cm) (figure 1). Non-contrast CT scan of the brain revealed an infarction in the left parietal region (figure 2)and MRI of the brain showed multiple septic emboli in the brain causing infarctions in the left parietal region, left cerebellar region, and focal subarachnoid haemorrhage in the right central sulcus (figure 3). The chest x-ray was compatible with previously documented findings before starting the anti-tuberculosis therapy with good resolution. Contrast-enhanced CT of the chest, abdomen, and pelvis revealed areas of consolidation in the right upper, and middle lobes with right-side pleural effusion.

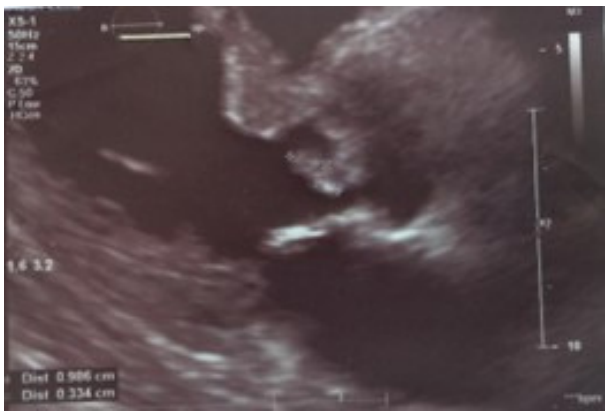

Figure 1 - Transthoracic echocardiogram demonstrates a 1*0.3 cm vegetation in the non-coronary cusp of the aortic valve

Case complexity required an intense multidisciplinary approach with the participation of medical, microbiology, cardiology, respiratory, haematology, and transfusion medicine teams. The patient received intravenous ceftriaxone 2 g twice a day for 10 days and intravenous vancomycin 1 g twice a day for 11 days with initial good clinical and biological improvement, including sterilisation of blood culture on day 9 of intravenous antibiotics.

However, at the end of day 10, the patient demonstrated deteriorating renal, and liver functions and coagulation profiles. Despite the coagulopathy correction, switching intravenous antibiotics from vancomycin to teicoplanin, and withholding anti-tuberculosis therapy may have contributed to the liver injury. The patient died on day 15 of the illness.

Table 1 - Laboratory investigations of the patient

Investigation	Day 1	Day 5	Day 10	Day 14	Ref. Range
WBC (/udL)	20.52	15.16	19.58	22.4	4-10
Hb (g/dL)	9.5	8.4	7.7	9.4	11-15
PLT (/udL)	55	36	95	115	150-400
CRP (mg/L)	165.3	84.2	96.4	60.1	0-5
ESR (mm/1st hour)	106	101			15-20
Serum creatinine (micm/L)	105.4	95.2	121	252.3	70-115
Na (mmol/L)	141	139	133	139	137-145
K (mmol/L)	2.9	3.8	4.1	3.6	3.5-5.1
AST (U/L)	46	101	164	42	0-35
ALT (U/L)	35	70	63	37	0-40
ALP (U/L)	98	96	101	106	46-116
GGT (U/L)	34	35	38	31	0-50
T. P (g/dL)	6.1	6.4	6.0	6.2	6-8
T. B (micm/L)	19.2	22.7	33.2	49.8	5-20
INR	1.73	1.15	2.78	3.21	1.1
APTT	27.4	29.9	47.5	35.5	25-35
Blood picture	MAHA	Fragmented red cells	MAHA	MAHA	
S. Ca (mmol/L)	1.9	1.8	1.7	1.8	2.1-2.5
Mg (mmol/L)	0.7	0.7	0.7	0.9	0.7-0.9
PO4 (mmol/L)	0.9	1.0	0.98	1.4	0.8-1.45
Trop I (ng/L)	269	76	13.2		<12
LDH (U/L)	442		345		140-240
S. Ferritin (ng/mL)		562	406		18-464
TG (mg/dL)		141	163		<150
UFR	[-]		[-]		
HIV 1 &2		Negative			

WBC: white blood cells, PLT: platelets, Hb: haemoglobin, CRP: C reactive protein, ESR: erythrocyte sedimentaation rate, S. Cr: serum creatinine, Na: sodium, K: potassium, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, T. P: total protein, T. B: total bilirubin, INR: international normalised ratio, S. Ca: serum calcium, Mg: magnesium, PO4: phosphate, LDH: lactate dehydrogenase, TG: triglycerides, UFR: urine full report

Discussion

Corynebacterium diphtheriae is a gram-positive bacillus that is now scarce due to global immunisation. A diphtheria toxoid vaccination was developed in 1923 from diphtheria toxin treated with formalin to inactivate the toxicity and maintain the immunogenicity,(5,6) minimising the morbidity and mortality of the disease, particularly in children. Nevertheless, infections caused by highly aggressive non-toxigenic strains are not prevented by the vaccine.(7) Similar to endocarditis caused by *Staphylococcus aureus, Corynebacterium diphtheria* infection is a very aggressive, and destructive disease, which often requires prompt surgical intervention, especially in patients with prosthetic valves. Even with adequate treatment, it often advances to a fulminant disease.

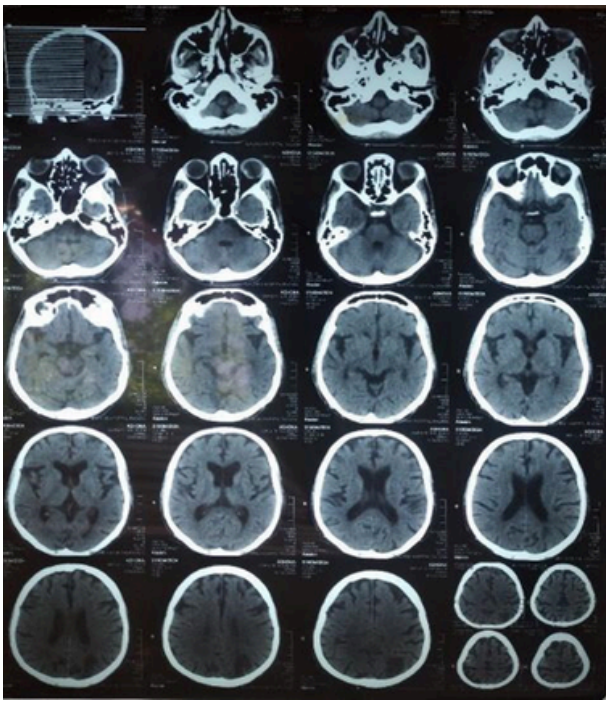

Figure 2 - Non-contrast CT scan of the brain demonstrates infarction in the left parietal region

Majority of patients with endocarditis due to *C. diphtheriae* have prosthetic valves, underlying cardiac conditions, or a history of intravenous drug use.(1,2) The use of inhaled drugs such as cocaine causes direct injury to the nasal mucosa which can also trigger periods of transient bacteraemia.(7)

The isolation of *Corynebacterium* in blood cultures is usually interpreted as contamination and it can impede the diagnosis of endocarditis, contributing to the mortality of this disease.(8,9) Its defining features are large valvular vegetation, valvular dysfunction, destruction, metastatic septic emboli with the development of peripheral aneurysms, pseudoaneurysms, and a high mortality rate.(1) Endocarditis is more common in left heart valves, with mitral valve being the most frequently affected site.(8)

A combination of antimicrobial therapy, typically an aminoglycoside and a beta-lactam antibiotic over 4-6 weeks is advised.(2) Cephalosporins combined with gentamicin, penicillin alone, or cephalosporins combined with vancomycin have also been successful

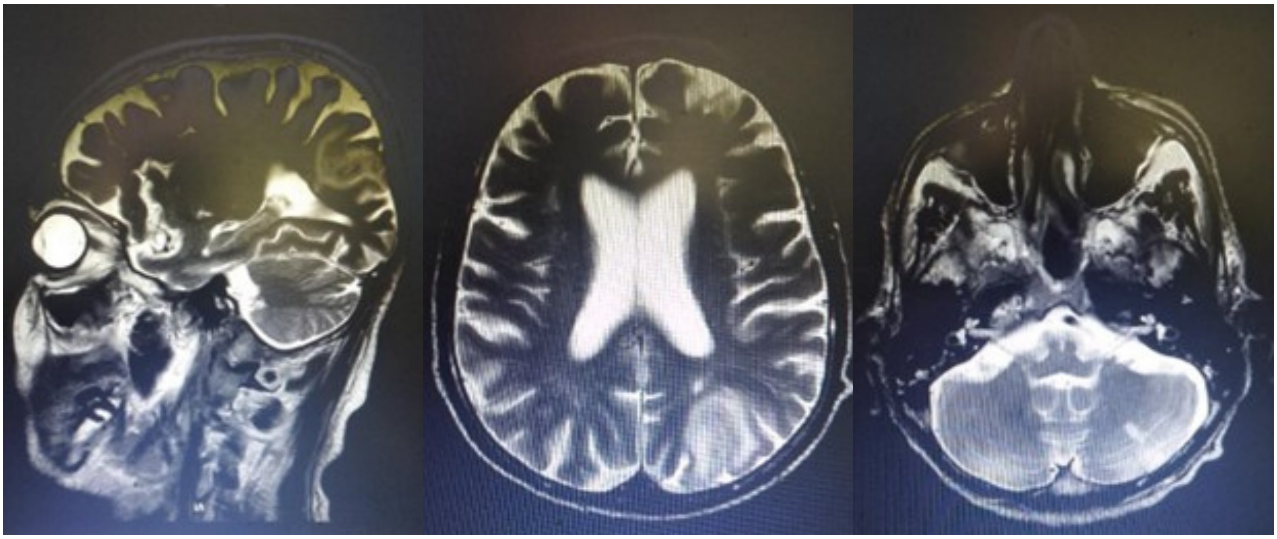

Figure 3 - MRI of the brain demonstrates multiple septic emboli in the brain causing infarctions in the left parietal and left cerebellar regions

remedies.(1) The antibiotics are chosen based on their synergistic properties when combined. When establishing a strategy for therapy, it's important to consider variables unique to each patient, such as ototoxicity or prior renal impairment, which may make monotherapy more favourable. (2) Surgical intervention involving valve replacement is mandatory in patients with heart failure, recurrent embolization, persistent bacteraemia with haemodynamic instability, and in patients who develop acute prosthetic obstruction in the presence of large vegetation. (10)

Our patient had long-standing diabetes, and active pulmonary tuberculosis with a history of frequent cannulation during the period of evaluation for tuberculosis, although he didn't have a significant history of intravenous drug use, or underlying cardiac disease. The condition was complicated with ATT-induced liver injury leading to coagulopathy. This case stands out for the severity of diphtheria bacteraemia causing endocarditis, complicated with septic emboli in the brain, and microangiopathic haemolytic anaemia causing a fatal outcome. Initially, we thought of a possible mycotic aneurysm in our patient since he had a focal subarachnoid haemorrhage in the right central sulcus, which was later reported as a focal bleeding most possibly due to ongoing disseminated intravascular coagulation, considering its location and radiological features. Our institution has no facilities for cardiothoracic surgeries which may have been necessary for the management of our patient considering the presence of multiple septic emboli.

Conclusion

This case underlines the challenges in the management of non-toxigenic *Corynebacterium diphtheriae* endocarditis on a native aortic valve in a patient with active smear-positive pulmonary tuberculosis with underlying diabetes mellitus and a history of frequent cannulation during the period of evaluation for pulmonary tuberculosis. Our patient had vegetation, embolization, and microangiopathic hemolytic anaemia despite intravenous antibiotic therapy, which may have necessitated surgical intervention.

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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Malignant hypertension as a rare cause of thrombotic microangiopathy associated with end-stage renal disease

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Abstract

Malignant hypertension (MH) can precipitate and worsen renal thrombotic microangiopathy. Also, renal thrombotic microangiopathies (TMA) can cause malignant hypertension. Case reports regarding this clinical presentation are limited. A 36-year-old man presented with low urine output and bilateral leg swelling for five days with two episodes of haemoptysis. He was identified as a patient with hypertensive emergency with hypertension mediated organ damage (HMOD) in cardiac and renal functions with thrombotic microangiopathy. Renal biopsy revealed focal acute tubular injury with moderate tubulointerstitial nephritis and hypertensive vascular changes. Multiple anti-hypertensive medications were used for adequate blood pressure control. Despite that, the patient had worsening renal function, and eventually became dependent on haemodialysis. Malignant hypertension has to be considered as one of the aetiologies of TMA as it can lead to end-stage renal disease (ESRD) and poor outcomes. Diagnosis is difficult when both entities are presenting together.

Keywords: malignant hypertension, thrombotic microangiopathy, tubulointerstitial nephritis, hypertension mediated organ damage

Introduction

Various mechanisms are implicated in the pathogenesis of thrombotic microangiopathies (TMA). (1) Haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopaenic purpura (TTP) are usually associated with TMA.(1) Each of these diseases is unique in pathophysiology. Several pathophysiological pathways are involved in developing TMA, including endothelial injury, intravascular platelet activation, and formation of platelet-fibrin thrombi.(1) Patients with atypical haemolytic uraemic syndrome (aHUS) and MH both present with concomitant hypertension and thrombotic microangiopathy (TMA), making management difficult.(2) The causes of TMA need to be identified and treated as they have therapeutic implications.(3)

Case presentation

A 36-year-old man, a previously known patient with essential hypertension, was transferred to our unit for plasma exchange due to TMA. He had not seen a primary care physician for many years and had defaulted treatment. He had a non-productive cough, mild fever, and a sore throat. He had been diagnosed with mild COVID-19 infection and had been admitted to the intermediate care centre one week prior to the current admission. He was found to have a low haemoglobin level (6 g/dL), low platelets (67,000), and a high creatinine level of 17 mg/dL (0.7-1.3 mg/dL), and was transferred to the base hospital for haemodialysis. He reported low urine output and bilateral leg swelling for the last five days with two episodes of a scanty amount of haemoptysis. He also said that he felt exhausted in the past few days. He

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had accelerated hypertension of 280/180 mmHg on examination. He had a blood pressure reading of 230/160 mmHg on his past records and had been advised on medical evaluation which he had defaulted. The patient did not have a family history of hypertension. He denied substance abuse. Examination revealed pallor, icterus, bilateral pitting leg edema, cardiomegaly, gallop rhythm, bilateral pleural effusions, and ascites. Fundoscopy revealed grade 4 hypertensive retinopathy.

Routine investigations were performed to assess end-organ damage. Initial laboratory data revealed a creatinine of 17.0 mg/dL which reduced to 8.0 mg/dL following haemodialysis (HD). His baseline creatinine was 1.3 mg/dL one year back. Haemoglobin was 6 g/dL (with a mean corpuscular volume of 88 femtoliters), indirect bilirubin was 2.0 mg/dL, and platelet count was 69 x 10^9 /L. Haemolysis was confirmed by a lactate dehydrogenase (LDH) of 1455 IU/dL. A blood smear revealed the presence of schistocytes /fragmented cells and polychromatic cells. The coexistence of haemolytic anaemia, thrombocytopenia, and schistocytes revealed thrombotic microangiopathy. He had left ventricular hypertrophy on the ECG.

His 2D echo showed severe left ventricular hypertrophy with diastolic dysfunction, which was suggestive of hypertensive heart disease. On admission, chest x-ray showed acute pulmonary oedema. HRCT also showed fluid overload with an atypical infection. The urinalysis showed 4+ protein, 3+ haemoglobin, 200 red blood cells/high power field, two red cell casts/low power field, and two granular casts/common power field. Urine protein creatinine ratio confirmed nephrotic range proteinuria (15 g/mmol). The patient was identified to have a hypertensive emergency with end-organ damage to the heart and the kidneys. The left ventricular strain manifesting was suggestive of cardiac dysfunction. The patient also had end stage renal disease (ESRD) at the time of admission. The underlying left ventricular hypertrophy and diastolic dysfunction were indicative of chronic uncontrolled hypertension. The cause of thrombotic microangiopathy is malignant hypertension.

Preliminary investigations were targeted to exclude the common causes of thrombotic microangiopathy. The patient denied diarrhoea over the past few days, making the diagnosis of HUS unlikely. Fever and neurological symptoms were absent, making TTP an unlikely aetiology. He had normal complement levels. USS abdomen revealed bilateral chronic renal parenchymal changes with altered corticomedullary demarcation (left and right renal sizes were 11.3 cm and 10.8 cm respectively). We didn't exclude aHUS, and further testing was not done due to low probability. Rapidly progressive glomerulonephritis (RPGN), vasculitis screens, such as anti-glomerular base membrane antibodies (Anti-GBM antibodies), ANA, Anti-dsDNA, C-ANCA, P-ANCA, HIV, and hepatitis screens, were negative. This patient had bilateral papilloedema with haemorrhages in fundoscopy. It was confirmatory of malignant hypertension, which was the likely cause of the TMA. Unfortunately, his renal disease was advanced requiring HD at the time of admission, and a renal biopsy was done. It revealed two completely sclerosed glomeruli, two partially sclerosed glomeruli, and three viable glomeruli with focal mesangial matrix hypercellularity and expansion. There was no evidence of glomerulonephritis. Focal acute tubular injury, moderate tubulointerstitial nephritis and hypertensive vascular changes were seen. Glomerulosclerosis favours chronic hypertension with hypertensive nephropathy. Secondary causes of hypertension were excluded through investigations.

Plasmapheresis was not considered as the aetiology for TMA was malignant hypertension. Multiple oral medications were used for aggressive blood pressure control. Despite the medications, his renal function did not improve, and he became dependent on dialysis. He was discharged after stabilisation. Family counselling was arranged regarding renal transplantation. He is currently followed up regularly in the clinic.

Discussion

Various mechanisms cause TMA, but the final event is platelet activation.(4) A tendency for platelet activation or endothelial damage is caused by various distinct aetiologies.(4) The formation of microthrombi in the microvasculature results from the activation of platelets.(1) Renal vessels are involved in this process, and impaired renal function is seen in TMA syndromes.(5) TTP, HUS, and aHUS usually cause TMA.(5) TTP is due to hereditary or acquired deficiency of ADAMTS13, an enzyme needed for von Willebrand factor (VWF) lysis.(6) Increased VWF at the site of endothelial injury increases platelet adhesion.(6) High shear stress-induced endothelial injury in TMA is postulated to be due to malignant hypertension.(6)

The presence of thrombocytopaenia due to microangiopathic haemolytic anaemia is needed to diagnose TMA.(1) Microangiopathic haemolysis is

Table 1 - Summary of investigations for the aetiology of end-stage renal disease (ESRD)

Investigation	Result
Hepatitis B surface antigen	Negative
HIV antigen & antibodies	Negative
Hepatitis C surface antibody	Negative
Anti-nuclear antibody (ANA)	Negative
perinuclear (P-ANCA) or cytoplasmic (C-ANCA) anti-neutrophil cytoplasmic antibodies	Negative
Complement levels	Normal
Serum protein electrophoresis	Normal study
Serum calcium level	9.2 mg/dl (8.5-10.5mg/dl)
Anti glomerular basement membrane antibodies (Anti GBM Ab)	Negative
Renal artery doppler	Normal study, no stenosis of renal artery

associated with the standard features of haemolysis such as normocytic anaemia, indirect bilirubinaemia, high LDH level, low haptoglobin level, and presence of schistocytes on blood picture additionally.(1) All TMA syndromes will have these findings regardless of the aetiology.(7) The aetiology must be treated promptly if TMA is identified.(7) If HUS is suspected, Shiga-like toxin PCR will help to confirm the diagnosis.(8) Neurological symptoms and fever are pathognomonic for TTP.(9) ADAMTS13 enzyme activity is also assessed.(6) Complement factors 3 and 4 levels may be low in patients with atypical HUS.(2)

However, aHUS is not ruled out by normal complement factor levels. aHUS can be confirmed by genetic testing.(10) However, the availability of genetic testing is limited. The presence of papilloedema is needed to diagnose malignant hypertension as per the previous definition.(10) However, recent definitions propose that damage to a minimum of three target organs is considered malignant hypertension.(11) The typical target organs involved are the brain, heart, kidney, and microvasculature.(11) TMA is also viewed as a manifestation of acute HMOD.(11) Extremely high pressure is noted in MH-induced TMA compared to hypertension secondary to TMA.(11) Alternative aetiologies for TMA need to be excluded through combined history, examination, and investigations.(12) If malignant hypertension is identified as an aetiology of TMA, there is no place for plasmapheresis or eculizumab therapy which are established therapies for other causes of TMA.(12) Blood pressure control is the only intervention that needs to be done in patients with malignant hypertension-induced TMA.(11)

Our patient had an unusual laboratory finding of a urinary red cell cast. These are usually associated with glomerulonephritis and renal vasculitis.(13) These sediments are distinctive in malignant hypertension-induced TMA.(14) However, severe malignant hypertension can have this sediment due to focal ischaemic necrosis associated with microangiopathic haemolytic anaemia.(14) Despite the global glomerular ischaemic injury, glomerular necrosis was not identified in our patient's renal biopsy. This may be due to the limited number of glomeruli extracted during the renal biopsy.

Conclusion

TMA is a unique clinicopathologic entity where the constellation of findings is identified through investigations. Aetiology for TMA has to be actively sought as it has therapeutic implications. If MH is found to be a cause of TMA, tight blood pressure control is the only available treatment. The incidence of renal failure is very high in patients with MH-induced TMA, and it signifies a poor prognosis.

Declarations

Author contributions
JCC and SY have contributed equally to the manuscript's conception and preparation. JCC and SY have been involved in the management of the patient. All authors read and approved the final manuscript.

Conflicts of interest
The authors declare that they have no conflicts of interest with respect to the research, authorship, and/or publication of this article

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Uncommon presentation of a patient with hereditary haemorrhagic telangiectasia

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Abstract

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder. It is clinically characterised by telangiectasia, recurrent epistaxis, and visceral vascular lesions. We report a case of HHT without a significant family history. A 16-year-old girl presented with multiple episodes of bleeding, including uncommon sites, over a period of ten months. She denied a family history of bleeding. Her clinical examination was unremarkable. Investigations including basic and second-line coagulation tests were normal. Subsequently multiple telangiectasias in the right nasal septum and capillary dilatation in the bladder wall were detected. According to Curaçao diagnostic criteria, a diagnosis of HHT was made. As her bleeding was self-limiting, follow up was arranged to monitor complications.

Keywords: hereditary hemorrhagic telangiectasia, haematuria, nipple bleeding

Introduction

Hereditary hemorrhagic telangiectasia (HHT) is a vascular disorder inherited as an autosomal dominant trait.(1) Most patients with HHT have only epistaxis, mucocutaneous telangiectasia and iron deficiency anaemia secondary to blood loss.(2) Urinary tract involvement occurs only in 3% of these cases.(3) We report a case of HHT with uncommon bleeding manifestations without a significant family history.

Case presentation

A previously healthy 16-year-old girl presented with recurrent episodes of bleeding from multiple sites of the body over a period of 10 months. She had several episodes of epistaxis, bleeding from nipples and haematuria 4 months ago. She also had two episodes of bleeding manifestations from the right eye three months apart. Episodes were mild and self-limiting. There was no history of bleeding into muscles or joints, haemoptysis or bleeding from gastrointestinal tract. She denied excessive bleeding from cut injuries or menorrhagia. She denied recurrent infec tions or symptoms to suggest anaemia. She was a product of a non-consanguineous marriage and had no family history of bleeding disorders. She was not on any routine medications.

Her body mass index was 23.4 kg/m^2. She was not icteric or pale. Her clinical examination was unremarkable. Investigations showed a normal white cell count of 10.8 x 10^9/L, Hb of 13.6 g/dL, platelet count of 274 x 10^9/L, and normal liver and renal functions. Initial coagulation screening showed a bleeding time of 3 minutes , prothrombin time (PT) of 12.2 s, activated partial thromboplastin time (APTT) of 29 s thrombin time (TT) of 16 s, fibrinogen of 358 mg/dL and negative D-dimers. Further coagulation studies revealed a factor XIII level of 97%, VWF antigen of 94% and normal VWF function of 96%. The peripheral blood smear showed normal neutrophil and platelet morphology, and early iron deficiency. A clot solubility study revealed a stable clot after 24

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hours. Factor VIII assay excluded minor factor VIII deficiency with a factor VIII level of 98%. Platelet aggregation studies showed normal aggregation with ADP, collagen, arachidonic acid and ristocetin.

Nasal examination revealed a deviated nasal septum and multiple telangiectasias in the right septum. Ultrasound examination of breasts was normal. Serum ferritin, rheumatoid factor, P-ANCA, C-ANCA, C3, and C4 levels were normal. MRI brain was unremarkable.

Urine full report confirmed haematuria and ultrasound scan of the abdomen followed by CT urogram revealed no structural abnormality. Subsequent cystoscopy revealed capillary dilatation in the bladder wall. Upper gastrointestinal endoscopy, and fibre optic laryngoscopy were normal and ocular examination failed to show abnormal blood vessels.

With the given clinical history, normal coagulation tests, nasal telangiectasia, and capillary dilation of the bladder wall, a clinical diagnosis of hereditary hemorrhagic telangiectasia was made. As her bleeding episodes were recurrent and self-limiting, we prescribed oral tranexamic acid during episodes of bleeding. Iron deficiency anaemia was managed with hematinics.

Discussion

Majority of patients with HHT are unaware of their diagnosis and have not been diagnosed at the time of hospital admission.(4) Recurrent epistaxis is the most common and earliest clinical feature of HHT. Telangiectasias of the skin and buccal mucosa are typically present from about the third decade of life.
HHT shows varying penetrance and expression. Pathogenic variants in multiple genes can cause HHT. Three major disease-associated genes that account for more than 80% of cases have been recognised. Absence of family history in the index case, can be due to the variable penetrance and expression of the disease. HHT presentation patterns are highly variable, even within the same family. Individuals with the same HHT pathogenic gene variant can have different clinical manifestations.

Our patient's disease onset was around 15 years of age, and she had bleeding manifestations from unusual sites, including haematuria, bleeding from nipples and from the right eye. In HHT, coagulation tests are normal. Laboratory investigations usually demonstrate only iron deficiency. Diagnosis is based on the international consensus of the Curaçao diagnostic criteria.(3,5)

As our patient had normal PT, APTT, TT and fibrinogen assay, von Willebrand disease, factor XIII deficiency, platelet function defect, minor factor deficiency or vessel wall abnormalities were considered as differential diagnoses. Subsequent tests revealed normal factor VIII, XIII, VWF and normal platelet aggregation studies. Her nasal examination demonstrated deviated nasal septum and multiple telangiectasia in the right septum. Cystoscopy demonstrated dilated blood vessels in the bladder wall.

Our patient had three out of four Curaçao criteria and accordingly the diagnosis of HHT was made. Genetic testing was not available.

Ocular involvement can be seen in about 50% of cases of HHT.(6) But nipple bleeding has not been described in the literature. Breast pathologies were excluded with ultrasound examination. Patients diagnosed with HHT should be screened for asymptomatic arteriovenous malformations (AVM). Her Gastroscopy was normal and the MRI brain failed to show cerebral AVMs. Screening for pulmonary AVMs was planned with a CT Chest.

Iron deficiency anaemia in HHT is treated with iron replacement.(7) In our patient oral tranexamic acid was prescribed during her episodes of bleeding and iron deficiency was managed with hematinics. Annual follow-up was arranged.

Conclusion

Although rare, HHT should be kept in mind when patients presenting with spontaneous recurrent epistaxis and bleeding from uncommon sites when the coagulation studies are normal. Absence of family history does not exclude HHT.

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Bilateral mydriasis as the first manifestation of Miller Fisher syndrome

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Abstract

Miller Fisher Syndrome (MFS) is a rare variant of Guillain-Barré Syndrome (GBS), characterised by a unique clinical triad of ophthalmoplegia, ataxia, and areflexia. MFS, which was first described in 1956 by Charles Miller Fisher, is frequently preceded by an infection, usually respiratory or gastrointestinal, and is believed to be triggered by an autoimmune reaction targeting peripheral nervous system components. However the MFS is further categorised into incomplete forms which can be present without the classical triad, such as acute ophthalmoparesis, acute ataxic neuropathy, acute ptosis and acute mydriasis. We report a case of a 50-year-old man presenting with dilated and unresponsive pupils, which progressed rapidly to ophthalmoplegia, ataxia, and areflexia. Given the clinical history supported by the cyto-protein dissociation in cerebrospinal fluid, the patient was diagnosed to have MFS and successfully treated with intravenous immunoglobulin. This case underscores the importance of recognising atypical features of MFS, such as primary mydriasis, and highlights the variable clinical spectrum within the syndrome. Clinicians should maintain a high index of suspicion for MFS, particularly when faced with unusual neurological presentations, to ensure timely intervention and optimal patient outcomes.

Keywords: Miller Fisher syndrome, atypical MFS, bilateral mydriasis, Guillain-Barré syndrome, ophthalmoplegia

Introduction

Miller Fisher Syndrome (MFS) is a rare neurological disorder characterised by a distinct constellation of symptoms, including ophthalmoplegia, ataxia, and areflexia. First described by Charles Miller Fisher in 1956(1), MFS represents a variant of Guillain-Barré Syndrome (GBS), exhibiting unique clinical features and diagnostic challenges. The atypical variants of MFS include isolated ophthalmoplegia, ptosis, pupillary abnormalities, ataxia, etc.(2) The pathogenesis of MFS is thought to involve an autoimmune reaction targeting peripheral nerve components, often triggered by a preceding infections.(3) Despite advancements in our understanding of MFS, its variable clinical presentation and atypical features continue to pose diagnostic dilemmas for clinicians.

Case presentation

A 50-year-old man presented to the medical ward complaining of progressively worsening blurred vision and photophobia over the course of one day. Notably, he denied any symptoms of double vision. Upon examination, his pupils were dilated to 6 mm and showed poor response to both light and near stimuli. Fundal examination did not reveal any signs of papilledema, and his visual acuity was normal. Extraocular movements were normal. There was no evidence of any limb muscle weakness. However his deep tendon reflexes were diminished. He denied any recent drug ingestion, ophthalmological procedures or snakebite. There was no history of preceding respiratory tract infections or acute gastroenteritis. The patient was admitted for close monitoring.

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On the following day, he reported diplopia, and clinical examination revealed bilateral abduction limitations. Within a day, this condition rapidly progressed to complete ophthalmoplegia. Additionally, persistent mydriasis was noted, accompanied by the absence of both light and accommodation reflexes. Although the patient denied lower limb weakness, deep tendon reflexes in both upper and lower limbs were diminished. Furthermore, he complained of numbness in his hands without any associated sensory disturbances, along with slight ataxia in the absence of other cerebellar symptoms.

Considering the clinical history and presentation, Miller Fisher syndrome was considered as a potential diagnosis. Neuroimaging in the form of NCCT brain and MRI brain scans was performed to exclude intracranial space-occupying lesions. Treatment was initiated with intravenous immunoglobulin (IVIG) administration at a dose of 0.4g/kg/day. Nerve conduction studies yielded normal findings apart from subtle nonspecific f wave changes, and cerebrospinal fluid analysis revealed cyto-protein dissociation, characterised by an elevated protein level of 120 mg/dL with no pleocytosis. However, anti-GQ1b antibodies were not tested due to unavailability.

The patient's condition significantly improved following IVIG therapy, supporting the diagnosis of Miller Fisher syndrome.

Discussion

Dilated and unresponsive pupils may occur due to either the paralysis of parasympathetic function or the stimulation of sympathetic activity. Paralysis of the parasympathetic system is often triggered by anticholinergic medications such as scopolamine or atropine, or by conditions such as oculomotor nerve palsy resulting from brain stem issues, injury, vascular events, or localised nerve damage.(4) Conversely, sympathetic stimulation can arise from the use of sympathomimetic drugs like cocaine or amphetamines.

On presentation, our patient only had bilateral mydriasis and diminished reflexes. He denied any drug ingestion. So he was kept under observation. With the development of ophthalmoplegia associated with areflexia and ataxia, we narrowed down the differential diagnoses to Miller Fisher syndrome.

MFS is a rare variant of Guillain-Barré Syndrome (GBS), characterised by a unique clinical triad of ophthalmoplegia, ataxia, and areflexia, first recognized by James Collier in 1932. Later, it was described in 1956 by Charles Miller Fisher as a possible variant of Guillain-Barré syndrome.(1)

In the classic presentation of MFS, patients typically experience ophthalmoplegia, ataxia and areflexia or hyporeflexia. Limb weakness and hypersomnolence are typically absent. However incomplete forms of MFS may lack certain features. So the patients can

Table 1 - Subtypes of Miller Fisher syndrome according to New diagnostic classification GBS classification group published in Vol. 10, Nature Reviews Neurology 2014

Category	Clinical features
Classic Miller Fisher syndrome	Ophthalmoplegia, ataxia and areflexia/hyporeflexia, absence of limb weakness and hypersomnolence
Acute ophthalmoparesis	Ophthalmoplegia
Acute ataxic neuropathy	Isolated ataxia
Acute ptosis	Ptosis without ophthalmoplegia or weakness
Acute mydriasis	Paralytic mydriasis
Bickerstaff brainstem encephalitis	Hypersomnolence, ophthalmoplegia and ataxia
Acute ataxic hypersomnolence	Hypersomnolence and ataxia

present with isolated ophthalmoparesis, acute ataxic neuropathy, acute ptosis and acute mydriasis, etc.(2) Subtypes of MFS with their clinical features are summarised in table 1. The presence of anti-GQ1b IgG antibodies would support the diagnosis.

The underlying pathophysiological mechanism of Miller Fisher syndrome is thought to be molecular mimicry. The immune system's activation of lipo-oligosaccharides (LOS) found on the membranes of some pathogens, most notably Campylobacter jejuni, which resemble gangliosides (GQ1b, GM1, and GD1a), would result in the formation of autoantibodies. If the antibody generated is GM1 or GD1b, the classic form of GBS with acute motor axonal neuropathy is produced, whereas GQ1b causes MFS.(3) GQ1b is a ganglioside found in paranodal myelin, namely in oculomotor nerves (III, IV and VI cranial nerves), dorsal root ganglia (DRG), and neuromuscular spindle fibres.(3) The location of the ganglioside explains the classical triad in MFS.(3) Serum IgG antibodies to GQ1b are commonly associated with Guillain-Barré Syndrome (GBS), whether the presentation is typical or atypical. These antibodies are particularly useful in diagnosing MFS, with a sensitivity of 85 to 90 percent. (5)

Tonic pupil in MFS was first described in 1977.(6) Later comprehensive literature reviews have described the association of fixed dilated pupils in cases of MFS.(7) Fixed dilated pupils are a result of involvement of the preganglionic parasympathetic pathway from Edinger-Westphal nucleus to the ciliary ganglion. Even though the exact pathophysiology is not known it is thought to be due to damage of the ciliary ganglion or short ciliary nerves caused by anti-GQ1b IgG antibodies.(6)

Conclusion

In summary, this case underscores the variable clinical presentation of MFS and the importance of recognising atypical features, such as primary mydriasis, in facilitating timely diagnosis and management.

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Severe bilateral retinal vasculitis as a delayed manifestation of rickettsial infection

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Abstract

Ophthalmic manifestations of rickettsial infections are reported as mostly asymptomatic and self-limiting. A 27-year-old woman, 29 weeks pregnant, recently treated for rickettsial infection, presented ten days following discharge with visual blurring and was diagnosed to have severe bilateral retinal vasculitis. Rickettsial antibody testing (indirect immunofluorescence assay) revealed Rickettsia conorii IgG titer >1:128. Antinuclear antibody, retroviral, syphilis and toxoplasmosis screens were negative. Bilateral intra-vitreous triamcinolone, azithromycin and prednisolone were administered. However, despite some improvement, a residual visual deficit remained. This case report highlights the possibility of debilitating visual loss following rickettsial infections, need for ophthalmic screening at diagnosis and prompt treatment initiation.

Keywords: rickettsia, spotted fever, retinal vasculitis

Introduction

Rickettsial diseases are caused by obligate intracellular bacteria of Orientia and Rickettsia genera and remain a significant cause of morbidity and mortality in the developing world.(1) Scrub typhus, caused by Orientia tsutsugamushi and spotted fever have been reported in Sri Lanka.(2,3) Many types of spotted fever group rickettsioses have been emerging in Sri Lanka. However, diagnostic tests in Sri Lanka for spotted fever frequently use group-specific antigens of Rickettsia conorii and may therefore be misinterpreted as exposure to Rickettsia conorii.(4)

Ocular manifestations caused by rickettsial disease are reported as generally self-limiting and asymptomatic.(5) We report a pregnant woman in Sri Lanka, presenting with rapidly progressing bilateral visual loss culminating in a diagnosis of severe bilateral retinal vasculitis as a delayed manifestation of spotted fever rickettsiosis infection. Retinal vascular disease may be seen in pregnancy with gestational hypertension, diabetes and pre-eclampsia. However, causes for retinal vasculitis are mainly infections (tuberculosis, syphilis, cytomegalovirus, herpes simplex virus, varicella zoster virus, toxoplasmosis and rickettsia) and systemic diseases (systemic lupus erythematosus, Behcet's disease and sarcoidosis).(6,7)

Case presentation

A 27-year-old previously healthy woman in her second pregnancy with a period of gestation of 29 weeks, presented with fever, myalgia and a maculopapular rash, to a local hospital in Sri Lanka.

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The rash was non-blanching and was noted three days following the onset of fever and had progressed from involving the arms and legs to the whole body sparing the face. She was from the south, an area endemic to scrub typhus. Since the rash was suggestive, she was diagnosed clinically to have scrub typhus and treated with intravenous ceftriaxone and azithromycin for five days. Testing for rickettsial infection at this acute stage had not been performed due to the lack of testing facilities. Her full blood count revealed a white blood cell count of 10.9 x 10^3/uL (4.0-10.0 x 10^3/uL), haemoglobin level of 11.0 g/dL (11.0-16.0 g/dL) and platelet count of 236 x 10^3/uL (150-450 x 10^3/uL). Her c-reactive protein (CRP) was 52 mg/L. Her fever settled by day two and she was discharged with oral cefixime. Ten days following discharge, she developed visual blurring of the right eye which progressed to involve the left eye in two days. Fundoscopy revealed bilateral cotton wool spots. Best corrected visual acuity was 6/60 on the right eye and 6/36 in the left eye.

She had no oral ulcers, photosensitive rashes, arthralgia, alopecia or any other evidence of connective tissue disease. She was afebrile and her pulse rate and blood pressure were normal. The cardiovascular, respiratory and neurology system examinations were normal. There were no abnormalities in the abdominal examination (a single live foetus with a symphyseal-fundal height appropriate for the gestation). She was initially pulsed with intravenous methylprednisolone 1g daily for 3 days at the local hospital on suspicion of connective tissue disease and commenced on oral prednisolone 1mg/kg daily with azathioprine 50 mg daily. She was transferred to a tertiary care hospital, for further evaluation approximately 3 weeks after the first presentation.

At the tertiary care hospital, her CRP was found to be 1.3 mg/L and electrolytes while liver enzymes, renal functions and urine full report were normal with no proteinuria. Her antinuclear antibody (ANA) test was negative.

Her antibody levels tested using immunofluorescence assay (IFA) for rickettsial diseases revealed a titre >1:128 for *Rickettsia conorii* IgG revising the diagnosis to spotted fever (Diagnostic cut off titre > 1:128). Antibodies to *Orientia tsutsugamushi* were negative. This was a convalescent sample taken approximately four weeks after the initial onset of symptoms. Retroviral screening and VDRL testing for syphilis were negative. Toxoplasmosis IgM was negative.

Azathioprine was withheld and bilateral intra-vitreous triamcinolone was administered, first to the right eye. Figure 1A depicts fundal images revealing multiple cotton wool spots with macular oedema and bilateral macular star. Optical coherence tomography (OCT) of the patient is depicted in figure 1B showing bilateral diffuse retinal oedema with cystoid macular oedema.

Upon confirmation of rickettsial infection she was commenced on azithromycin 500 mg daily for further fourteen days and prednisolone tapering regimen with a starting dose of 40 mg daily. She reported some improvement in vision following two weeks of treatment. However, regrettably, three months on, she continued to have residual visual deficit.

Discussion

The ophthalmic manifestations caused by rickettsial disease are mostly reported to have a self-limited asymptomatic course resolving by 3rd- 10th week of illness without causing scarring.(5) Retinal findings are more commonly reported in spotted fever than scrub typhus.

A case series and a study, involving patients diagnosed with spotted fever found that retinal vasculitis is present in 55.9% of cases, frequently venous and mostly asymptomatic. Focal arterial sheathing, venous sheathing, branch retinal artery occlusion and cotton-wool spots were noted. Both studies mention that due to the frequency of occurrence, retinal vasculitis could be considered a clinical sign of spotted fever in areas of endemicity. (8,9) Another study including 50 serologically confirmed rickettsial disease, reported 54% with ocular involvement where most patients were asymptomatic.(10)

Early antibiotic therapy with doxycycline 100 mg 12 hourly for 7-10 days is the treatment of choice for rickettsial infection with macrolides used in pregnant women.(5) The antibiotic treatment for severe ocular involvement may be extended for 2-4 weeks. There is currently no consensus guideline for the management of the ophthalmic manifestations of rickettsial disease in Sri Lanka.

A case report describing optic neuritis following *Rickettsia conorii* infection reported significant improvement with oral doxycycline 200 mg daily for 15 days in combination with 1 mg/kg/day corticosteroids tapered over 4 weeks.(11) However, another case report of bilateral rickettsial retinitis reported worsening of sight with systemic steroids which responded dramatically to therapy with oral

doxycycline and tapering off of steroids.(12)

Post-infectious causes of retinal vasculitis were not initially considered in the index patient and she was treated with methylprednisolone pulses with autoimmune aetiology in mind which led to an unfortunate delay in initiating appropriate antibiotics. Hence, this case highlights the importance of considering infectious causes at the forefront in a patient presenting with retinal vasculitis. As retinal changes may be similar, in a pregnant patient, diabetes, hypertension and pre-eclampsia need to be excluded by checking the blood sugar levels, blood pressure, urine for proteinuria, and other organ functions.(6)

Rickettsial infections are diagnosed using indirect immunofluorescence antibody assays. However, this investigation is not widely available in Sri Lanka.(13) The absence of an acute stage antibody level to demonstrate a four-fold rise to be diagnostic of acute spotted infection was a limitation of this case report. However, other possible causes of retinal vasculitis were excluded.

Conclusion

This patient developed debilitating ocular symptoms two weeks after spotted fever indicating the possibility of severe delayed manifestations of retinal vasculitis in rickettsial infections. The presence of retinal involvement provides a diagnostic clue for spotted fever rather than scrub typhus, in areas with no access to serology.

This case sheds light on the importance of early detection of rickettsial ophthalmic involvement by routine screening, the need to consider infectious causes in a patient presenting with retinal vasculitis at the outset itself and the need for a consensus management guideline for the management of retinal vasculitis in rickettsial disease in Sri Lanka.

Declarations

Author contributions

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

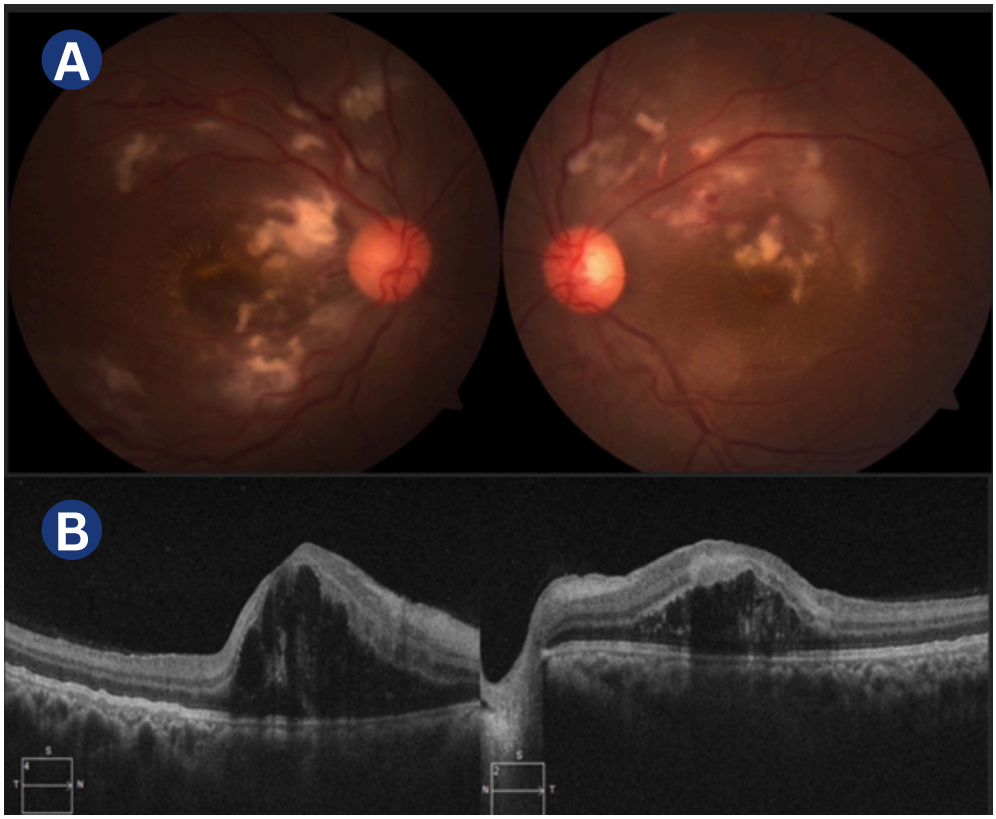

Figure 1 - Fundal images depicting bilateral cotton wool spots with macular oedema and bilateral macular star **(A)** and Optical coherence tomography showing bilateral diffuse retinal oedema with cystoid macular oedema **(B)**

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest with respect to the research, authorship, and/or publication of this article

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An unusual presentation of dermatomyositis: dermatomyositis sine dermatitis presenting with rapidly progressive myositis

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Abstract

Dermatomyositis sine dermatitis (DMSD) is a rare variant of dermatomyositis where progressive muscle weakness presents without the characteristic rash but with muscle histology of dermatomyositis. A 55-year-old woman presented with progressive severe proximal limb, neck, pharyngeal and respiratory muscle weakness, without dermatologic manifestations. Elevated muscle enzymes and myopathic electromyogram pointed towards inflammatory myositis while the muscle biopsy confirmed DMSD. Her condition improved with steroids, intravenous immunoglobulin, methotrexate, and rituximab. This case emphasises the necessity of maintaining a high index of suspicion for dermatomyositis, even when a classic skin rash is absent and the criticality of early aggressive treatment. Anti-NXP-2 antibody positivity could indicate severe disease.

Keywords: dermatomyositis sine dermatitis, rapidly progressive myositis, proximal muscle weakness, rituximab

Introduction

Idiopathic inflammatory myopathies (IIMs) encompass a diverse group of immune-mediated disorders where chronic muscle inflammation leads to a spectrum of clinical features, response to treatment, and long-term outcomes.(1) Dermatomyositis (DM) is an IIM defined by the presence of progressive, symmetric proximal muscle weakness and characteristic skin manifestations such as heliotrope rash, Gottron's papules, v-neck, shawl and holster signs.(2,3)

In classic DM, cutaneous disease precedes the myositis by 3–6 months in 30–50% of patients, while 10% of patients present with muscle symptoms prior to the development of skin findings.(4,5) DM can also present with the characteristic skin rash without muscle disease (amyopathic DM).(1) However, it is rare for DM to present without the characteristic skin rash with only clinical evidence of myositis and classic histopathological features of DM on muscle biopsy.(1) This subset of DM is termed as dermatomyositis sine dermatitis (DMSD).

We report the case of a 55-year-old woman who presented with rapidly progressive myositis without classic DM skin manifestations who was diagnosed with DMSD with the aid of a muscle biopsy.

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Case presentation

A 55-year-old, previously well woman presented with progressively worsening proximal muscle weakness for 1 month. Initially, she developed a gradual weakness and tenderness in proximal muscles of the lower limbs. Within the next week, the weakness involved her proximal upper limbs. Later, she developed difficulty in keeping her head erect, difficulty in swallowing and breathing and poor cough effort, which led to hospitalisation.

She denied facial, ocular, extra-ocular or bulbar muscle weakness. Her muscle weakness did not show diurnal fluctuation or fatigability. She did not have features to suggest distal weakness or peripheral neuropathy. She had normal bladder and bowel functions.

There was no history to suggest connective tissue disease such as systemic lupus erythematosus, systemic sclerosis or mixed connective tissue disease. She did not have Raynaud's phenomenon or sicca symptoms. She had no features to suggest a thyroid disorder. She was not on long-term medications. There was no personal or family history of malignancy. She was a non-smoker and teetotaler.

On examination, her body mass index was 22 kg/m2. There were no skin manifestations characteristic of DM or muscle wasting. On neurological examination, her proximal muscle power was 2/5 and 3/5 in the lower and upper limbs respectively, according to the Medical Research Council (MRC) grading. Her neck flexors were weaker than extensors (MRC 2/5) and there was evidence of bulbar weakness. Her deep tendon reflexes, sensory and cerebellar systems were normal.

Her ambient air oxygen saturation was 96% with clear lung fields. Her cough effort was poor, and single breath count (SBC) was 16, indicating respiratory muscle weakness. The cardiac examination was normal.

Her haematological and biochemical investigations and the autoimmune profile are summarised in table 1. Elevated creatine phosphokinase, lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase revealed myositis. Antinuclear antibody (ANA) titre was positive (1:80) with normal complement levels.

A myositis-specific antibody (MSA) panel was not performed due to non-affordability. Her thyroid functions and 25-hydroxyvitamin D levels were normal. Electrocardiography and transthoracic echocardiogram were normal. High-resolution computed tomography of the chest excluded interstitial lung disease (ILD) or infection.

Electromyogram revealed abnormal myopathic low-amplitude, short-duration polyphasic motor unit potentials indicating severe inflammatory myopathic abnormalities. Magnetic resonance imaging (MRI) of the thighs revealed increased T2 signal intensity, suggestive of active myositis in the bilateral vastus, quadriceps and rectus femoris muscles (figure 1A). An open muscle biopsy from the rectus femoris revealed myofibers with perifascicular fibrosis and atrophy, prominent endomysial lymphocytic infiltration surrounding necrotic myofibers with vascular proliferation and perivascular lymphoplasmacytic infiltration, confirming dermatomyositis (figures 1B-D). Age-appropriate malignancy screening was negative.

The treatment was with intravenous methylprednisolone (1 g/day for 3 days) and intravenous immunoglobulin (IVIG) 2 g/kg divided over 5 days, followed by oral prednisolone 1 mg/kg/day and methotrexate gradually increased to 20 mg/week. She developed impending respiratory failure, and was observed in the intensive care unit. Her respiratory and neck muscle weakness and dysphagia gradually improved while the muscle enzymes normalised. Since her proximal muscle power improvement was suboptimal by the 4th week of treatment, she was given 2 doses of intravenous rituximab 500 mg 2 weeks apart, following which the muscle power improved. Chest and limb physiotherapy were continued. Prednisolone was maintained at a high dose with bone protection for 6 weeks before gradual reduction to 5 mg/day while continuing methotrexate at 20 mg/week. After being discharged, the patient was closely followed up and assessed using the MMT8 scale (Manual Muscle Testing and a subset of Eight Muscles). Over the next several months she gradually regained her baseline muscle strength and returned to her activities of daily living.

Discussion

In 2003, the European Neuromuscular Centre (ENMC) proposed a criteria for possible DMSD, including insidious onset symmetric proximal myopathy with the exception of rash, elevated serum creatinine kinase, electromyogram findings suggestive of myopathy and a muscle biopsy with characteristic DM findings.(7) However, the 2017 European League

Table 1 - Haematological and biochemical investigations and autoimmune profile

Laboratory parameter/Investigation	Result	Reference range
Haematology		
Total white cell count (x10^3/uL)	7.52	4 -11
Neutrophil count (x10^3/uL)	5.08	1.5-8.0
Haemoglobin level (g/dL)	12.1	12-16
Platelet count (x10^3/uL)	257	150-450
Erythrocyte sedimentation rate (mm/1st hour)	45	
Biochemistry		
C-reactive protein (mg/dL)	16.3	<6
Serum sodium (mmol/L)	139	135-148
Serum potassium (mmol/L)	4.4	3.5-5.1
Serum creatinine (mg/dL)	0.86	0.7-1.2
Creatine kinase (U/L)	21829	<200
Lactate dehydration (U/L)	494	<225
Aspartate aminotransferase (U/L)	324	10-40
Alanine aminotransferase (U/L)	260	7-56
Alkaline phosphatase (U/L)	93	53-128
Total protein	7.8	6.6-8.3
Albumin	4.6	3.5-5.3
Globulin	3.2	2.0-3.5
Serum calcium (mg/dL)	9.6	8.5-10.2
Serum phosphate (mg/dL)	3.8	2.5-4.5
Serum magnesium (mg/dL)	1.9	1.7-2.2
Autoimmune profile		
Anti-nuclear antibody titre	1:80 (nuclear pattern)	
Anti-double-stranded DNA antibodies	Negative	
Extractable nuclear antigen antibodies (anti-Jo-1, anti-PM-Scl, anti-RNP, anti-Sm, anti-Ro and anti-La)	Negative	
Rheumatoid factor (U/mL)	8	<20
Anti-cyclic citrullinated antibodies	Negative	
Complement 3 (C3) (mg/dL)	87	65 - 190
Complement 4 (C3) (mg/dL)	24	14-40

Against Rheumatism (EULAR)/ American College of Rheumatology (ACR) classification criteria has not included DMSD.(8) Our patient's diagnosis of DMSD was supported by histologically proven DM with clinical and laboratory evidence of severe myositis in the absence of typical DM skin lesions.

In a cohort study of 182 patients with muscle biopsy-confirmed dermatomyositis, 14(8%) had DMSD.(9) Out of them, 4 patients had developed characteristic dermatomyositis skin rashes following muscle biopsy and the interval between the biopsy and onset of rash varied from 0.5 to 30 months.(9) At the time of this publication, 14 months have elapsed since our patient's presentation, and characteristic dermatomyositis skin manifestations remain absent. The same study reported that 86% of DMSD patients tested positive for anti-nuclear matrix protein-2 (anti-NXP-2) autoantibodies, while the two remaining patients each were positive for anti-transcriptional intermediary factor1-γ (anti-TIF1-γ) and anti-Mi 2 antibodies.(9) Anti-NXP-2 antibody-positive DM patients tend to have prominent myositis and a higher risk of malignancy.(1) Similarly, our patient also had a severe form of myositis. A case of DMSD showing positivity for anti-melanoma differentiation-associated protein (anti-MDA5) antibody has also been reported.(10) In our case MSA panels including anti-NXP-2 autoantibodies were not done due to non-affordability.

In addition to myositis, other manifestations of DMSD include myocarditis, neuromyositis, dysphagia and ILD.(11) Except for dysphagia, our patient did not demonstrate the others at diagnosis or follow-up. Given her established severe muscle weakness on presentation, our patient was given high-dose intravenous methylprednisolone and IVIG, as per the

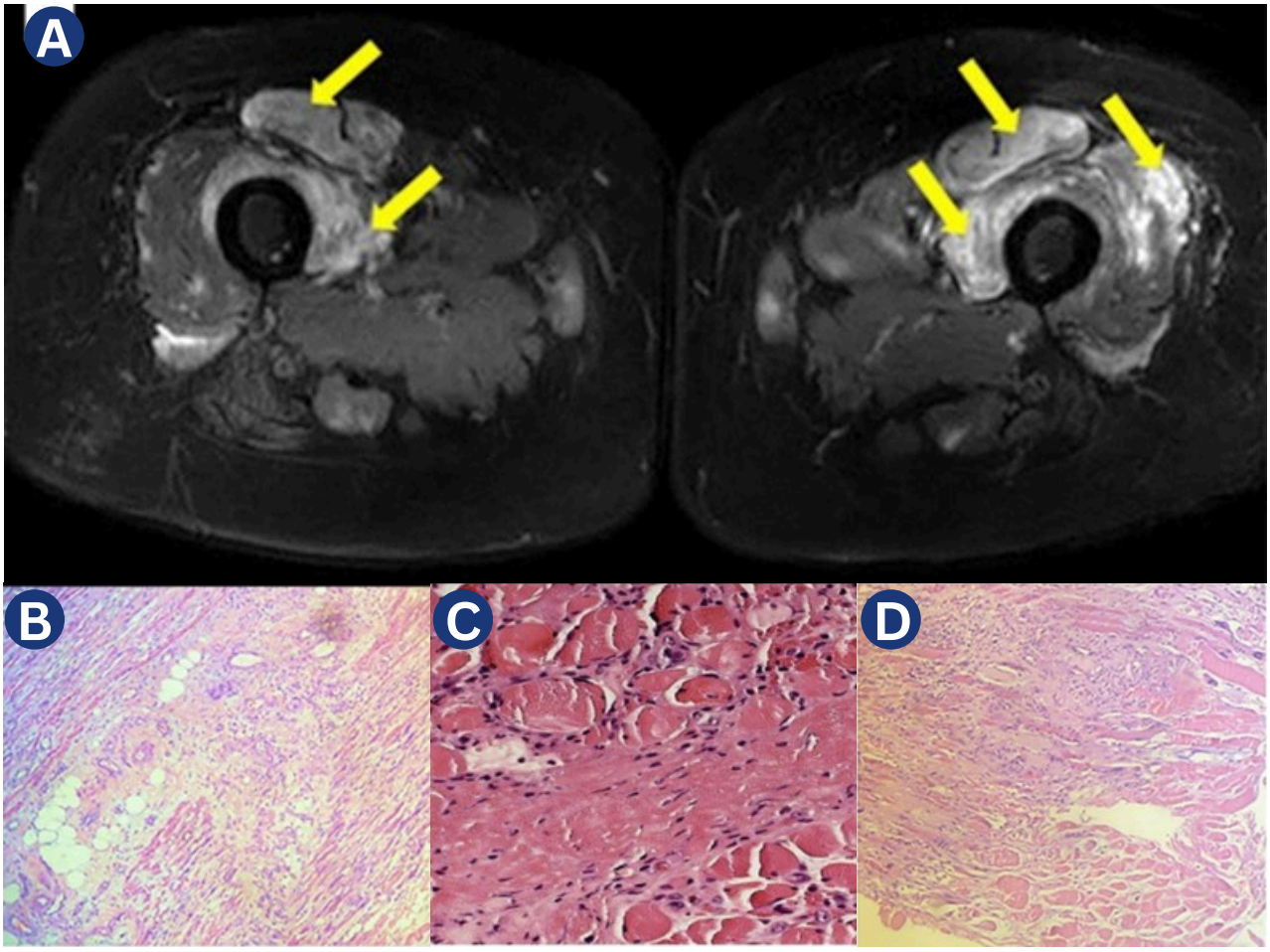

Figure 1 - **A**: T2-MRI thighs demonstrating active myositis (yellow arrows); Muscle biopsy (haematoxylin and eosin staining) showing features of dermatomyositis; **B:** (10x) Myofibers with perifascicular fibrosis and atrophy, and adipose tissue infiltration; **C:** (100x) Endomysial mononuclear cell infiltrates including lymphocytes and histiocytes with focal muscle fibre necrosis and regeneration; **D:** (10x) Endomysial inflammation with necrotic myofibers

current guidelines. However, since the rapidly progressive myositis showed an incomplete response to steroids and IVIG during the acute presentation, rituximab was given to the patient, to which she responded well. The guidelines also advocate the early use of a steroid-sparing agent such as methotrexate alongside oral prednisolone to induce and maintain disease remission and facilitate steroid-free treatment.(12)

Conclusion

This case highlights the importance of considering DMSD in the differential diagnosis of IIMs. Although it may be a diagnostic challenge, early recognition of DMSD and prompt initiation of aggressive treatment are crucial for preventing potential complications and improving patient outcomes.

Declarations

Author contributions
All authors contributed to the conceptualization and design of the study. Dr H Karunatilake contributed to revising the manuscript. All authors read and approved the final manuscript.

Conflicts of interest
The authors declare that they have no conflicts of interest with respect to the research, authorship, and/or publication of this article

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Lateral rectus palsy as the first presentation of Kikuchi Fujimoto's disease

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Abstract

Kikuchi Fujimoto's Disease (KFD) or histiocytic necrotising lymphadenitis is recognised as a disease with a benign and indolent course. The common clinical symptoms of KFD include fever, headache, arthralgia and cervical lymphadenopathy. The diagnosis is based on clinical grounds and histological findings of lymph node biopsy. Kikuchi disease presenting with neurological manifestations is seldom seen. Out of all reported neurological manifestations, aseptic meningitis, brainstem encephalitis and cerebellar ataxia are common. We report a case of a 16 year old girl presenting with right sided lateral rectus palsy as the first presentation of KFD.

Keywords: aseptic meningitis, Kikuchi Fujimoto's disease, lateral rectus palsy, lymphadenopathy

Introduction

Kikuchi-Fujimoto disease (KFD) is a form of necrotising lymphadenitis that was first described in Japan in 1972.(1) It is most commonly seen in women younger than the age of 30 years.(2) The typical presentation includes cervical lymphadenopathy, headache and fever.(3) Although neurological manifestations are rare, there have been few cases reported worldwide with brainstem encephalitis and aseptic meningitis. The case we are reporting highlights the importance of considering KFD as a differential diagnosis, most importantly in the younger population when the presentation includes features of meningitis, focal neurological signs and lymphadenopathy.

Case presentation

We report a 16-year-old girl with no previous illnesses presenting with sudden onset diplopia on binocular vision and intermittent low grade fever for one month, later diagnosed to have an isolated ipsilateral abducens nerve palsy after cranial nerve examination. The diplopia had worsened over three days. Further questioning revealed a history of a headache which was temporal and throbbing type. She denied any history of recent weight loss, loss of appetite, chronic cough, contact history of tuberculosis or past history of tuberculosis, history of any chronic disease, malignancy, illicit drug use and alcohol abuse.

In the neurological examination, except for the isolated lateral rectus nerve palsy, the cranial nerve examination was normal including visual acuity. Kernig's sign was negative with no demonstrable neck stiffness. Her respiratory and cardiovascular examinations were unremarkable, with vesicular breathing and normal heart sounds. Her abdomen was soft, non-tender with no organomegaly. The basic haematological and serological investigation profile is shown in table 1.

Upon admission to the ward, the patient was subjected to an non-contrast enhanced computed tomography scan (NCCT). As it did not reveal any cerebral oedema or space occupying lesion, a lumbar puncture (LP) was performed. She was promptly

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Table 1 - Basic haematological and serological investigation profile

Investigation	Value	Reference range
WBC (x10^9/L)	7.27	4.00-10.00
Hb (g/dL)	14	12-16
PLT (x10^9/L)	345	150-450
AST (U/L)	28.4	<50
ALT (U/L)	30.9	<50
Gamma GT	31.2	
Total bilirubin (umol/L)	6.92	5-21
Direct bilirubin (umol/L)	0.97	0-3.4
CRP (mg/L)	6.7	<5
Serum creatinine (umol/L)	80	74-110
Urea (mmol/L)	4	2.8-7.2
Sodium (mmol/L)	134.8	36-146
Potassium (mmol/L)	4.0	3.5-5.1
Albumin corrected Calcium (mmol/L)	2.39	2.06-2.60
LDH (U/L)	235 later risen to 537	125-243
ESR (mm/1st hour)	75	0-10
CPK (U/L)	77	<17
Blood picture	Red cell changes and anaemia suggestive of acute illness and early iron deficiency.	

started on IV ceftriaxone in meningitic doses as an intracranial infection was suspected with the presenting complaint. Cerebrospinal fluid (CSF) examination revealed a CSF sugar of 62.97 mg/dL, red cells - 2/uL, lymphocytes-55/uL, polymorphs - 10/uL and protein 26.4 mg/dL. Random blood sugar level was 110.52 mg/dL with CSF ADA 1.9 U/L and CSF genexpert for tuberculosis (TB) was negative. CSF cultures were negative and HSV PCR was also negative. Although the patient was continued on ceftriaxone at meningitic doses, the patient's lateral rectus palsy persisted and fever spikes continued. Her blood cultures and urine cultures were negative despite many intermittent fever spikes. A decision was taken to repeat the LP after completing 10 days of IV antibiotics on the twelfth day after the first lumbar puncture. Second LP report revealed; CSF sugar- 69.4 mg/dL, red cells- 9/uL, lymphocytes 2/uL and polymorphs 3/uL, protein 13.4 g/dL. The CSF cultures were repeatedly negative. Due to the young age of the patient along with headache, a space occupying lesion that compresses the sixth nerve was also considered a possibility, however the fundoscopy examination was normal without papilledema while NCCT and MRI brain were normal. As this is a case of mononeuritis with on and off fever, TB meningitis was considered to be the first differential diagnosis because tuberculosis is on rise among young Sri Lankans. But normal CSF proteins, CSF genexpert and CSF ADA being negative and absence of basal exudates in MRI suggested otherwise. The patient being a young female, presenting with mononeuritis, systemic lupus erythematosus (SLE) was also considered a differential diagnosis, but both her ANA and anti dsDNA were negative. Neurosarcoidosis was excluded as serum ACE level and serum calcium levels were normal. She tested negative for HIV. Though she initially didn't have cervical lymphadenopathy, during the ward stay she

developed shotty cervical lymphadenopathy. There were firm, non-tender, palpable cervical lymph nodes bilaterally, with a maximum size of 7x9x3 mm^3.

She was referred to the surgical team for excisional cervical lymph node biopsy. The biopsy was obtained from the posterior cervical lymph nodes. The elevated LDH levels along with lymphadenopathy further raised the suspicion of a lymphoma. Therefore excision of the lymph node and tracing the biopsy was prioritised. The lymph node biopsy revealed a lymph node with preserved architecture, reactive follicles with secondary germinal centre formation and sheets of histiocytes. (figure1). This prompted the diagnosis of KFD. As the CSF cultures were persistently sterile, the patient was diagnosed to have aseptic meningitis and was started on prednisolone 30 mg daily which was tailed off gradually over 2 weeks. Over the course of 2 months, the patient's lateral rectus palsy resolved markedly suggesting the indolent and self-limiting nature of KFD. Her cervical lymph nodes gradually decreased in size. She is still being followed up and she remains healthy and asymptomatic 6 months after the discharge.

Discussion

Most common KFD manifestations include fever, lymphadenopathy, anorexia, generalised malaise and hepatomegaly. Overall, the disease course is benign. Spontaneous self-resolution tends to occur within weeks to months and the recurrence rate is low as 3-4%. Long-term follow up of patients with KFD is recommended, because of the risk of recurrence and due to its postulated association as a precursor to autoimmune diseases like SLE. Reported neurological manifestations of KFD are rare, but literature published so far has explained cases of aseptic meningitis, acute cerebellar ataxia and acute brachial neuritis and brain stem encephalitis.(4) Total incidence of neurological manifestations is 11%.(5) Since KFD was not identified as a well-known cause for cranial nerve palsies, several differential diagnoses associated with such presentation were first suspected in this patient. Therefore our patient was thoroughly investigated for alternative more plausible pathologies which are more prevalent such as TB, in these parts of the world. Having excluded all possible aetiologies such as TB, lymphoma and SLE, the team involved in the management was in a great diagnostic dilemma. The lymph node biopsy report was instrumental in reaching the diagnosis.

Central nervous system (CNS) involvement is rarely reported as the first symptom of this disease. A study by Huang et al from China summarises the clinical features of patients diagnosed with KFD combined with the involvement of the central system, at Children's Hospital of Chongqing Medical University (CHCMU). There sixteen patients had been diagnosed with aseptic meningitis while headache (78.9%) was the most common symptom among them.(6) Kucukardali et al. have analysed 244 published cases of KFD since 1991 and reported that neurological involvement was observed in only 4.5% of the patients.

A case published in Japan by Hidenori Kido has

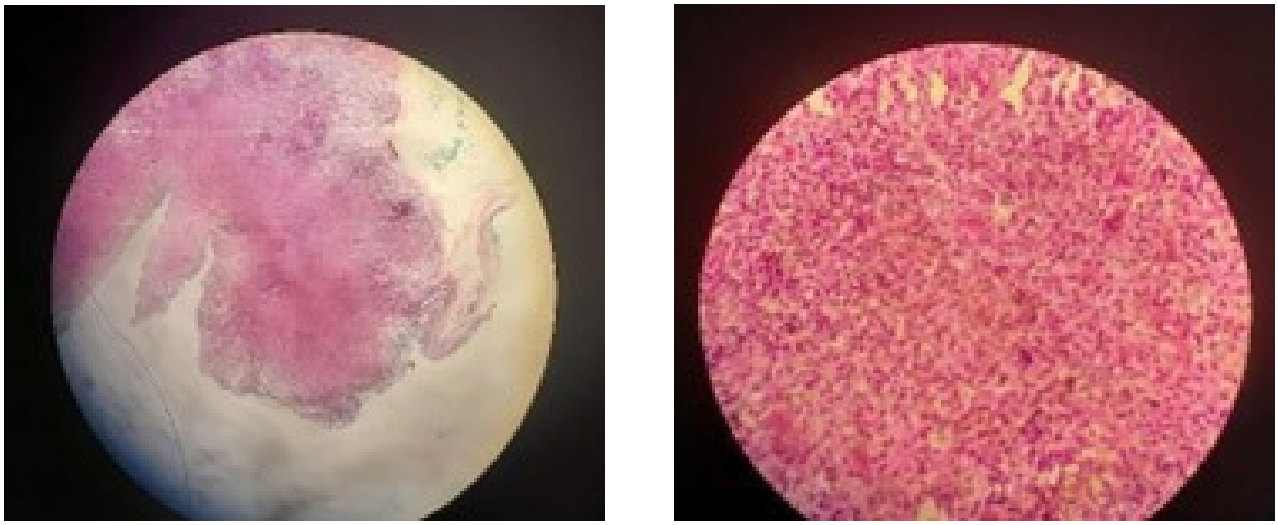

Figure 1 - Lymph node biopsy showing a lymph node with preserved architecture, reactive follicles with secondary germinal centre formation and sheets of histiocytes

highlighted a case of a 19-year-old boy who was managed for encephalitis associated with KFD further highlighting CNS manifestations, although rare.(7) Nalika et al from Sri Lanka have reported a case of recurrent aseptic meningitis and further highlighted the familial occurrence of the disease.(8) Another case published in India by Jasti et al has shown KFD presenting as brainstem encephalitis with secondary blepharospasm. Aseptic lymphocytic meningitis was described in 9.8% cases in Japan. Our patient also exhibited a lymphocytic predominance in CSF. Cerebellar ataxia, diplopia, and confusion have also been described in a few cases. Furthermore F Rocher et al have reported a case of a 10-year-old girl with third nerve palsy with papilledema and highlights the importance of considering KFD in children with ocular manifestations, lymphadenopathy and fever.(9) A case report from Pakistan published by Hashmat et al has revealed a young girl with KFD having aseptic meningitis developing lateral rectus palsy subsequently during the course of the illness.(9) In Sri Lanka there was only one case which highlighted the neurological complications in Kikuchi-Fujimoto disease.(8) The unusual and rare feature of our case report is that it is the first to be reported about a patient presenting with acute onset lateral rectus palsy as the first presentation of KFD along with aseptic meningitis.

KFD management involves supportive as well as a specific treatment. In KFD, spontaneous resolution is typical(10), and treatment is warranted in certain conditions. Symptomatic treatment is the most effective treatment strategy for KFD. Supportive measures include nonsteroidal anti-inflammatory drugs and antipyretics to relieve fever, lymph nodal tenderness, malaise, and arthralgia. Corticosteroids are reserved for severe cases or where supportive measures fail to control symptoms.(11) However, an optimal method of treatment has not been established yet. Our patient was prescribed a course of steroids as there was evidence to support the use of steroids in many cases with CNS manifestations.(8)

Conclusion

Though neurological complications of KFD are rare, it's important to consider KFD as a differential diagnosis in young patients presenting with focal neurological signs, fever, lymphadenopathy and headache, as that would help in avoiding unnecessary and excessive treatment. Since the disease can be mistaken clinically and histologically for SLE, lymphoma or TB, it is of utmost importance to differentiate it from these conditions. Our case also emphasises the importance of recognising KFD as the culprit in young patients presenting with lymphadenopathy, meningitis and focal neurological signs.

Declarations

Conflicts of interest
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A rare bleeding disorder with severe haemorrhagic manifestation

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Abstract

Factor V is a major part of the coagulation system and maintains a balance in pro-coagulant and anticoagulant pathways. Any deficiency or mutation can lead to disequilibrium in coagulation. Factor V deficiency can be congenital or acquired. Congenital factor V deficiency (parahemophilia or Owren's disease) is a rare autosomal recessive condition. We present a case of an adolescent unmarried girl presenting with an acute abdomen and deranged coagulation parameters. It was confirmed that the bilateral haemorrhagic ovarian cysts and hemoperitoneum were due to factor V deficiency. In her case, the bleeding was likely due to a ruptured corpus luteum during ovulation. She was successfully managed conservatively with red cells and fresh frozen plasma transfusions, tranexamic acid and combined oral contraceptive pills (COCP) with instructions to continue the use of COCP to prevent such bleeding manifestations.

Keywords: congenital factor V deficiency, ruptured corpus luteum, hemoperitoneum, acute abdomen

Introduction

Factor V deficiency (parahemophilia or Owren's disease) is a very rare serious coagulation disorder. About 1/1,000,000 may be affected by this rare disease. Factor V deficiency can be congenital or acquired. Congenital factor V deficiency is inherited through an autosomal recessive pattern. Only 150 cases have been identified worldwide to date.(1) Factor V is an important component of the procoagulant and anticoagulant pathway in our clotting system. It interacts with Factor X to activate the prothrombin into thrombin. It also interacts with activated protein C (APC) to inactivate factor VIII. Factor V is synthesised in hepatocytes, megakaryocytes and bovine aortic endothelial cells. (2) The disequilibrium in the coagulation pathway can be due to Factor V deficiency or Factor V Leiden. Conversely, acquired factor V deficiency (AFVD) develops due to autoantibodies against Factor V after the exposure of bovine thrombin through antibiotics, infection, autoimmune disease and malignancies.(3)

On work up, prothrombin time (PT) and activated partial thromboplastin time (APTT) are prolonged. The condition is treated using fresh frozen plasma (FFP) infusion with a target factor V level of 20-30%.(4)

Case presentation

A 16-year-old girl was admitted to the emergency department of teaching hospital Batticaloa with abdominal pain for 3 days. She was a known patient with congenital factor V deficiency. She was born to healthy, non-consanguineous parents with no known bleeding disorders in the family. She was diagnosed to have factor V deficiency at the age of 3 years when she was investigated for gum bleeding. The diagnosis was confirmed by factor V assay. Her factor V level was 1.5% (50% - 150%). She had undergone tooth extraction at the age of 9 years with FFP coverage without any active bleeding. Our patient attained menarche at the age of 12 years and she has had regular menstrual cycles without any heavy bleeding.

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However, her medical records confirmed that she received two blood transfusions at the age of 14 years and 15 years due to iron deficiency and later she was started on iron supplements. In addition, her younger sister was also diagnosed to have factor V deficiency at the age of 6 months. Her younger sister had excessive bleeding following trauma at the age of 6 months and no other spontaneous bleeding manifestations.

She was in good health prior to the current presentation. She developed a sudden onset, moderately severe generalised abdominal pain. The pain was colicky in nature, non-radiating, and aggravated by walking and movements. There were no relieving factors for the abdominal pain. She did not have any associated nausea, vomiting, diarrhoea or melena. Upon systemic inquiry, there was no joint pain, redness of eyes, photosensitivity, mouth ulcers, hair loss, dry mouth or dry eyes. There were no complaints to support heat or cold intolerance, change in voice, change in appetite or weight. There were no urinary symptoms to suggest a urinary tract infection or renal or ureteric colic. . Central nervous system inquiry was unremarkable. Her last regular menstrual period was 2 weeks back from the current admission.

On general examination, her BMI was 17.1 kg/m^2. She was afebrile, with a GCS of 15. She was in pain and severely pale. There was no jaundice, cyanosis, evidence of dehydration, clubbing/koilonychia, bone tenderness or ankle edema. Her vital signs on arrival were as follows: pulse; 120 beats per minute; blood pressure; 100/60 mmHg and respiratory rate; 24 per minute. Jugular venous pressure was not raised and there were no murmurs. The respiratory system examination was normal. The abdominal examination revealed guarding and tenderness in the lower quadrant. There was positive shifting dullness to clinically support free fluid in the abdomen. Her bowel sounds were audible. Examination of the central and peripheral nervous systems were unremarkable.

The summary of laboratory test results are presented in table1.

Blood film showed features of iron deficiency and her iron studies showed low serum iron, ferritin and increased total iron binding capacity (TIBC) levels. Urgent ultrasound scan of the abdomen and pelvis revealed a moderate amount of free fluid in abdomen, and a thick walled cystic lesion measuring 3.5 cm x 4.5 cm with multiple septae in the left ovary and 3.2 cm x 3.2 cm size lesion in the right ovary, favouring bilateral haemorrhagic ovarian cysts. The right ovary was seen posterior to the uterus associated with a 5.8 cm x 2.4cm size hypoechoic area in Pouch of Douglas favouring a pelvic haematoma. All these findings were consistent with a ruptured ovarian cyst with pelvic haematoma and moderate haemoperitoneum.

She was kept nil by mouth and transfused with two units of packed red blood cells and urgent multidisciplinary team (MDT) opinion was sought which included haematology, obstetrics and surgical teams. According to the plan, 15 mL/kg fresh frozen plasma was transfused two times and intravenous tranexamic acid 500 mg was administered 8 hourly. She was monitored closely with supportive care. Her haemoglobin (Hb) improved to 9.6 g/dL and coagulation parameters normalised within 2 days. She was slowly started on oral fluids followed by solids over the next few days. She was observed and managed in the ward for 7 days and discharged in a stable condition with oral iron supplements, along with combined oral contraceptive pills (COCP) and instruction to continue COCP without stopping. On discharge her repeat abdominal ultrasound scan showed reduction in size of the pelvic haematoma and disappearance of haemoperitoneum. She was clinically and haemodynamically stable with a haemoglobin of 11.8 g/dL at the clinic.

Discussion

Factor V deficiency is an extremely rare coagulation disorder. Usually it presents with minor mucosal bleedings., However there are case reports about life threatening bleeding like intracranial bleeding due to factor V deficiency (5). Treatment of factor V deficiency involves FFP (mainstay of treatment) and antifibrinolytics, as isolated factor V replacement is not available. Refractory cases require prothrombin complex concentrates, activated factor VIIa and platelet transfusions along with steroids or immunosuppressives in severe cases.(4) Patients with acquired inhibitors (factor V inhibitors) require the above products along with steroids or immunosuppressives in severe cases.(3,5)

Our patient was admitted with an acute abdomen most likely due to a ruptured and bleeding corpus luteum following ovulation. The role of FFP and antifibrinolytics are pivotal in the management of patients with factor V deficiency. In our case, we transfused packed red cells and intravenous

Table 1 - Summary of investigations on admission

Investigation	Results
Full blood count	
Haemoglobin (g/dL)	7.6 (11.0-15.0)
Haematocrit (%)	26.1(37.0-47.0)
Mean corpuscular volume (fL)	65.4 (80.0-100.0)
Mean corpuscular haemoglobin concentration (g/dL)	29.0 (32.0-36.0)
Red cell distribution width - coefficient variation (%)	17.9 (11.0-16.0)
White Blood Cell (X1000/uL)	10.69 (4.00-11.00)
Platelets (X1000/uL)	318 (150-450)
Coagulation profile	
Prothrombin time (seconds)	19.3 (13)
International normalised ratio	1.48 (1.08)
Activated partial thromboplastin time (seconds)	53.5 (27-42)
Serum sodium (mmol/L)	144
Urine full report	Normal
Renal function test	
Sodium (mmol/L)	135 (136-145)
Potassium (mmol/L)	3.5 (3.5-5.1)
Creatine (umol/L)	88 (53-88)
Liver enzymes	
Alanine transaminase (U/L)	23 (12-78)
Aspartate transaminase (U/L)	42 (15-37)
Amylase (U/L)	46 (40-140)
C-reactive protein (mg/L)	16 (0-5)
Urine HCG	Negative

tranexamic acid followed by FFP after MDT discussion on admission. Our management definitely helped to control further bleeding, correct the anaemia and correct the factor V levels. It is recommended that a single daily dosage of 15-20 mL/kg FFP is transfused to control soft tissue and mucosal bleeding.(6) Factor

V activity level should be monitored until a target level of 30% is achieved. Oral contraceptives like depo-provera and gonadotropin releasing hormone (GnRH) agonists can also be given to females who do not actively desire pregnancy.(7) These options not only avoid menorrhagia, but also minimise the chances of bleeding during ovulation. As our patient improved significantly with medical management and surgical treatment was not needed.

Conclusion

Factor V deficiency is a rare bleeding disorder which is suspected in patients with prolonged PT, APTT and mild, recurrent mucosal bleeds, when other causes are ruled out. The diagnosis is confirmed by demonstrating low factor V levels. It is observed that patients with factor V deficiency present early in life with mucocutaneous bleeds. Although PT and APTT are prolonged, factor V assay is important to confirm the diagnosis. Early diagnosis and prompt management play a pivotal role in avoiding complications. FFP remains the treatment of choice in presentations with acute bleeding.

Declarations

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

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A rare occurrence of myocarditis with acute heart failure as an extraintestinal manifestation of Crohn's disease in a young male

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Abstract

Crohn's disease (CD) is an idiopathic inflammatory bowel disorder, which can be associated with various extraintestinal manifestations. Cardiac and pulmonary manifestations of CD are rare with only a few cases being reported. Myocarditis is an unusual and rare extraintestinal manifestation of CD. Only a few case reports associating CD with the above manifestation are found in the literature. Here, we report a case of an 18-year-old man diagnosed with CD for two years, on optimum treatment, presenting with the symptoms of myocarditis with acute heart failure, as extraintestinal manifestations in the absence of bowel symptoms, while being negative for infective and non infective aetiological screening. This case highlights the importance of knowing the rare extraintestinal manifestations of CD, which will ultimately guide the treating physicians.

Keywords: Crohn's disease, myocarditis, acute heart failure

Introduction

Crohn's disease (CD) is one of the major inflammatory bowel diseases, characterised by transmural inflammation, and can involve any portion of the gastrointestinal tract, from the oral cavity to the perianal area. Moreover, it can affect other systems causing extraintestinal manifestations. These manifestations are related to inflammatory disease activity and include musculoskeletal, ocular, dermatological, hepatobiliary, immunologic, haematological, renal, respiratory, and cardiac manifestations.(1) Although, certain extraintestinal manifestations are commonly associated with CD, cardiac and pulmonary involvement are deemed rare and unusual.

Myocarditis, complicated with acute heart failure in the absence of bowel symptoms, is one such rare manifestation of CD and is hardly found in the literature.(2)

Case presentation

An 18-year-old man, diagnosed with CD 2 years back, currently on maintenance therapy with oral azathioprine and tapering doses of oral prednisolone, presented to us with sudden onset shortness of breath at rest with mild bilateral ankle oedema for one-day.

He complained of sudden onset shortness of breath at rest, which had progressively worsened over time and had been associated with orthopnea and paroxysmal nocturnal dyspnoea. There was no

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associated chest pain, palpitations, or autonomic symptoms. He denied fever, cough, or other respiratory symptoms.

He had also developed bilateral ankle oedema within the course of one day which had progressively worsened with time. There was no abdominal distention, facial swelling, jaundice, frothy urine, oliguria, or haematuria. He was clinically euthyroid and didn't give any history suggestive of an underlying connective tissue disorder. Interestingly, he didn't have any bowel symptoms. There was also no history of alcohol consumption or use of illicit drugs.

On examination, he was dyspnoeic with a respiratory rate of 28 breaths per minute. His Oxygen saturation on air was 72% and there were bilateral diffuse, fine, end inspiratory crepitations on auscultation. He was tachycardic with a pulse rate of 120 beats per minute and the blood pressure was 140/100 mmHg. The Jugular venous pressure was elevated. There were no murmurs. There was bilateral pitting ankle oedema. Abdominal examination was normal. There were no focal neurological deficits. Bilateral fundi didn't have chronic hypertensive changes or papilloedema. There were no features suggestive of connective tissue disorder.

His full blood count revealed a white blood cell count of 11200 cells/uL with neutrophil predominance. Haemoglobin was 11.6 g/dL and platelet count was 442 000 cells/uL. C reactive protein (CRP) was 38.4 mg/dL(normal 0-5) and erythrocyte sedimentation rate (ESR) was 59 mm/1st hour(normal <20).

The electrocardiogram showed sinus tachycardia with nonspecific tall T waves and ST-T changes in the lateral leads (figure 1). Troponin I was significantly elevated with a level of 580 ng/mL (<0.03). 2D Echocardiogram revealed moderate to severe left ventricular dysfunction with an ejection fraction of 30% and global hypokinesia with mild pulmonary hypertension. Unfortunately, BNP levels were not available. The overall features were suggestive of myocarditis associated with heart failure.

The arterial blood gas analysis showed a PO2/FiO2 ratio of 200 and the chest x-ray showed bilateral diffuse patchy shadows more in the apical region suggestive of heart failure (Figure 2). Computed tomography pulmonary angiogram (CTPA) was performed to exclude pulmonary embolism which eventually revealed bilateral lower lobe patchy areas of consolidation and ground glass opacification compatible with acute respiratory distress syndrome (ARDS) without any evidence of thrombosis. However he did not fulfil the criteria of ARDS by definition.

Other basic investigations such as liver function tests, renal function tests, and serum electrolytes were normal. Screening for dengue, hepatitis B, hepatitis C, influenza A,B virus cytomegalovirus, Epstein Barr virus, and mycoplasma were negative. His thyroid-stimulating hormone level was also normal. Serum antinuclear factor(ANA) was marginally positive(1:80). Anti dsDNA and complement levels were negative.

The patient was initially resuscitated with high-flow oxygen via a facemask. Management for heart failure was commenced with diuretics and angiotensin-converting inhibitors. Beta blockers were introduced when he was much stable. He was ultimately managed for myocarditis with acute heart failure which is considered as an extraintestinal manifestation of CD. His maintenance dose of azathioprine was continued and a course of steroids was reintroduced at a higher dose. The patient was discharged after 12 days of hospital stay and the follow up-2D echocardiogram showed good biventricular function with an ejection fraction of 60%.

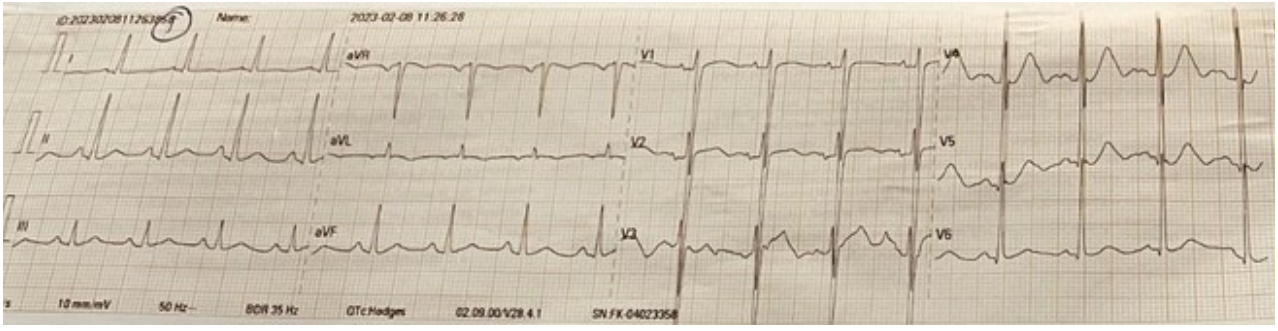

Figure 1 - Electrocardiogram showing sinus tachycardia

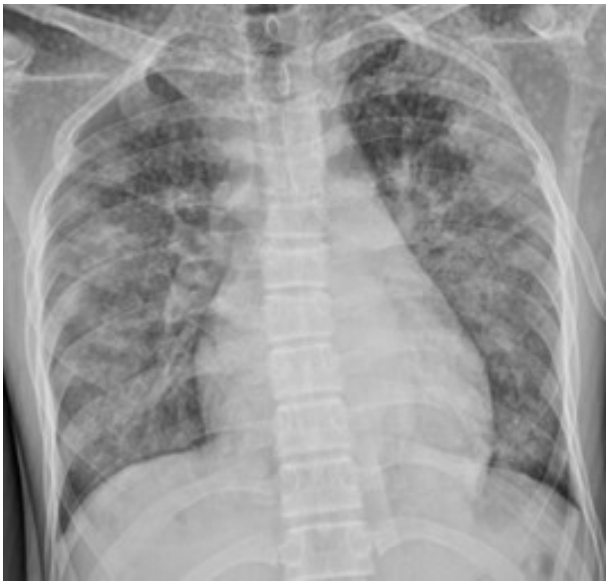

Figure 2 - Chest X ray shows diffuse bilateral patchy shadows suggestive of pulmonary oedema

Discussion

Inflammatory bowel disease (IBD) comprises two major disorders: ulcerative colitis (UC) and Crohn's disease (CD). UC affects the colon and is characterised by inflammation of the mucosal layer. CD is characterised by transmural inflammation and may involve any portion of gastrointestinal tract, from the oral cavity to the perianal area.(3)

Extraintestinal manifestations of CD are common and are seen in up to 25-30% of the population . However, myocarditis and acute respiratory distress syndrome (ARDS) are very rare manifestations and are seen in less than 1%.(2)

The cardiac manifestations of CD are pericarditis, pericardial effusion, myocarditis, endocarditis, arrhythmia and conduction anomalies. Crohn's myocarditis can occur with or without acute flare up of the bowel disease activity and this can be complicated with heart failure, arrhythmia and death. (2,3)

The most common causative aetiologies of myocarditis can be categorised as infectious and non-infectious diseases. Infectious causes account for the majority and include viral (e.g.: hepatitis viruses, cytomegalovirus, human immunodeficiency virus, influenza A and B), bacterial (including tuberculosis), parasitic and fungal pathogens.(3)

The noninfectious causes of myocarditis include systemic diseases such as inflammatory bowel diseases, thyroid disorders, sarcoidosis, hypereosinophilia, rheumatoid arthritis, collagen-vascular diseases, hypersensitivity reactions, cardiotoxins and radiation exposure.(2,3) Interestingly, our patient demonstrated global hypokinesia with an ejection fraction (EF) of 30% in the 2D echocardiogram and negative blood cultures with negative screening for dengue, hepatitis B, hepatitis C, influenza A,B, cytomegalovirus, Epstein Barr virus and Mycoplasma serology.

There have been few documented cases of inflammatory bowel disease-associated myocarditis in America, Australia, and South Korea. However, there are no such reports from South Asia. One American study showed Crohn's myocarditis involving inferior and septal hypokinesia with an EF of 30%.(3) A Korean study reported a young man with initial presentation of myocarditis associated with CD, with global hypokinesia and an EF of 38%.(1) An Australian study revealed myocarditis with an ejection fraction of 50% and endocarditis.(2)

Management of Crohn's myocarditis in the absence of bowel symptoms is mainly symptomatic, involving the management of complications such as heart failure, arrhythmias and increasing the dose of steroids(1-3) Our patient also received high dose of steroids after excluding the infective causes and showed a good clinical improvement.

ARDS is a complex response of the lung to direct and indirect insults. Numerous aetiological factors may cause this acute respiratory distress syndrome such as toxic inhalation, diffuse infection, sepsis, pancreatitis, etc.(4) Among patients with inflammatory bowel disease, up to 30%-50% have demonstrated pulmonary abnormalities according to available data such as bronchiolitis, bronchiectasis, organising pneumonia, alveolitis and acute respiratory distress syndrome. In addition, drug-induced lung injuries have also been reported in IBD patients.(5) However, ARDS occurring as an extraintestinal manifestation of CD is extremely rare.

Conclusion

Crohn's myocarditis is an uncommon, extraintestinal manifestation and can occur independent of any intestinal symptoms. It is important to suspect myocarditis when patients present with tachycardia and haemodynamic instability in the absence of sepsis. This requires a high level of suspicion and immediate treatment for myocarditis.

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Swollen hands and feet syndrome: an uncommon presentation of Hansen's disease

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A 61-year-old man with type 2 diabetes mellitus and hypertension presented with painful hand and foot swelling over 2 months. He had asymmetric, tender, pitting edema of the dorsum of both hands and feet extending beyond the joint line, thickened greater auricular and ulnar nerves, clawed fingers, sensory loss of the feet, neurotrophic foot ulcers, and an erythematous edematous patch over the knee (figure). Investigations ruled out cardiac, renal, liver, thyroid, haematological, and autoimmune abnormalities contributing to the oedema. A slit skin smear stained positive for mycobacteria. A diagnosis of multibacillary leprosy and Type 1 Lepra reaction was made. The acral swelling improved slowly over weeks following the initiation of multibacillary anti-leprosy treatment and prednisolone.

Hands and Feet syndrome, which resembles remitting seronegative symmetrical synovitis with pitting edema (RS3PE), is an uncommon musculoskeletal presentation of leprosy.(1,2) It is due to extensor tenosynovitis, which may be visualised ultrasonographically or by magnetic resonance imaging. In the upper limbs, edema can extend from the metacarpophalangeal joints to the mid-forearm. (1) A biopsy of an inflamed tendon nodule may reveal granulomata with mycobacteriae.(1)

The most common musculoskeletal manifestation in leprosy is acute symmetric small and large-joint

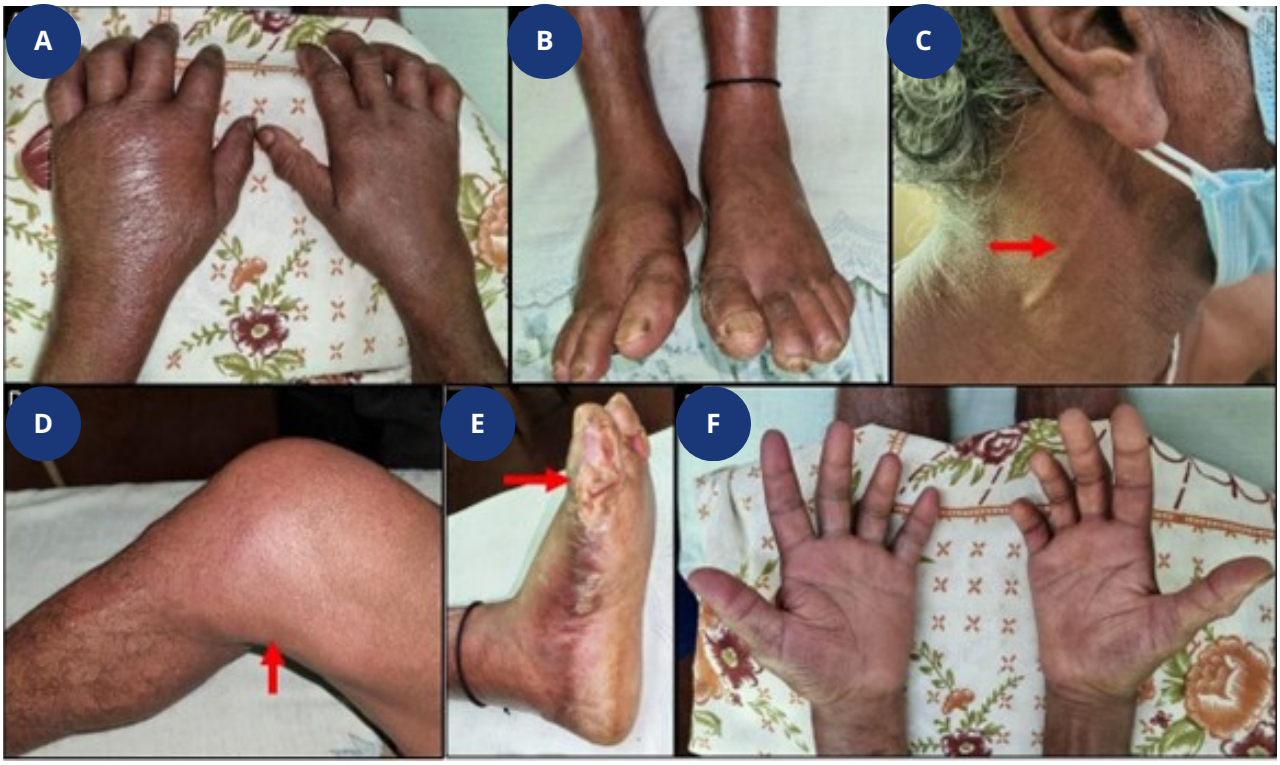

Figure 1 - **Panel A**: asymmetric swelling of dorsum of both hands; **Panel B**: swelling of dorsum of both feet; **Panel C**: visible right greater auricular nerve (arrow); **Panel D**: erythematous patch over right knee due to type 1 Lepra reaction (arrow); **Panel E**: neuropathic ulcer under left big toe (arrow); **Panel F**: bilateral ulnar claw

polyarthritis resembling rheumatoid arthritis seen in Lepra reactions.(3) Other manifestations such as chronic monoarticular osteoarthritis, neurogenic or Charcot's arthropathy, spondyloarthropathy, sacroiliitis, enthesitis, dactylitis, and dermatomyositis, systemic lupus erythematosus or systemic sclerosis-like presentations have also been reported.(3)

Consent for publication was obtained from the patient

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(1) Answer E

Malignancy associated dermatomyositis

The picture shows an erythematous rash over the photo-exposed area of the chest and neck (the 'V' sign) seen in dermatomyositis (DM). DM can present as a paraneoplastic manifestation in which case it might be associated with antibodies such as anti-TIF-1 (anti-transcriptional intermediary factor-1) and anti-NXP2. Myositis specific antibodies such as anti-synthetase antibodies (anti Jo-1), anti-Mi-2, anti-SRP and anti-MDA5 are often negative in cancer associated DM.

(2) Answer C

Cutaneous larva migrans

The picture shows an erythematous serpiginous cutaneous track (which is pruritic) characteristic of cutaneous larva migrans. The larvae of the infected parasite migrate within the epidermis producing an inflammatory reaction along the cutaneous tract of their migration, which may continue for weeks. This patient had a habit of lying on the ground bare-chested which possibly led to the infection.

(3) Answer A

Sweet syndrome

Sweet syndrome is an acute febrile neutrophilic dermatosis of inflammatory origin characterised by the abrupt appearance of painful, oedematous and erythematous papules, plaques, or nodules on the skin. Fever and leukocytosis frequently accompany the cutaneous lesions. The upper extremities appear to be the most common site of involvement whilst the trunk, lower extremities, head, and neck are the other sites of frequent involvement. Sweet syndrome can be associated with a variety of autoimmune diseases, malignancies and drugs. Fever and rash will show a swift response to glucocorticoids. Painful (tender) nature of the rash and abrupt response to treatment are clues to differentiate it from leukaemia cutis, which is a close differential diagnosis here.

(4) Answer B

McCune-Albright syndrome

McCune-Albright syndrome is a condition consisting of the triad of characteristic café-au-lait spots, fibrous dysplasia of bones and endocrine hyperfunction (commonly peripheral precocious puberty but also thyrotoxicosis, Cushing's syndrome and acromegaly). The café-au-lait spots have a characteristic appearance with jagged borders (described as "coast of Maine" appearance) which may follow the lines of Blaschko and do not usually cross the midline.

(5) Answer E

Cutaneous sarcoidosis

This lady has lupus pernio (LP) rash on her nose which is one of the common dermatological manifestations of sarcoidosis. LP is characterised by violaceous or erythematous, indurated, infiltrative plaques distributed on the central face, particularly the nose and cheeks. She also has a lesion of plaque sarcoidosis over her upper neck which often presents with oval or annular, indurated, discrete plaques that are skin coloured, erythematous or brown. She had significant pulmonary involvement which explained her persistent cough.

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