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CASE REPORT

Acute kidney injury after breast augmentation using hyaluronic acid injection – A case series and review of literature

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SUMMARY

Breast augmentation (BA) is a common aesthetic surgery to attain the desired breast fullness or to rectify potential asymmetries. The use of injectable hyaluronic acid (HA) has become conveniently popular as an alternative to breast implant. We reported a series of four individuals who underwent BA with HA and subsequently experienced severe kidney injury requiring kidney replacement therapy (KRT). These individuals had their procedures done by unlicensed personnel. HA however is not a licensed product in Malaysia as breast implants. We aim to raise the awareness of the implications of such malpractice, including potential toxic effects and severe complications associated with HA injections.

INTRODUCTION

Breast augmentation (BA), is a popular surgical technique to enhance breast size and shape. This procedure involves the insertion of breast filler, enabling individuals to achieve their desired breast size with the use of injectable materials. Unlike traditional surgical interventions, BA with injectable fillers offers several advantages, including reduced hospitalization requirements and shorter recovery periods.[1]

One of the newest products utilized in BA procedures is Hyaluronic acid (HA).[2] However, the safety and efficacy of using HA specifically for BA remain unknown due to the scarcity of published scientific data.

By presenting this case series, we aimed to shed light on the potential risks and common complications associated with the use of HA for BA. Understanding such adverse outcomes is crucial for both medical professionals and patients, as it can aid in making well-informed decisions regarding the most appropriate and safe choices for breast enhancement procedures.

CASE PRESENTATION

Case 1

A 35-year-old woman with a history of bronchial asthma presented to the hospital with symptoms of dizziness, nausea, vomiting, and seizures, approximately four hours after her second BA procedure: involving the injection of 200ml of HA into her breasts under local anesthesia (LA). Her first BA, done a month prior, had no complications.

Upon arrival at the emergency department, the patient exhibited a Glasgow Coma Scale (GCS) score of E4V2M1 and required double inotropic support. She experienced two generalized tonic-clonic seizures and displayed physical signs of breast engorgement and erythema at the injection sites.

Blood tests revealed leucocytosis, high anion gap metabolic acidosis with serum lactate level of 9.1 and acute kidney injury (AKI). The patient was intubated for airway protection and admitted to the intensive care unit (ICU). In the ICU, she received continuous veno-venous hemodiafiltration (CVVHDF) and intravenous (IV) antibiotics.

After 19 days in the hospital, she was discharged home with improved kidney function. In her three-month follow-up, the patient exhibited full kidney recovery.

Case 2

A 42-year-old female patient, with no prior medical history, underwent her second BA procedure, receiving an injection of 2ml of LA followed by 200ml of HA as a breast filler. Immediately after the injection, she experienced dizziness, nausea, and multiple seizure episodes. Her condition upon arrival was critical, with a low GCS score and hemodynamic instability, necessitating inotropes and intubation.

The patient exhibited hypertonicity, hyperreflexia, and clonus during neurological examination, alongside erythema and swelling of the right breast at the injection sites. Blood investigations revealed leucocytosis, severe metabolic acidosis, AKI, and urine analysis showed proteinuria and microscopic hematuria.

She was admitted to the ICU and underwent CVVHDF while receiving IV antibiotics. Blood culture results were negative. Throughout her admission, she was closely monitored, underwent extubation, and received intermittent hemodialysis (IHD) as needed. A kidney biopsy was advised but declined by the patient. Ultimately, the patient chose to discharge herself against medical advice and was lost to follow-up.

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Table I: Clinical characteristics and outcome of the patients

Clinical Data	Patient No.			
	1	2	3	4
Age, yr	35	42	41	31
Sex	F	F	F	F
Race	M	M	M	M
Comorbidities	None	Bronchial Asthma	None	None
CKD status	No history of CKD	No history of CKD	No history of CKD	No history of CKD
Treatment Centre	Temporary Rental Apartment	Temporary Rental Apartment	Aesthetic Centre	Aesthetic Centre
Admission Urea, mmol/L	3.8	4.2	31.9	23.4
Admission Scr, mcmol/L	105	108	1097	616
Peak Urea, mmol/L	14.6	36.4	42.3	20.7
Peak Scr, mcmol/L	388	1014	1261	1142
Urinalysis Protein	3+	3+	NA	2+
Urinalysis Blood	4+	4+	NA	1+
Blood Culture	NG	NG	Serratia marcescens	NG
Breast Tissue Culture	NG	NG	Burkholderia cenocepacia	Candida and Aspergillus species
Kidney size, cm, right/left	NA	10.5/10.5	12.9/13.1	13.0/12.5
Vasopressor use at time of AKI	Yes	Yes	Yes	Yes
Risk factors for AKI	Hypotension, Infection	Hypotension, Infection	Hypotension, Infection	Hypotension, Infection
Kidney biopsy diagnosis	NA	NA	NA	Acute Interstitial nephritis and acute tubular injury
Dialysis	Yes	Yes	Yes	Yes
ICU admission	Yes	Yes	Yes	Yes
Mechanical Ventilation	Yes	Yes	Yes	Yes
Length of Hospital Stay, days	19	87	24	39
Clinical outcome of the AKI	Patient needed dialysis; AKI subsequently improved and patient came off dialysis	Dialysis dependent, however patient discharge against medical advice and defaulted follow up.	Dialysis dependent, patient died	Patient needed dialysis and became dialysis independent; develop CKD (eGFR 24 mls/min/1.73m^2)
Death	No	No	Yes	No

F, female; M, Malay; CKD, chronic kidney disease; Scr, serum creatinine; AKI, acute kidney injury; ICU, intensive care unit; NA, not available/applicable; NG, no growth.

Table II: Presenting signs and symptoms in Case 1 – 4,

Clinical signs and symptoms	Case No.			
	1	2	3	4
Seizure	•	•	×	×
Hypotension	•	•	•	•
Nausea/Vomitting	•	×	•	•
Body weakness	×	×	•	•
Urinary Retention	×	×	•	•
Breast infection	•	•	•	•
Blindness	×	×	•	×
Hearing loss	×	•	•	×

•, Indicates the presence of the clinical signs or symptoms; ×, Indicates the absence of the clinical signs or symptoms

Case 3

A healthy 41-year-old female sought BA at an aesthetic center who receiving 500ml HA injection. She later presented at a district hospital with a 3-day history of anuria after few days. Blood tests indicated AKI, transaminitis, and hypercalcemia, prompting her transfer to a tertiary hospital. During her hospitalization, the patient experienced sudden bilateral sensorineural hearing loss, and bilateral papilledema. She also developed bilateral breast abscesses due to breast filler injections. Her kidney function continued to decline, necessitating intubation and CVVHDF. Wound debridement was performed. Blood cultures revealed Serratia marcescens while breast tissue and pus cultures showed Burkholderia cenocepacia. Unfortunately, her condition continued to deteriorate and she succumbed to severe infection with multi-organ failure.

Case 4

A previously healthy 31-year-old woman was admitted to the hospital with epigastric pain, vomiting, and reduced urination two days after underwent a bilateral BA procedure involving HA filler injections at multiple sites. Physical examination revealed signs of sepsis, lethargy, and gangrenous tissues at the breast injection sites. She developed

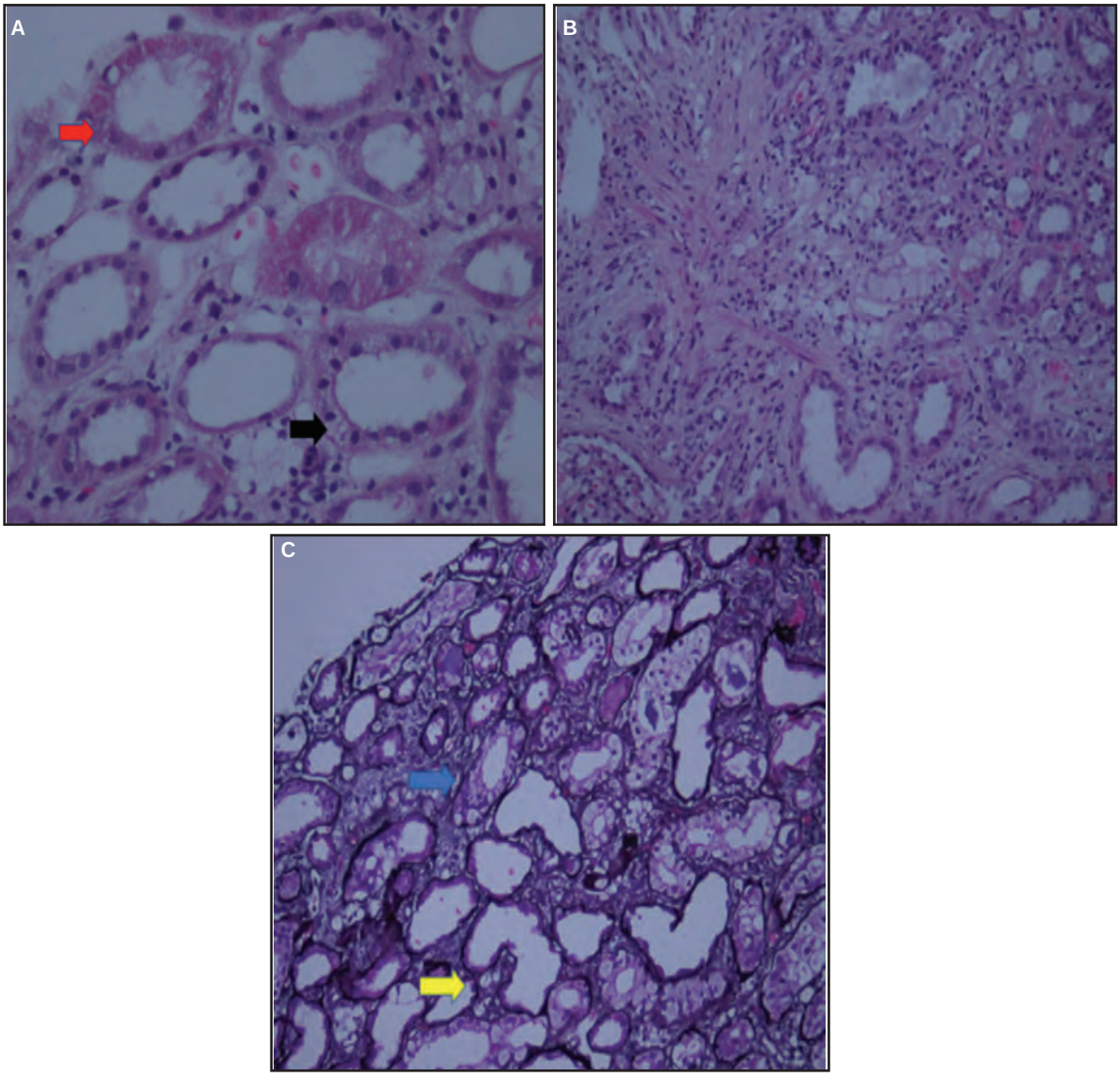

Fig. 1: Renal pathologic features associated with breast augmentation procedure in patient 4
(A) Tubular cell with loss of brush borders (red arrow) and presence of epithelial cells with cytoplasmic vacuolization (black arrow)
(B) Moderate inflammatory infiltrates in the interstitium
(C) Presence of dilated tubules (yellow arrow) and epithelial cell with vacuolization (blue arrow)

All images were obtained under polarized light microscopy. Images in A and B were stained under hematoxylin and eosin staining. Images in C was stained via silver stain

oliguric AKI with severe metabolic acidosis secondary to bilateral breast myonecrosis.

She received CVVHDF with slow kidney function recovery necessitated IHD for three weeks. Multiple wound debridement sessions were conducted with cultures revealing Candida and Aspergillus species. Antifungal treatment was administered in stages.

A kidney biopsy was performed in the fourth week of hospitalization revealed features of acute interstitial nephritis (AIN) and acute tubular injury. Inflammatory cell infiltrates were present, mainly consisting of lymphocytes with scattered neutrophils and occasional eosinophils. Glomeruli appeared normal.

In the fourth week of her hospital stay, the patient showed improved urine output and kidney function recovery. Follow-up assessments indicated healing breast wounds and improving kidney function over the subsequent weeks and months. Creatinine 232 mcmol/L at 6 months post discharge.

DISCUSSION

Within a span of four weeks in November 2021, four unusual young females with acute kidney injury admitted to four different hospitals in the southern state of Johor, Malaysia. The cases were collaborated on with in-house nephrologists, using clinical information derived from medical case notes.

We have summarized the findings, including patient characteristics, comorbidities, chronic kidney disease status, admission and peak serum creatinine levels, vasopressor use at the time of AKI, risk factors for AKI, dialysis initiation in the hospital, and patient outcomes as in Table I. The average age of the patients was 37 years, with minimal or no premorbid history. Among the four patients, all had severe AKI requiring kidney replacement therapy, and the mortality rate was 25%. Symptomatology and signs are provided in Table II, while Figure 1 shows the serial clinical data of the patients.

These four cases of AKI were caused by unlicensed and unsupervised injections of HA. Presently, neither the Food and Drug Administration nor the National Pharmaceutical Regulatory Agency has authorized any of the above liquid injectable substances for cosmetic use.

HA is a glycosaminoglycan polymer composed of repeating disaccharides (glucuronic acid and N-acetyl-glucosamine). It is naturally found and produced in cells and tissues such as joints, basement membranes and the vitreous of the eye. It provides structural and mechanical support.[3] Studies have postulated that HA interacts with CD44, leading to increased formation of fibrotic molecules and subsequent tubular damage.[4,5] These findings support the plausibility of HA as a contributor to the AKI observed in these cases.

Furthermore, ischemia-reperfusion injury is a well-known cause of AKI, involving hemodynamic changes, inflammation, and tubular injury.[5] Recent studies have hypothesized that HA may promote a pro-inflammatory environment during ischemia-reperfusion, leading to AKI. While the molecular weight of HA involved in this process remains uncertain, our presented cases prompt further exploration of its potential role in ischemic renal damage.

The above case series also reported other minor adverse events associated with cosmetic hyaluronic injections, such as swelling, hematoma, and pain.[6] Infections can occur as a result of a breach of the skin's surface integrity by injectable fillers, with infectious agents ranging from fungal, bacterial to viral.6 Severe infections were described in the above cases, leading to multi-organ failure, as evidenced by imaging, inflammatory markers, and positive cultures. In the renal biopsy of case 4, we saw AIN and acute tubular injury, with potential etiologies of infections and ischemia of the kidneys. Unsupervised cosmetic procedures performed by unqualified practitioners may compromise sterility and result in severe complications, as evidenced by our reported cases. The presence of Candida and Aspergillus in case four raises concerns about the risk of infections associated with injectable fillers.[6] This aligns with existing literature that highlights the potential for infections, including fungal, bacterial, or viral, to occur following cosmetic filler injections.[6]

Furthermore, the severity of the injury and poor outcomes linked to AKI worsen when there is a delay in recognition and subsequent treatment.[7] This is clearly illustrated in cases 3 and 4, where both patients delayed seeking treatment, resulting in severe kidney damage with a higher risk of mortality and morbidity.

In addition, vascular occlusion following filler injections is a recognized major complication, causing skin necrosis through localized obstruction or blindness or cerebral ischemic events due to distant obstruction.[6] Studies have postulated that high filler injection pressure could trigger embolization to the retinal circulation, causing loss of vision or into the intracranial circulation, causing cerebral ischemic events.[8]

According to the HA Safety profile document, there were rare but serious events included partial or complete vision loss following upper face injections, as well as brain infarcts or hemorrhage. The overall quality of evidence is moderate.[9]

Hearing issues are frequently mentioned in the context of surgical breast implant procedures, with hearing loss and tinnitus being the most prevalent complaints. The link between breast implants and hearing problems is thought to be associated with autoimmune or inflammatory responses triggered by adjuvants.[10] There are reports indicating substantial symptom improvement, partly with self-reported tinnitus, after the removal of breast implants.[10] Further research involving larger cohorts of women with breast implants is essential to confirm the presence of hearing impairments in this population.

Alternative options to hyaluronic acid injections include autologous fat transfer, which uses the patient's own fat harvested through liposuction to augment breast volume; however, it carries risks such as fat necrosis and cyst formation.[6] Breast implants use silicone gel but carry risks of capsular rupture and rare cases of implant-associated anaplastic large cell lymphoma.[6]

Our case series has several limitations. The limited number of kidney biopsies performed restricts the generalizability of our findings. Consent issues, patient choices, and the severity of illness prevented two patients from undergoing kidney biopsy, which may confirm various types of kidney injuries. Additionally, alternative inflammatory biomarkers were unavailable, which might have provided more insight into distinguishing inflammation from infection.

Crucial information of the specific components such as the concentration of HA derivatives and details about the injection and sterility techniques, were unavailable in most cases. This lack of information may impact the interpretation of our results and conclusions. Moreover, since there is no clear data on the total number of people undergoing BA in Malaysia, we cannot establish a clear incidence rate of such acute kidney injuries following BA procedures. Furthermore, the relatively short follow-up period and limited number of patients in our study prevented us from identifying specific patient characteristics or clinical features associated with more severe presentations, slower recovery or the need for dialysis.

Despite these limitations, our case series provided important insights into the potential risks and adverse effects associated with HA injections for BA. These cases also underscore the need for stringent regulation and licensing of practitioners administering cosmetic injections. Public awareness campaigns regarding the risks associated with seeking cosmetic treatments from non-licensed individuals are essential to promote informed decision-making by patients. Proper education on the potential hazards of unregulated procedures can empower patients to prioritize their safety and seek treatment from qualified medical professionals. We have reported to the enforcement unit of the State Health Department of Johor, Malaysia to tighten the policing of such malpractices. Since then, we are pleased that no such complications were seen over the subsequent two years.

CONCLUSION

This report highlights the troubling cases of four adult females who developed acute kidney injury (AKI) following breast augmentation with hyaluronic acid injections administered by unlicensed personnel. The outcomes varied, with one patient achieving full recovery, another succumbing to her condition, and a third progressing to chronic kidney disease. These findings emphasize the urgent need to raise awareness about the serious risks and potential toxic effects associated with unauthorized HA injections. We stress the critical importance of seeking cosmetic treatments exclusively from licensed and qualified medical professionals operating in regulated and hygienic facilities. The awareness generated from this report can play a pivotal role in safeguarding patient health and well-being when undergoing cosmetic procedures involving injectable substances like HA.

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DECLARATION

It is hereby affirmed that consent for publication has been obtained from the patient or their caregiver. Furthermore, it is declared that the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia (MOH) has determined that this study, being a case series, does not require MREC review or approval. The authors declared that there was no fund applicable for this study. The authors declare that there are no conflicts of interest regarding the publication of this paper.

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CASE REPORT

Recurrent falls as an initial presentation of dementia: A case report

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SUMMARY

Falls among the elderly are quite common, particularly as the aging population continues to grow. Physicians are likely to encounter more patients presenting with either their first fall, multiple falls, or those identified as being at risk for future falls. Investigating the circumstances surrounding a fall, gathering eyewitness accounts, and conducting a thorough physical assessment of the patient can provide valuable insights into the underlying causes. This information is crucial for developing strategies to prevent future falls. We present an elderly man who presented to primary care with a history multiple falls in the absence of underlying neurological or gait issues and later was found to have vascular dementia on radiologic imaging. This case report describes the approach, assessment and management of falls among elderly with dementia highlighting the role of the multidisciplinary team approach and management based on the latest evidence.

INTRODUCTION

Fall in elderly is described as an event which results in a person coming to rest inadvertently on the ground or other lower level.[1] Falls can happen anywhere, whether indoors or outdoors. Recurrent falls are defined as two or more falls reported over the last 12 months.[2] More than 25% of elderly experience one fall each year which leads to hospitalisation, disability and death. In Malaysia, the prevalence of falls and recurrent falls in among older adults in the community is about 72.5% and 27.5% respectively and the common causes are advancing age, sensory deficit, reduced lower limb strength, medication use, sarcopenia and cognitive impairment.[2] However, identifying cognitive impairment as a major cause for fall is challenging, as all other possible underlying causes must first be ruled out.

People with Alzheimer or any type of dementia commonly present with memory issues and deterioration in functional activities of daily living which are either noticed by the patients themselves or by their family members. However, people with dementia are at risk of falls up to 4 years preceding the diagnosis and peak at the point of diagnosis of dementia. Hence, screening for cognitive disorders among elderly with falls is essential.

We present an elderly man who complained of recurrent falls over 3 years. His, gait, balance, general and neurological examination were all normal. However, on further evaluation, he was detected to have vascular dementia which was later attributed as the cause for his recurrent falls. The approach and management of patients presenting after a fall is summarised based on the current evidence and guidelines.

CASE PRESENTATION

A 70-year-old man presented to primary care with history of recurrent falls. He experienced three to four falls a year over the past 3 years which mostly occurred outdoors. The last fall was 3 weeks earlier when he was walking towards his car at the carpark. He did not trip over anything but felt that he could not stop walking when he reached the car hence knocked himself against the car and fell. He sustained abrasions on his face and right knee during that episode of fall. He claimed that the previous episodes of falls were similar and occurred while he was walking. There was no history of any aura, dizziness or seizures prior to the falls. There were also no eyewitness to these incidents. He had underlying type 2 diabetes, hypertension, dyslipidaemia and underwent cardiac bypass surgery in the year 2018. His current medications were aspirin 100 mg OD, metformin 500 mg BD, gliclazide MR 120 mg OM, atorvastatin 40 mg and dapagliflozin 10 mg OD. On further questioning, he described occasional memory issues such as forgetting where he parked his car or kept his keys for about a year which he attributed to advancing age. He also suffered from frequent insomnia and inability to sustain his focus. The patient was a widower and lived with his daughter. Their relationship was strained and there were no other family members. Over the years, he experienced isolation and lost interest in life.

Physical examination showed a well kempt elderly man. General physical examination was normal. His height was 160.5 cm, weight was 53.3 kg and BMI was 20.8 kg/m2. There was no orthostatic hypotension (repeated blood pressure on lying down was between 120/69 to 125/70 and standing blood pressure was between 121/78 to 130/80 mmHg). There were no spinal deformities. There was bilateral knee crepitus suggestive of osteoarthritis without any joint abnormality. His vision with glasses, hearing and gait were also normal. Clinically, sarcopenia was absent as patient had acceptable hand grip and was able to rise from the sitting position. Signs of Parkinson's disease such as tremors, muscle stiffness or bradykinesia were all absent. His cardiovascular and neurological examination were normal.

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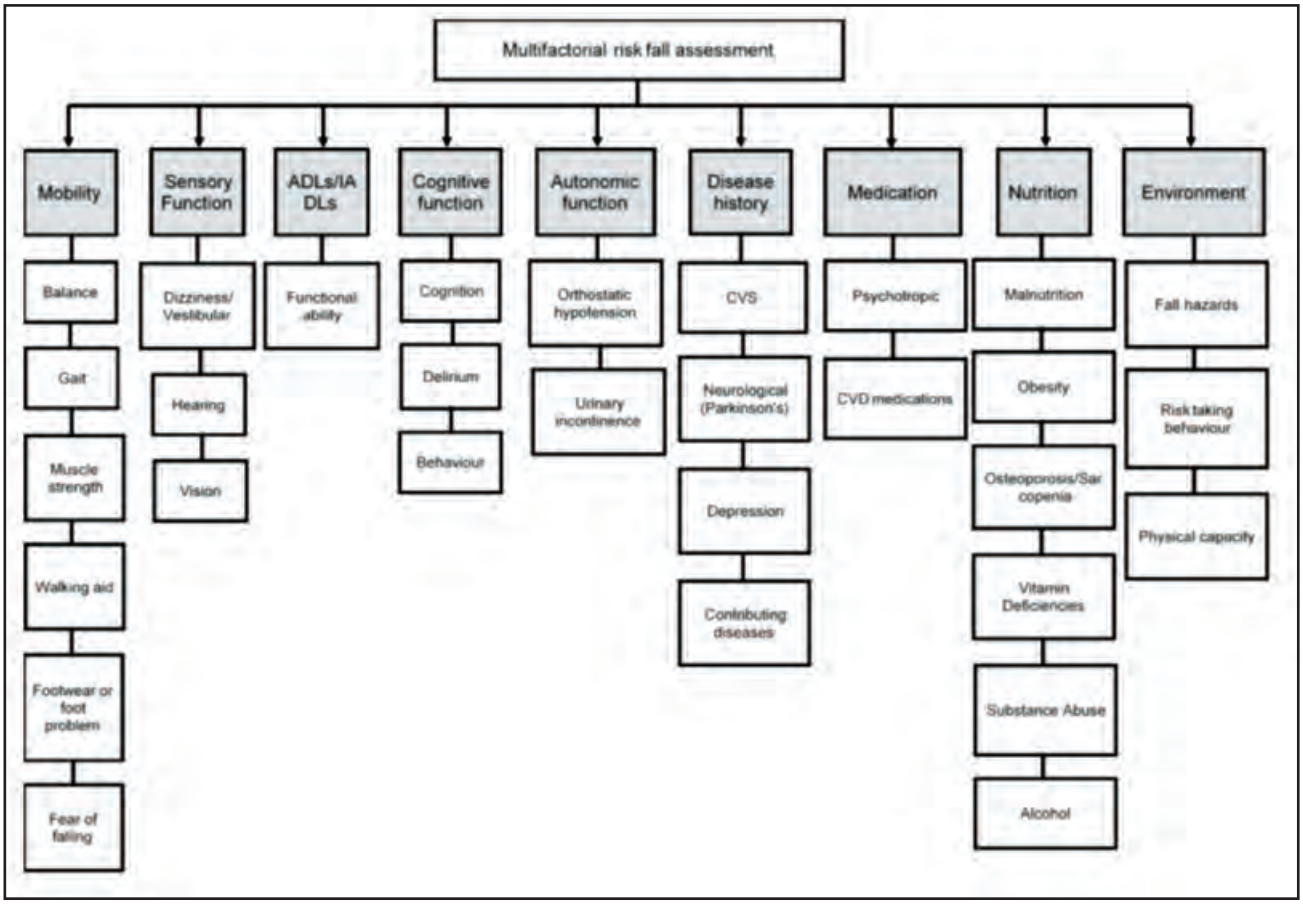

Fig. 1: Flow chart summary of assessment of elderly with fall.[2]

His balance was good. (tandem stand test) His gait was assessed using the Timed Up and Go (TUG) test which was completed in less than 15 seconds without assistance. His instrumental activity of daily living (IADL) showed that he had high function and was independent (7/8 score using the Lawton-Brody IADL scale). Screening for depression using the Patient Health Questionnaire-9 (PHQ9) revealed mild depression (score 7/27). Cognitive assessment using the Montreal Cognitive Assessment (MoCA) showed moderate cognitive decline with a score of 17/30 with difficulties in memory, attention, language, delayed recall and cognition, suggesting dementia.

Initial investigations to rule out causes for dementia such as full blood count, thyroid function test and vitamin B12 level were all normal. His HbA1c was 7.9%. Computed tomography (CT) brain showed multifocal chronic infarcts with cerebral atrophy suggesting vascular dementia. A possible diagnosis of recurrent falls due to underlying vascular dementia with mild depression, suboptimal glucose control due to poor compliance and social issues was made. The long-term plan for him was to prevent future falls, to improve glycaemic control and to be referred to the neuro-medical team for management of vascular dementia. He was referred to physiotherapy for lower limb muscle strengthening exercises and balance. His medication for diabetes, hypertension and dyslipidaemia was continued.

Efforts to contact his family to discuss support, medication supervision and adherence issues, were unsuccessful however, his friend helped to accompany him for follow up appointments at the clinic and a referral to social worker was made. After the third follow up, the patient defaulted on all appointments and remained uncontactable. One year later, patient was brought unconscious to a near by hospital after a fall. He had sustained subdural haemorrhage and passed away a few days later in the ward.

DISCUSSION

As the world aging population increases, falls and fall related injuries among elderly will become a growing challenge. About one third of adults above the age of 65 years would experience a fall or fall related injuries annually leading to disability, hospitalisation or death.

People with cognitive impairments are eight times more likely to experience falls compared to those without.[3] This is due to the decline in the executive function which is the cognitive domain controlling decision making and problem

solving, which are essential requirements for execution of complicated tasks such as gait, balance, memory and attention.[4] This causes changes in gait, restricts mobility, and increases the risk of fall. Vascular dementia can be classified as post-stroke dementia and vascular dementia without a recent infarction. The latter is also known as Covert cerebral small vessel disease (ccSVD) which is commonly found on neuroimaging among people who do not have any obvious neurological symptoms such as the patient in this case report.[5]

Approach of Elderly with Falls

Understanding the nature of fall, identifying the potential contributing risk factors of fall and assessing the psychosocial effects following a fall are all important components of assessment. A detailed history should include circumstances of fall, mechanism of fall and activity at the time of fall and associated symptoms. Presence of any functional deficits, injuries and psychological impact of each episode of fall should also be assessed. Delirium and behavioural problem should be ruled out. All this information helps to predict the likelihood of future falls and helps to individualise the management plan for each patient. However, elderly patients with dementia may not be able to provide these details as they suffer with recall issues. Hence details on the circumstances of fall from the family members, caregivers or eyewitness would be helpful.

The approach to fall can be daunting as there is a long list of possible causes. The suspicion of cognitive impairment as a possible cause for the recurrent falls is based on the exclusion of all other possible causes. The World Guideline for Falls Prevention and Management for older adults recommends a comprehensive multifactorial falls risk assessment in nine major domains for patients presenting with falls.[2] This includes mobility status, physical examination and cognitive assessment. Initial investigation for people with suspected cognitive impairment include full blood count, biochemistry tests, thyroid function test, serum vitamin B12 and folate levels to exclude dementia-mimicking conditions. Non-contrast CT or MRI brain modalities help to exclude neurological cause such as infarct, haemorrhage or brain tumour. The summary of the recommended approach to elderly with falls by the world guidelines for falls prevention and management for older adults is depicted in Figure 1.

Management of Elderly with Falls

The main objective of managing elderly after an episode of fall is to minimise the risk and prevent future falls. This can be done by identification of risk factors and addressing the cause of fall by implementing individualised intervention strategies.

Since patients with dementia lack the ability to care for themselves, a shared decision-making between physician, patient and their family members or caregivers is crucial as it helps to enhance treatment adherence and prevent future falls. The World Guideline for Falls Prevention and Management in older adults recommends a comprehensive approach involving a multidisciplinary team involving physiotherapist and occupational therapist. Physiotherapists can provide supervised exercise programs with an aim to enhance muscle strength, posture and balance. Exercise has been shown to be one of the most effective methods to reduce risk and rate of fall using balancing, challenging and functional exercises such as sit-to-stand and stepping.[2] Tai chi practice has been shown to reduce the risk of fall among elderly by 50%.[6] Occupational therapists are able to identify potential hazards in the home environment and suggest safe home arrangement.[2]

Management of patients who have cognitive impairment with clinical or radiological evidence of cerebrovascular pathology require strict management of vascular risk factors such as stop smoking, optimal blood pressure, glucose and dyslipidaemia control. The role of aspirin in the management of cognitive impairment remains uncertain however, it helps to reduce the risk of further infarcts among patients without previous intracranial haemorrhage. Cholinesterase inhibitor may be tried in patients with vascular dementia with cognitive decline although its effectiveness in reducing falls among people with dementia is inconclusive as studies show contradicting evidence.[7]

Managing our patient was particularly challenging as he had social issues and frequently defaulted follow-up appointments. This case report shows that managing the elderly with dementia and fall requires collaboration of a multidisciplinary team consisting of physician, physiotherapist, occupational therapist, family members and social worker to manage the medical condition and to execute effective fall prevention strategies.

CONCLUSION

Falls are more common among elderly with cognitive decline compared to those with intact cognition. Hence, physicians must be vigilant to detect possible dementia in elderly presenting with falls as this may be an early sign. A comprehensive assessment of history, physical examination and investigations to rule out all other possible causes for fall is essential before considering dementia as a possible cause for falls in the elderly. Individualised intervention is important as these patients will need long term support and care in a safe living environment to prevent fall related morbidity and mortality. Absence of support for these patients renders management more challenging and can result in poor prognosis.

ACKNOWLEDGEMENT

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DECLARATION

The authors declare no actual or potential conflict of interest in relation to this article.

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CASE REPORT

Unusual case of fungal cervical spine osteomyelitis in a patient with amyloidosis causing quadriparesis: A case report

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SUMMARY

We present an unusual case of a 68-year-old lady who was diagnosed to have amyloidosis following chronic anaemia. She was put on systemic corticosteroid therapy for a year. She presented with rapidly progressive quadriparesis. Computed tomography/magnetic resonance imaging imaging showed pathological fracture/dislocation of Cervical C5 vertebrae with cord signal changes, raising suspicion of a metastasis or tuberculous infection. A two-level corpectomy and cervical plating were done as part of a staged procedure. Posterior fixation could not be carried out due to postoperative acute myocardial infarction and exposure to COVID in the ward. Histopathology showed strong positivity of fungal bodies. This case discusses an unsuspecting fungal infection that needs to be investigated in elderly and immunocompromised patients. She subsequently refused further surgery, and instead, long-term rigid cervical collar was applied. She significantly improved from Modified Rankin Scale 5 to 3 in 3 months. Fungal infection should be suspected in similar cases, and ideally, a posterior fixation following 2 level or more corpectomy is a good option. Confounding medical conditions can interfere with surgical planning. Long-term rigid collar is a viable option in selected patients.

INTRODUCTION

Fungal spinal infection is an uncommon condition.[1] We could not identify any reports on patient who were treated for amyloidosis who later developed cervical fungal osteomyelitis. Prolonged systemic steroid therapy is an independent risk factor for fungal infection. When spinal instability ensues, this may result in spinal cord or root compression, resulting in neurological deficit. In general, unless urgent surgical decompression is performed, the prognosis for return of function is questionable. Surgery involves removal of compressing elements and reconstruction of spine by way of spinal instrumentation. The stabilisation allows bone fusion of the involved segments. This process depends on the patient factors as well as spinal construct and may take time. Any immunocompromised state or poor surgical planning may result in delayed or nonunion, and hence, lead to neurological deficits.

Among review of 60 cases of candida vertebral osteomyelitis by Miller (2001), mean age is 50 years old and the commonest location is lower thoracic or lumbar. Patients typically present with chronic back pain (83%), fever (32%) and neurological deficit (19%) with preceding risk factor of central venous catheterisation, antibiotic usage, immunosuppression or injection drug usage.[2] There is elevation of ESR in 87% of cases and positive culture in 51%. Management involves surgical debridement and prolonged antifungal therapy, of which commonly used agents include amphotericin B, voriconazole, itraconazole and fluconazole. Prognosis is generally good with cure rate of 85%.[3]

Williams et al.[4] reported three cases of fungal spinal osteomyelitis in immunocompromised (post-organ transplant) patients, in which key imaging features include hypointensity of vertebral bodies in T1-weighted sequence, signal changes and enhancement extending into posterior elements, multilevel diseases, preservation of intranuclear cleft in affected discs as well as lack of disc hyperintensity on T2-weighted imaging.

CASE PRESENTATION

We present an interesting case of a 68-year-old lady who initially presented with symptomatic anaemia and was treated for amyloidosis. She was given systemic corticosteroid therapy for 12 months, and her general condition including hematological parameters steadily improved. She was subsequently back to her premorbid state and tapered off corticosteroid treatment.

One year after the systemic corticosteroid treatment, she started developing chronic neck pain and weakness over all four limbs, which progressed over 1 month period. By the time she presented, she was fully alert but bedbound with all limb power of 1-2/5. Modified Rankin Scale as well as Nurick scale was 5. Computed tomography (CT) showed pathological fracture and retropulsion of C5 vertebral body whereas Magnetic resonance imaging revealed the involvement of C4 and C5 vertebral bodies with signal changes, collapse and retropulsion of C5 vertebral body causing spinal cord compression (Figure 1).

We suspected infective or neoplastic pathology causing the compression fracture of C4 and C5 vertebral bodies. Inflammatory marker as well as tumour markers including ESR, CRP, White cell counts, CEA, AFP, CA125, CA19-9 and

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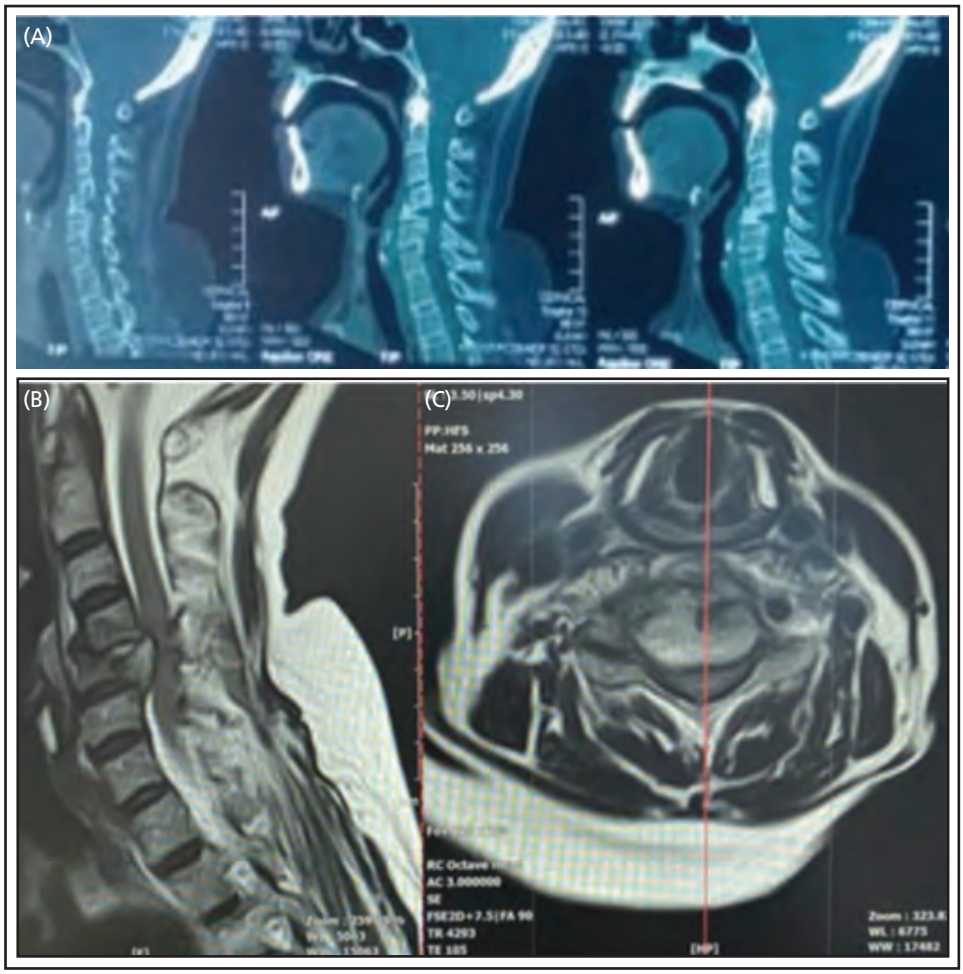

Fig. 1: Preoperative CT cervical (A) and MRI cervical (B, C) showing signal changes and pathological fracture of C5 vertebral body causing spinal cord compression

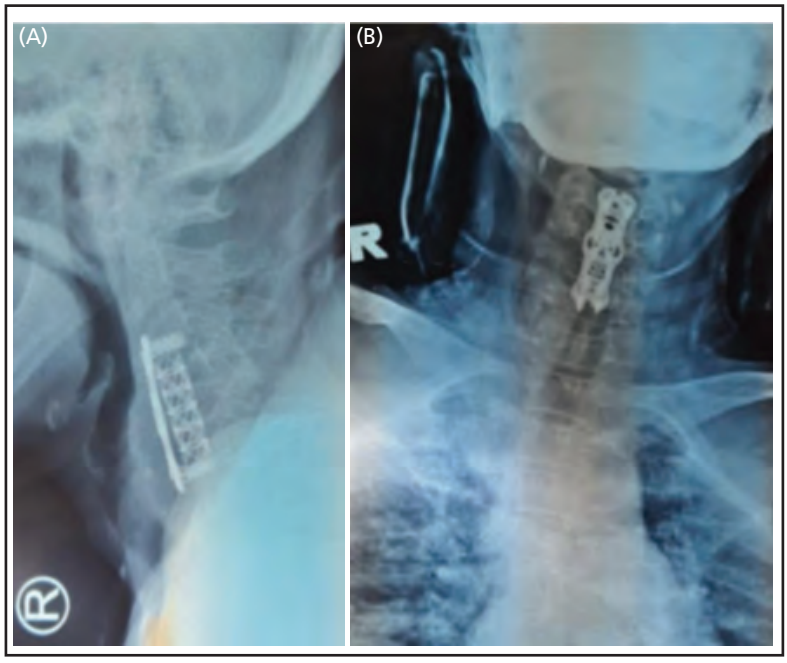

Fig. 2: Showing lateral (A) and anteroposterior (B) view of immediate postoperative cervical X-ray

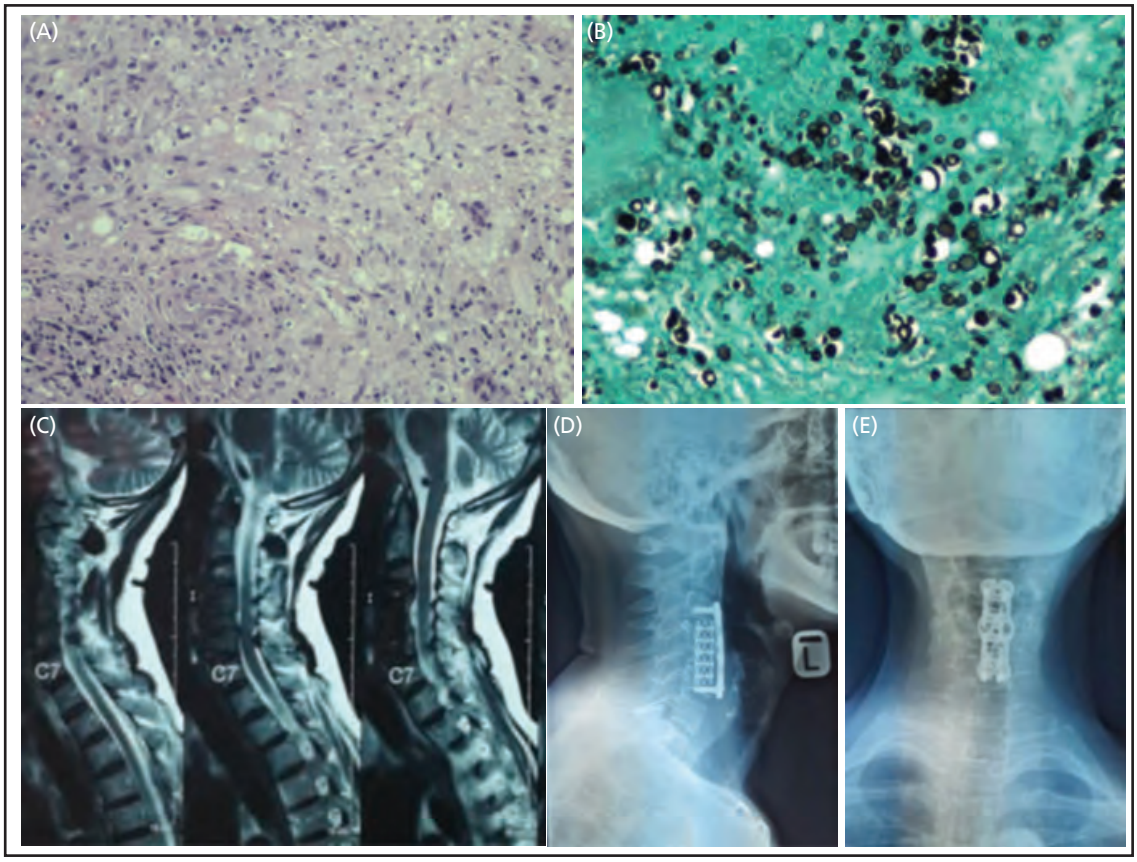

Fig. 3: Histopathological examination of the removed tumour demonstrated bland spindle cells in myxoid stroma with some fibroadipose tissue, smooth muscle, bone (A), and cartilage (B) with overall features suggestive of endobronchial hamartoma. (×40 magnification, haematoxylin and eosin stain)

bHCG were not raised. Workups for tuberculosis were negative. Full septic workups did not reveal any positive growth. Hence, main suspicion was neoplastic process causing the pathological fracture of affected vertebral bodies.

In view of the frank vertebral instability and rapidly progressive neurological deficit, she was planned for a combined anterior and posterior approach for decompression as well as stabilisation with C4-C5 corpectomy and posterior stabilisation in single setting. Intra-operatively the C4 and C5 vertebral bodies were clearly affected with poor bone quality suggestive of involvement of disease. There was greyish lesion, which was moderately vascular, poorly demarcated and unencapsulated noted over the affected vertebral bodies. Intervertebral discs were spared.

C4 and C5 corpectomy, Cage and anterior cervical plate insertion over C3 and C6 vertebral bodies were performed. The quality of C3 and C6 vertebral bodies were also felt to be poor, with less satisfactory screw purchase during anterior cervical plating. Hence, she was planned for a posterior C3 to C6 posterior instrumentation to supplement the anterior fixation. However, after the first stage of surgery, she developed non-ST elevation myocardial infarction on table and was felt to be unstable for the posterior surgery. Hence, it was postponed.

Immediate postoperative X-ray was as shown in Figure 2. Postoperatively, patient improved neurologically to all limb power of 3-4/5 and was able to mobilise with assistance by the end of first week postoperatively. She also developed lower gastrointestinal haemorrhage secondary to antiplatelet treatment from the Non-ST Elevation Myocardial Infarction and was also exposed to COVID in the hospital. In view of the multiple issues, she subsequently was not keen to proceed with the second surgery. As an alternative, she was put on rigid cervical collar, planned for 3–6 months and subsequently discharged with regular physiotherapy and rehabilitation.

1 week postoperatively, histopathological examination revealed chronic inflammatory cells, epithelioid macrophages and fungal spores interspersed in between the inflammatory cells on Haematoxylin and Eosin stain. Grocott–Gomori's (or Gömöri) methenamine silver stain revealed diffuse positivity for fungal infection (Figure 3(A, B)). Ziehl–Neelsen stain was found to be negative for Acid fast bacilli. However, bacterial and fungal cultures including fungal PCR were negative, and it was not possible to determine the fungus species based on histopathology alone.

In view of the histopathological findings, infectious disease consult was sought and she was started on course of antifungal treatment- intravenous amphotericin B for 6 weeks followed by oral fluconazole for 6 months. With

surgery and medical treatment, her neurology continued to improve and she was able to ambulate independently, with a modified Rankin and Nurick scale of 3 by the third month postoperatively. Follow-up MRI revealed adequately decompressed spinal cord (Figure 3C). Dynamic X-rays revealed graft subsidence. Nevertheless, there was evidence of fusion with no subluxation or mobile segment, hence rigid collar was removed by then (Figure (3D, E). There were no new complications from surgery or medical treatment.

DISCUSSION

We intend to share this case because it is both a rare unsuspecting condition to find the cause of patient condition to be fungal infection. We are also highlighting the management aspect where we were forced to settle for anterior construct only although we had planned an anterior and posterior fixation. This is because in the senior author's experience, two-level corpectomy would need posterior augmentation to produce a firm construct and avoidance of graft subsidence. In this case, we are showing circumstances where patient condition and the autonomy of patient decision dominated over our surgical planning of front-back fixation. Follow up has resulted in mild graft subsidence, which has remained stable both radiologically and clinically. The patient has improved from bedbound quadriparesis to ambulance with a Nurick Grade 3. We also emphasise the importance of requesting for histopathology on top of cultures, which brought to light the diagnosis of this condition.

In this case, our provisional diagnosis was malignancy or tuberculosis. The fungal positivity was unexpected. Nevertheless, it was not possible to determine the fungus species based on histopathology alone. There was also a question of possible contamination, however with the diffuse positivity Grocott–Gomori's stain, the possibility was ruled out. Challenges of conventional culture tests in diagnosing fungal infections include the low sensitivity, long turnaround time, laborious process and failure of many cryptic fungal species to be isolated and grown on common fungal culture media.[5] Despite advances in molecular-based diagnostic methods, it has limitations if the volume of fungal DNA is low in relation to proportion of human DNA, test amplification control and suboptimal analytical sensitivity of PCR, which can be strain dependent.[6] In our case, another factor was the bone biopsy sample was sent for PCR analysis 1 week postoperatively, which could lead to sample degradation and hence false negativity.

We also believe her chronic steroid usage to treat her symptomatic anaemia secondary to amyloidosis could have predisposed her to cervical fungal osteomyelitis.

This patient presented with progressive neurological deficit, which required surgical decompression and stabilisation. Ideally, this would need a two-level corpectomy and posterior fixation. Although the C4 vertebral body is seemingly normal on the CT scan, it appeared to show hypointensity on T1WI MRI and intraoperatively, appeared to be diseased with the presence of greyish lesion. Prolonged steroids, age and poor nutrition could be contributing factors to the poor bone quality of C3 and C6 vertebrae. Posterior C3–C6 instrumentation was initially planned in the same setting to augment the anterior construct. However, the second stage surgery was abandoned due to intraoperative hemodynamic instability and non-STEMI. Our main concern at that point was possible graft subsidence and instability on follow-up. However, she continued to improve neurologically with the rigid cervical collar and follow-up imagings revealed evidence of fusion with adequate decompression. Hence, after long discussion with family and patient, we decided to treat her conservatively.

From our literature review, there are so far no cases of patients treated for amyloidosis who later presented with fungal vertebral osteomyelitis requiring decompression and stabilisation. Hence, the rarity of this condition adds to the value of reporting this case.

CONCLUSION

Fungal culture should indeed be added to the array of investigations in elderly, immunocompromised and those with systemic corticosteroid therapy. Ideally, posterior fixation is needed in cases of two or more levels of corpectomy. When medical condition prohibits, prolonged cervical collar is a viable alternative with regular surveillance to ensure bone fusion.

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CASE REPORT

Dravet syndrome: A case report

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SUMMARY

We report a rare case of Dravet syndrome in a 13-year-old boy who presented due to pleomorphic multi-drug resistant seizures. He was initially treated for generalized epilepsy after repetition of several febrile seizures in the first year of life. But, due to the resistance of seizures to one antiepileptic drug, additional drugs were added over time. Generalized seizures started at the age of 8 months as febrile seizures, repeating often at each febrile episode until the age of 5 when they became pleomorphic, and cognitive and motor function decline was noted. There was no relevant family history and no consanguinity. EEG showed severe epileptic discharge in both hemispheres and brain MRI revealed cortical atrophy. Consequently, the child was referred for genetic testing for Dravet syndrome which confirmed the diagnosis of a positive mutation on the SCN1A gene.

INTRODUCTION

Dravet syndrome (DS), formerly referred to as severe myoclonic epilepsy in infancy (SMEI), is classified as an epileptic encephalopathy characterized by prolonged seizures occurring within the first year of life. These seizures frequently manifest in conjunction with fever or illness and are often initially misidentified as febrile seizures. The accurate diagnosis of DS and subsequent follow-up care are usually postponed. At the onset, the electroencephalogram (EEG) appears normal, and neuroimaging does not indicate any structural abnormalities. Although early developmental milestones are typically met, signs of regression may emerge during the second year of life, often accompanied by convulsive status epilepticus, alternating hemiconvulsions, and myoclonic seizures. Genetic testing, which is now accessible, can confirm the diagnosis by identifying mutations in the SCN1A gene. Timely recognition and diagnosis of DS, along with the implementation of suitable anticonvulsants and a comprehensive treatment plan, may help alleviate the frequency of seizures and enhance long-term developmental outcomes.1 We report a case of a 13-year-old boy who presented with drug-resistant seizures and deteriorated neurological, cognitive, and behavioural status.

CASE PRESENTATION

A 13-year-old Albanian boy was referred to the Department of Neurology at the University Clinical Centre of Kosovo due to pleomorphic drug-resistant seizures, cognitive and motor function decline. Prenatal and postnatal history did not include any pathology. He started to walk at 18 months and say his first words between 12 and 15 months. His growth and development were going well at the beginning. He was diagnosed with epilepsy in the first year of life.

He had a febrile seizure at the age of 8 months old, during a viral gastroenteritis associated with high fever. At 13 months, he had the second febrile generalized seizure, as part of a viral infection and was treated accordingly. Eight months later, he had the third febrile seizure and was referred to the neurologist. At 15 months, due to a recurrence of seizures, he was prescribed an antiepileptic drug (AED), valproic acid, which he tolerated well. Six months later, he got a generalized seizure again. Since seizures persisted during febrile episodes, the second drug, clonazepam, was added. However, seizures continued during febrile episodes, despite compliance with therapy. Seizures were generalized and mostly occurred while the child was awake. At the age of 5 years, seizures occurred more frequently, almost on a monthly basis, and were no more febrile. They occurred during sleep too, and also in circumstances of sleep deprivation. The nature of the seizures varied too, from generalized tonic-clonic, alternating hemiconvulsions, myoclonic, and status epilepticus. Developmental delays started to appear. Different combinations of therapy were administered during these years, apart from the initial antiepileptic drugs, including phenobarbitone, levetiracetam, lamotrigine, phenytoin, rufinamid, synacthen, but with no full control over seizures.

At the age of 5, a decline in motor skills was noted, deteriorating from 7 to 13 years, with the child losing the ability to run, do sports, or any other moderate physical activity. Speech was also impaired, and occasionally ataxia was present. Cognitive decline was noted, including behavioural and psychological difficulties. Therefore, he dropped out of school, affecting his social life, too. When the recent general decline was noted, he was referred for genetic testing, and mutation of SCN1A gene was detected. As a result, stiripentol was added gradually, while other drugs were discontinued. Parental testing was recommended, as well as genetic counselling. Due to social, cognitive and behavioural status, the psychologist was involved in the care for an initial assessment and provision of professional service regularly. Electroencephalogram was performed regularly over the years and brain MRI, too. The next step for his further management includes vagal nerve stimulation.

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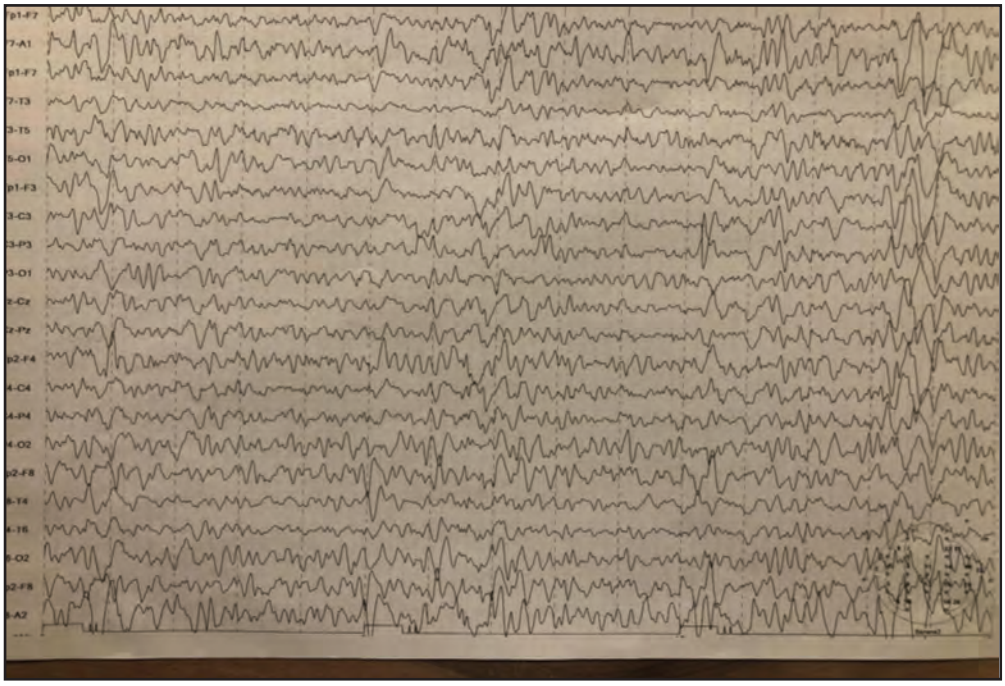

Fig. 1: EEG showing severe epileptic paroxysm activity in both hemispheres

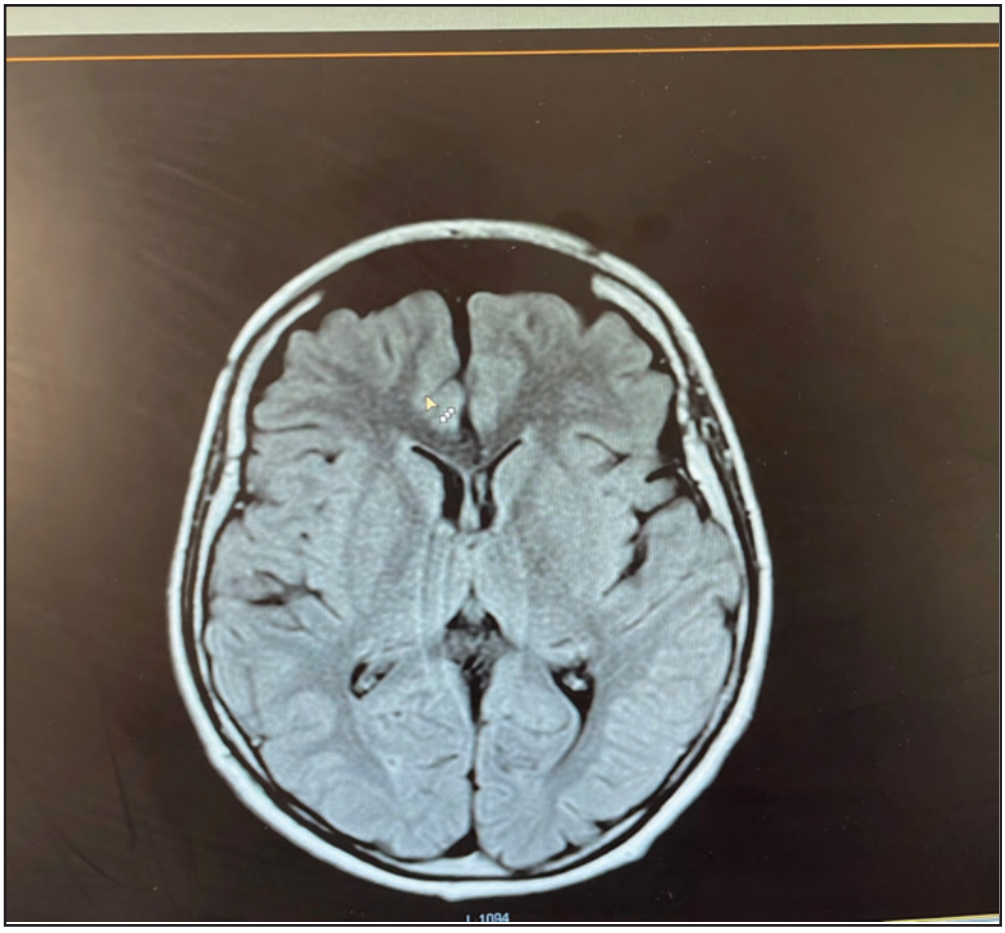

Fig. 2: Brain MRI showing cortical atrophy

DISCUSSION

DS evolves with age and after seizure onset during infancy, neurodevelopmental delays progress to severe neurological disability.[1] Patients develop an unsteady gait and general motor impairment, language delay, and behavioural disturbances such as attention-deficit/hyperactivity, autism traits, aggressiveness, irritability, and other social difficulties.[1,2] Although optimal treatment of seizures may improve outcomes, these neurodevelopment delays result from both, the genetic variant and the epilepsy.[2] These impairments cause poor quality of life and impact the long-term course.[3] First line treatments include valproate, clobazam, stiripentol, topiramate, and bromide whereas cannabidiol and fenfluramine were shown to be effective and become standard second-line drugs in Dravet syndrome.[4] Conventional antiepileptic drugs are usually insufficient for most patients as DS is highly drug-resistant and seizure freedom is rare. Stiripentol, cannabidiol, and fenfliramine have shown reductions in seizure frequency and are well tolerated.[5] Timing of introduction of these "add-on" treatments is subject to availability in different countries, patient features, and health professional's decision.6 Later therapeutic options include other ASM, ketogenic diet, and vagus nerve stimulation.[3] In any case, early diagnosis is important to avoid medications that exacerbate seizures, such as carbamazepine, oxcarbazepine, vigabatrine, lamotrigine, phenytoin.[7] Genetic testing should be conducted as early as possible in a previously healthy child presenting with refractary seizures, initially during febrile episodes, and neurodevelopmental decline over time.[8] It is important to emphasize that not all treatments, in particular the new ones, are available in all of the countries making it even more challenging optimal management of Dravet syndrome in such circumstances.[5] EEG are initially normal but after 2 years they reveal generalized spike-wave and polyspike activity with multifocal discharge, while imaging in normal or nonspecific, such as atrophy.[7]

In our case, the clinical manifestations were typical with generalized tonic clonic seizures in the first years of life, triggered by febrile episodes due to common childhood infections. Febrile seizures continued during the first two years despite antiepileptic drugs. Later on, additional seizure types appeared including alternating hemiconvulsiones, myoclonic, and status epilepticus. Seizures were highly resistant to multi-drug combinations. Between the age of 5 and 7 years, general deterioration was noted progressing to general neurological and cognitive decline over the years. EEG of our patient comprise severe epileptic discharge while brain MRI revealed nonspecific findings, such as cortical atrophy. These changes are in line with those described in the literature and provide a solid basis for considering Dravet syndrome in differential diagnosis and undertaking genetic testing for the same. This could lead to early diagnosis and targeted better management of seizures, as well as other comorbidities occurring during the course of the disease. However, it is important to mention that not all the treatment options are available in all the countries, as well as diagnostic possibilities for that matter, such as genetic testing, which poses a burden on the health professionals, as well as the families themselves. Millions of patients with suspected neurogenetic disorders around the world have no access to genetic testing.[7] Apart from that, multi-disciplinary approach to providing care for patients with Dravet syndrome is as equally important. Severe behavioural problems, which are common in patients with Dravet syndrome, should receive specific professional attention during clinical management.[9]

In our case, the clinical status of the patient worsened over time as described in the literature and he is now limited to basic motor functioning and significant general decline. As such, his social life has been highly affected too, by dropping out of school, as well as the life of his parents as the main caregivers, and the whole family in general. As suggested, one of the steps to help families of patients with Dravet syndrome, apart from the right diagnosis and appropriate treatment, is to address burden of the disease on the family and provide all the possible assistance to reduce that burden.[10]

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DECLARATION

The authors declare no conflict of interest.

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CASE REPORT

Complicated appendicitis manifesting as bladder tumour in a child: A case report and literature review

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SUMMARY

Cases of complicated appendicitis have a spectrum of different clinical presentation, the array of which vary greatly depending on adjacent structures the inflamed appendix is in contact with. Urological manifestations are not uncommon. A wide array of symptoms; from urinary retention, obstructive uropathy with hydronephrosis, cystitis, appendicovesical fistula, perinephric abscess and even formation of inflammatory mass with contiguous structures bring an added risk of misdiagnosis should the physicians not be sufficiently diligent. We herein report a case of an eight-year-old girl who underwent bladder dome tumour laparotomy, with rhabdomyosarcoma being the suspected cause. Intra-operatively, the bladder dome tumour identified with the tip of the appendix. The omentum was adhering densely to the tip of the appendix with the fused structure forming a mass-like lesion. An en bloc excision of the bladder dome together with the appendix was done. A postoperative pathological examination found no evidence of malignancy and a diagnosis of chronic xanthogranulomatous inflammation sequela of perforated appendicitis was rendered. A later literature review of similar cases with bladder tumour like appearance suggests initial non-operative management with interval appendicectomy have lower complication rates.

INTRODUCTION

The appendix is often found in intimate proximity to the bladder. Appendiceal pathologies thus on frequent occasions present with urinary symptoms which maybe apparent singularly or in any combination of; urinary retention, obstructive uropathy with hydronephrosis, cystitis, appendicovesical fistula, perinephric abscess and formation of inflammatory mass with contiguous structures.[1-7] These urological manifestations quite often confound the examiner / investigator clouding radiological examinations and rendering results, inconclusive. Only subsequent laparoscopic examination and/or exploratory surgery can in the end provide for a confident and definitive diagnosis. We herein document in our report, an exceptionally rare case of appendicular phlegmon masquerading as bladder tumour in a child. It is a new complicated appendicitis case which we would like to document and share with fellow medical practitioners in the public domain.

A literature review of documented cases of complicated appendicitis in combination with radiological appearances consistent with bladder tumour served as a preamble to the writing of this report. Pertinent articles were collected and compiled. Data were sorted with respect to relevant parameters namely; gender, age, presentation duration, intraoperative finding, treatment given and histopathological examination observations were arranged in Table I.

CASE PRESENTATION

An eight-year-old girl with no known comorbidities, and no past surgical history was admitted on suspicion of having acute appendicitis. She presented with lower abdominal pain, dysuria and low grade fever for a duration of 2 weeks prior. Clinically a mass was palpable at the suprapubic region and ultrasound of the abdomen revealed a lobulated heterogeneous pelvic mass at the superior aspect of the bladder dome measuring approximately 5.0 x 6.4 x 4.6cm (AP x W x CC) as shown in Figure 1(a). Minimal vascularity was observed within. There was also focal irregular thickening of the adjacent urinary bladder wall. The appendix was obscured by overlying bowel gas. As such, proper visual examination by ultrasound was not possible. An abdominal computerized tomography (CT) revealed a well-defined, lobulated, heterogeneously enhancing solid lesion with internal hypodensities seen arising from the dome of the bladder as shown in Figure 1(b). It measured approximately 5.0 x 5.5 x 4.5 (AP x W x CC). No internal calcifications or fat density was identified. The appendix could not be clearly delineated. Laboratory biomarkers were non-specific. C-reactive protein (CRP) was raised (69.23mg/L), however white blood cell count was normal (7.5 x 10^9/L). Urine biochemistry showed ketone 1+ and protein 2+. Consequently, a provisional diagnosis of urinary bladder malignancy (likely rhabdomyosarcoma) was rendered. It was decided that a primary excision of what appears to be a tumour to be made intraoperatively. The medical team reasoned that a preoperative cystoscopic biopsy would have subjected the child to general anaesthesia twice in rapid succession and was judged to be unnecessary considering its functional limitations when used to obtain biopsy sample from muscular layer. The bladder dome tumour was identified with the tip of the appendix and the omentum

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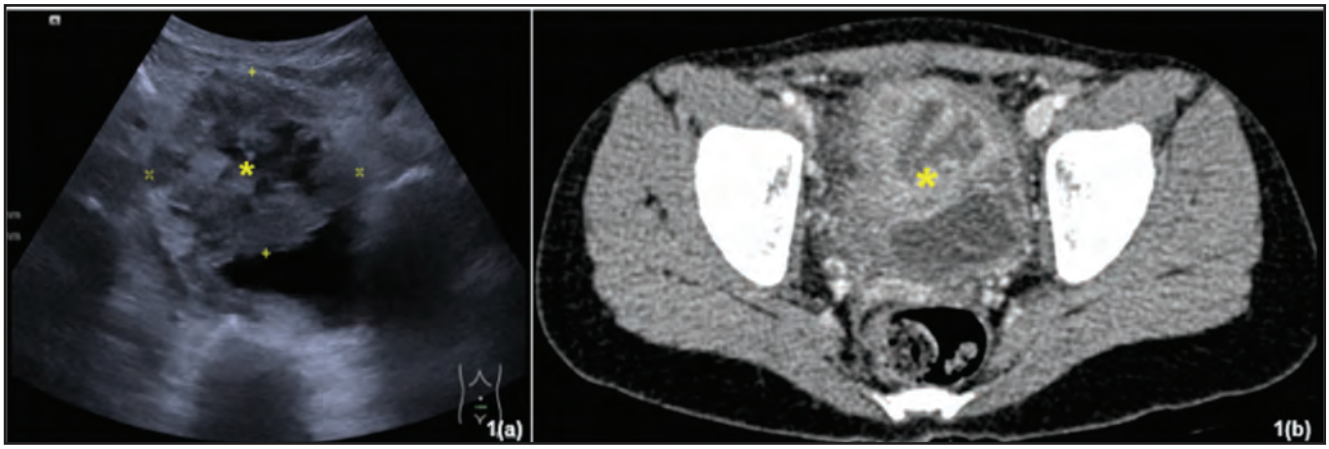

Fig. 1: Preoperative abdominal ultrasonography showing a pelvic mass at the superior aspect of the bladder dome (a) and the solid lesion was confirmed on the contrast enhanced computerized tomography of the abdomen (b)

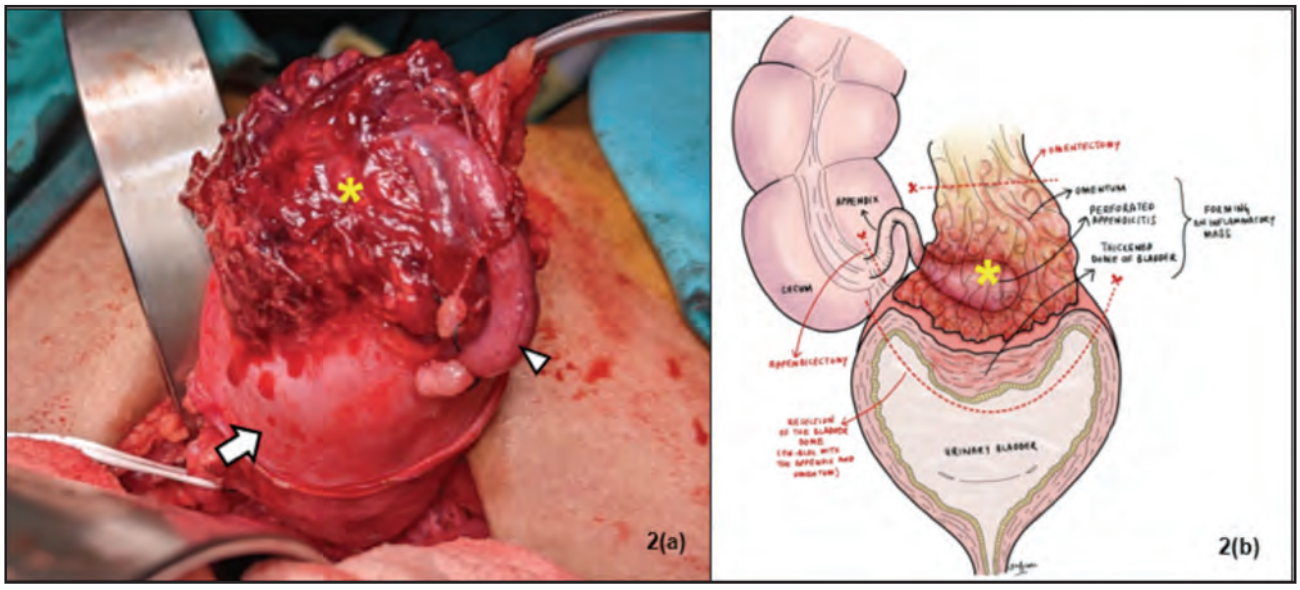

Fig. 2: Intraoperative photo (a) and the illustration (b) demonstrate the mass seen at the bladder dome (asterisk) with tip of appendix adhered within it (arrow head shows the appendiceal body and arrow is pointing to the bladder)

appeared to adhere to it forming a mass-like lesion as shown in Figure 2(a) and Figure 2(b). Otherwise, both ovaries appeared normal. Subsequently, an en bloc excision of the bladder tumour together with the appendix was performed. This was done to better facilitate histopathological examination as opposed to separating the mass from the bladder. Opting to perform the latter would have resulted in a much-reduced degree of confidence in the resulting histopathological interpretation. The bladder dome was excised and primary repaired in two layers. Postoperative recovery was uneventful. Oral feeding was initiated 1 day post-surgery and the patient discharged 1 week post operatively.

Histopathological examination revealed near total effacement and transmural large collections of foamy macrophages and histiocytes with abundant foamy to granular eosinophilic cytoplasm admixed with variable amounts of lymphocytes, plasma cells, eosinophils, and neutrophils representing xanthogranulomatous inflammation as shown in Figure 3(a), Figure 3(b) and Figure 3(c). There was no evidence of malignancy. The overlying bladder mucosa at the resection margin was lined by a benign urothelial epithelium. Focal surface erosion and subepithelial vascular congestion are observed. The adhered part of the appendix shows focal mucosal ulceration, perforation of the muscularis propria, and subjacent transmural collections of xanthogranulomatous inflammation as described above as shown in Figure 3(d). A pathological diagnosis of chronic xanthogranulomatous inflammation, a possible sequelae of perforated appendicitis was rendered.

Table I: A summary of available literature on bladder tumour as a complication of appendicitis

Author (year)	Age / Gender	Presentation	Duration of presentation	Investigation	Appendicitis Suspected	Intraoperative finding	Treatment	Histopathological examination
Our case (2023)	8 / Female	Abdominal pain, fever & dysuria	2 weeks	1) USG: lobulated heterogenous pelvic mass in continuity with the urinary bladder dome, possibly infected urachal cyst 2) CT: urinary bladder malignancy (rhabdomyosarcoma)	No	Bladder tumour arising from the dome of the bladder Tip of the appendix & omentum adhered to the tumour.	Excision of bladder tumour and appendicectomy	Operative specimen: Chronic xanthogranulomatous inflammation as sequelae of perforated appendicitis
Johal et al.[14] (2005)	27 / Female	Intermittent right iliac fossa pain, dysuria, anorexia & weight loss	5 months	1) USG: suggestive a bladder tumour. 2) Cystoscopy: erythematous urothelium with solid mass bulging into the bladder posteriorly 3) CT: mass from the right superior aspect of the bladder	No	Diagnostic laparoscopy: appendiceal phlegmon adherent to the bladder and omentum tethered in the pouch of Douglas	Systemic antimicrobial treatment and a repeat CT scan at 6 months revealed complete resolution of the phlegmon. No surgical intervention planned	Both cystoscopic biopsy and CT biopsy showed inflammation with no malignancy
Lombay et al.[15] (2003)	12 / Male	Gross haematuria & right lower quadrant abdominal pain	4 weeks	1) USG: bladder wall thickening & soft-tissue mass with central calcification 2) IVU: normal pelvicalyceal systems & ureters 3) CT: extravesical mass with central calcification	Yes	Inflammed small-bowel mass involving the bladder wall together with a perforated appendix	Appendicectomy	
Palnaes et al.16 (1991)	35 / Male	Recurrent gross haematuria & frequency	2 years	1) IVU: calcified density adjacent to the right side of the bladder 2) CT: a process located close to the bladder wall but without relation to the urinary tract 3) Cystoscopy: friable polypoid bleeding tumour at the right side on the bladder wall	No	4 X 4 cm large tumour between the cecum and the terminal ileum adherent to the bladder. Dissection revealed an abscess with a 2-cm long appendix stump and a 3 X 2 cm large fecalith	Appendicectomy	1) Cystoscopic biopsy: chronic inflammation and glandular metaplasia with dilated cystic glands of colonic type without signs of malignancy 2) Operative specimen: Chronic inflammatory process in the appendix mucosa without signs of malignancy
Richie et al.[17] (1975) (case 1)	64 / Female	Bilateral lower abdominal pain, watery diarrhea, emesis, dysuria, foul-smelling urine & fever	24 days	1) IVU: medial deviation of the right ureter 2) Cystoscopy: marked edema of the trigone and bladder base 3) Sigmoidoscopy: normal 4) Barium enema: appendicovesical fistula	No	Inflammend appendix & a probe-patent fistulous tract containing an olive pit was found between the appendix and the bladder. Marked edema and cystitis were present in the bladder.	Appendicectomy & partial cystectomy	1) Cystoscopic biopsy: atypical transitional cell hyperplasia with severe acute inflammation 2) Endometrial biopsy: negative for malignancy
Richie et al.[17] (1975) (case 2)	66 / Male	Midabdominal pain, fever, emesis & gross haematuria	36 hours	IVU: delayed emptying from the right kidney and a possible bladder tumour	No	Acutely inflammed appendix	Appendicectomy	Operative specimen: Periappendiceal perforation
Richie et al.[17] (1975) (case 3)	34 / Female	Crampy lower abdominal pain, fever, purulent greenish per vaginal discharge	10 days	1) IVU: right ureteral obstruction at the pelvic brim 2) Cystoscopy: trigonitis	No	Perforated pelvic appendix with abscess and drainage through the vaginal cuff	Appendicectomy, cystostomy & right ureterolysis	Vaginal cuff biopsy: negative

USG: Ultrasonography, CT: Computed Tomography scan, IVU: Intravenous Urography

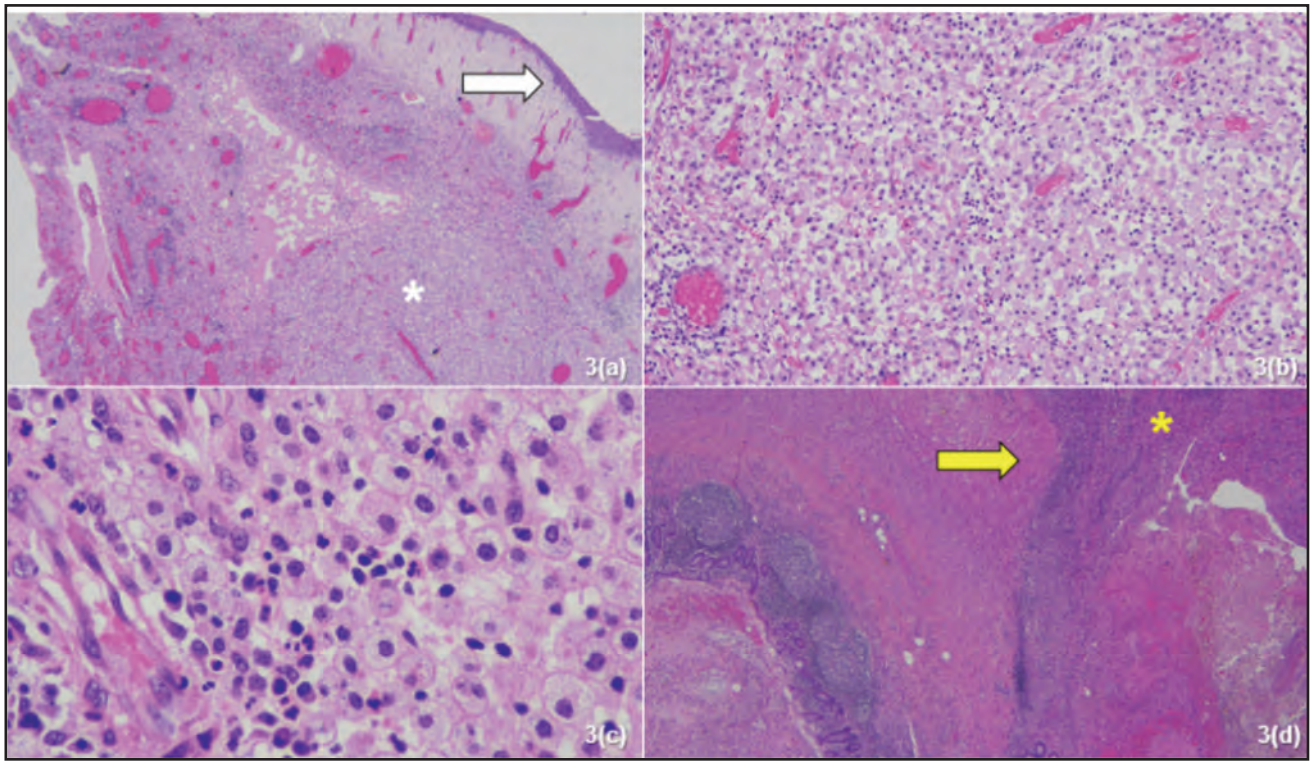

Fig. 3: Histopathological examination of the bladder tumour showed a large collections of foamy macrophages and histiocytes with abundant foamy to granular eosinophilic cytoplasm admixed with variable amounts of lymphocytes, plasma cells, eosinophils, and neutrophils representing the xanthogranulomatous inflammation (white asterisk), and the overlying bladder mucosa at the resection margin is lined by a benign urothelial epithelium. Subepithelial vascular congestion is observed (white arrow) (a) and its magnification at 10x (b) and 40x (c). The adhered part of the appendix shows focal mucosal ulceration, perforation of the muscularis propria (yellow arrow), and subjacent transmural collections of xanthogranulomatous inflammation (yellow asterisk)

DISCUSSION

Complicated appendicitis has a wide range of different clinical manifestations depending on the location of the inflamed appendix in relation to the surrounding structures. Due to close proximity, urological manifestations often accompany appendicitis. These may lead to misdiagnosis and delay in appropriate treatment. Several urological manifestations have previously been reported such as hydronephrosis resulting from compression of the ureter by an undiagnosed appendiceal abscess and can be unilateral or bilateral.[2,3] Appendicitis may also present with perinephric abscess when the appendix is in the retrocaecal position. If an enlarged or ruptured appendix accompanies the perinephric abscess, appendicectomy and abscess drainage is required.[7]

Diana et al. concluded that inflamed or ruptured appendix can affect bladder function, and even more likely when the appendix is located in the pelvic position.[8] Reported complications include cystitis, appendicovesical fistula, irritative bladder, and urinary tract infections. Both Brewster et al and Lemieux et al reported cystitis as symptoms of appendicitis.[4,5] Appendicovesical fistula was reported by Rainuli et al although it is a rare complication of appendicitis typically accompanied by coprosuria, pneumaturia, and recurrent urinary tract infections.[6] In several cases, appendicular abscesses may present as bladder tumours such as in this case. It is hence important to consider differential diagnosis upon identification of bladder tumours either via cystoscopy or CT scan.

Concerning bladder tumour, the most common 'true' bladder tumour in paediatric age group is rhabdomyosarcoma. Its morphology tends to be botryoid and is commonly located at the trigone or bladder neck. Tissue diagnosis (endoscopic or percutaneous) may be necessary when complete excision is not feasible or would result in significant morbidity, such as radical cystoprostatectomy.

Bladder tumour in children is not similar in adults where mucosal biopsy from cystoscopy is feasible without the need for general anaesthesia. Rhabdomyosarcoma require deeper mucosal sampling thus in a well localized tumour as in this case, we think primary resection is feasible for both therapeutic and diagnostic purposes, while minimizing number of general anaesthesia and avoiding treatment delay.

For this case, we were considering rhabdomyosarcoma as our first differential diagnosis despite the unusual location in this case i.e. bladder dome rather than the trigone or bladder neck which is most prevalent. The tumour was resected for

both diagnostic and therapeutic measures as it was feasible with assumptions that other medical therapies would ensue thereafter if deemed necessary. Intraoperatively, we suspected complicated appendicitis with appendicular mass but we could not dismiss the relevance of significant thickened bladder wall from preoperative imaging. Hence, the decision for partial cystectomy together with appendicectomy.

St. Peter et al. published a recent review of operative management of appendicitis specifically those categorized as complicated.[9] The authors described a recent meta-analysis of complicated appendicitis patients published in 2010 encompassing 847 patients who underwent interval appendicectomy and 725 who underwent early appendicectomy. Those who make up the interval appendicectomy group were found to experience less complications overall. Their surgical wounds were also less likely to become infected. It was also noted that likelihood of requiring reoperation was also lower.

When the same sensitivity analysis was deliberated exclusively for pediatric patients, the interval appendicectomy group also had an overall much lower complication rate.[9,10] On the basis of this data, one can conclude that initial non-operative management with interval appendicectomy is well tolerated in selected patients, specifically those who present with an abscess or well-formed phlegmon. Early suspicion of a complicated appendicitis could see initial non-operative management with antibiotics prescribe followed by interval appendicectomy. This should permit avoidance of unnecessary bladder resection.

Table I summarizes the six (6) reported cases of bladder tumour mimicry in association with appendicitis we found in our literature search. We have included our own case in the same table thus making it seven (7) cases in total. Of the six, only one case was reported in children before this to our knowledge. This case is the youngest of age in the series.

In every one of the seven (7) cases, definitive diagnosis was only rendered intraoperatively. Out of all seven (7), only in one case was appendicitis suspected i.e., the one reported by Lombay et al.[11] Based on the aforementioned observation; the likelihood of an accurate preoperative diagnosis is at a low 14%.

CONCLUSION

Rhabdomyosarcoma is the commonest paediatric soft tissue sarcoma and most commonly sited in the trigone or bladder neck. A lesson reinforced is that unusually located bladder tumour should raise one's suspicions of other aetiology such as an inflammatory mass from a complicated appendicitis. A second lesson is that with ever improving quality of imaging, we still need to balance this tool with proper clinical assessment.

Complicated appendicitis patients with an abscess or well-formed phlegmon who receive initial non-operative management with interval appendectomy have lower complication rate compared to early appendicectomy.

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DECLARATION

The authors declare no actual or potential conflict of interest in relation to this article. The patient's legal guardian formally consented to publication of this case report on May 25, 2023 by putting signature to an informed consent form.

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CASE REPORT

Superior mesentric artery syndrome in pediatric population: An ardous manifestation of duodenitis

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SUMMARY

Superior mesenteric artery (SMA) syndrome is a rare duodenal 'sandwich' due to narrow SMA-aorta angle, particularly observed in the pediatric age group. This compression can lead to acute or chronic abdominal pain. In this case report, a 11 years old active boy came with chronic upper gastrointestinal symptoms. Initially treated with anti-reflux medication, the patient's condition worsened with the emergence of red-flag symptoms. The diagnosis was established after computerized tomography (CT) scan was done that revealed acute angulation of SMA and aorta. This case report stresses the challenges in diagnosing the disease due to its' vague symptoms manifestation and the importance of early detection for effective management.

INTRODUCTION

Superior mesenteric artery (SMA) syndrome is a rare condition where the third portion of the duodenum is compressed by the narrow angle between the SMA and the aorta. Several factors contribute to the acute angulation between the SMA and the aorta, as shown in Table I. The prevalence in pediatric patients is not well-known, but studies suggest it is rare, ranging from 0.013 to 0.30 percent in the general population. SMA Syndrome was first described by Rokitansky 1 in 1861 diagnosed by a series of upper gastrointestinal (GI) barium studies. Subsequently, in 1984, Gustafsson describe the hypotonic duodenography combined with simultaneous SMA arteriography a more accurate investigation superior to barium study. Diagnosis is usually challenging and requires a high index of suspicion due to the nonspecific presentations and its rarity, while computerised tomography (CT) is considered a gold standard for diagnosis.[1]

We describe the rare case of SMA syndrome in pediatric age group manifested as chronic duodenitis.

CASE PRESENTATION

A healthy 11-year-old boy with recurrent epigastric and umbilical pain, nausea, aggravated by food intake and constipation (Bristol Stool Form Scale 1). Tolerating orally and active. Clinical examination revealed soft, non-tender abdomen and palpable fecaloma at left iliac fossa. He was initially treated with proton pump inhibitors and laxative, with a 2kg weight drop at two weeks follow-up. He was able to tolerate solid and liquid in moderate amount. There was subsequent worsening symptoms included non-bilious vomiting, intolerance to oral intake, and weight fluctuation (27kg to 28kg). BMI: 11.7kg/m^2. Therefore, he was admitted for close observation due to mild tenderness in epigastric and umbilical regions. No mass felt on clinical examination.

His laboratory investigation was normal with an albumin of 40g/L. Esophagogastroduodenoscopy (OGDS) revealed mild gastritis with extensive duodenitis, presence of bile reflux. Maximum anti reflux medication was initiated but no improvement was noted. CT angiogram showed no dilatation of stomach and proximal duodenum. Aortomesenteric angle was 18.3 degrees with aaortomesenteric distance of 5.3mm, suggestive of Superior Mesenteric Artery (SMA) Syndrome. Nasojejunal tube was inserted with guided by OGDS for enteral feeding in hoping weight gaining. After six weeks of nasojejunal tube feeding, there has been no significant weight gain, necessitating the addition of parenteral feeding. Furthermore, due to the previous tube being noted as malposition, a gastrojejunostomy tube was inserted. The child exhibited good tolerance to enteral feeding and a successful weight gain has been attained through a blend of enteral and parenteral nutrition.

DISCUSSION

This case report scrutinized the diagnostic challenge of a pediatric patient suffering from chronic abdominal pain attributed to SMA syndrome. SMA syndrome is characterised by "sandwich" of the transverse part of the duodenum as it traverses the space between the SMA and abdominal aorta due to reduced aorta-mesenteric angle. The name "sandwich" refers to the anatomical situation where the duodenum becomes trapped between these two structures. It is hypothesized that loss of the retroperitoneal fat pad and connective tissue narrows the aortomesenteric angle, creating a mechanical obstruction of the duodenum.

In general population, predisposing factors for acute angulation between the SMA and the aorta as shown in Table I. In pediatric age group, SMA syndrome is frequently associated with low BMI, weight loss, rapid linear growth

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Table I: Predisposing factors in acute angulation in SMA syndrome

Intrinsic cause	Extrinsic cause
i. Physiology of severe weight loss causing retroperitoneal fat depletion. ii. Anatomical variant such as a high insertion of the Treitz ligament. iii. Surgical alterations cause mesentric tension and compression. (i.e spine surgery or ileoanal pouch anastomosis)	i. External compression by belts or body spica casts ii. Mechanical force from intra-abdominal tumor microenviroment push against the SMA, causing the acute angle.

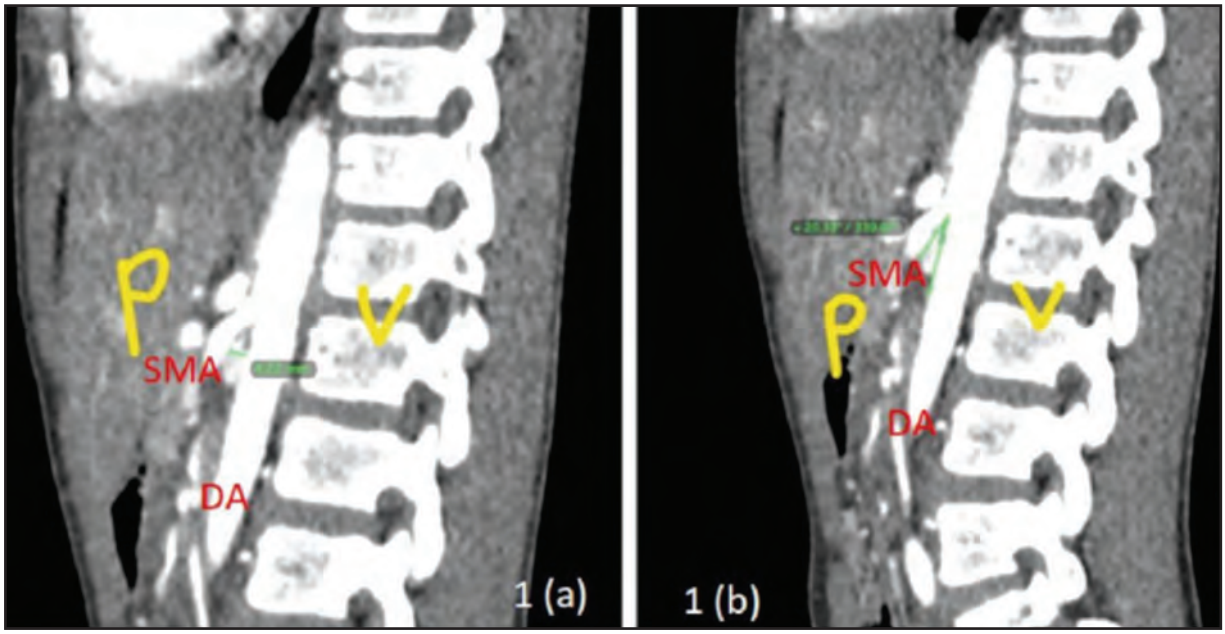

Fig. 1: Sagittal view of CT angiogram. (a) shows aortomesenteric distance of 4.22mm. (b) shows aortomesenteric angle of 20.33 degree. P = Peritoneum; V = Vertebrae; SMA: Superior Mesentric Artery; DA = Descending Aorta

spurt without weight gain are well-known risk factors of SMA syndrome. Retrospective studies conducted in western and eastern part of the world show similar figures of risk factors that develop SMA syndrome in pediatric age groups. The most common risk factor related to the development of SMA syndrome is low BMI and weight loss. Both studies also had a similar opinion that weight loss or low BMI is not a prerequisite for the development of SMA syndrome as half of study population show no recorded weight loss.[1-2] Despite having a low BMI, the patient has not experienced significant weight loss due to their active lifestyle and excellent academic performance.

A study by Ozbulbul et al. developed a theory that correlated SMA angle and visceral fat.[3] The research found that BMI correlated more strongly with subcutaneous fat than with visceral fat, and that the distance between the aorta and the SMA had a stronger correlation with visceral fat area than with BMI. In early puberty, a rapid linear growth spurt without weight gain can be a contributing factor to the manifestation of SMA Syndrome in children. SMA syndrome gets aggravated alongside malnourishment which substantially reduces the retroperitoneal fatty cushion support. Shin MS et al have shown that three out of four children with SMA syndrome, who experienced growth spurts without appropriate weight gain, responded to medical treatment.[2] Rapid linear growth without weight gain can result in an elongated mesentery as well as loss of the mesenteric root fat pad, which explains why SMAS occurred in our four patients during their growth spurt.

Early puberty is a crucial stage in children's development, as boys undergo significant changes, including increased muscle mass and reduced body fat, leading to thinning of the aortomesenteric space. This strongly supports the theory of puberty-related development during middle childhood or early adolescence. This case supports previous findings that weight loss is not necessary for pediatric SMA syndrome development. The rare presentation of SMA syndrome in children without weight loss may be linked to inadequate weight gain relative to height growth, leading to decreased visceral fat and predisposition to SMA syndrome.[3-4] We postulate that, two exacerbating factors for SMA syndrome in the patient were rapid linear growth spurt without weight gain and duodenitis symptoms. SMA syndrome is typically a diagnosis of exclusion, considered after extensive evaluation. Patients may present with persistent or intermittent gastrointestinal tract obstructive symptoms, requiring a thorough examination.

Patients with SMA syndrome may experience various upper gastrointestinal (UGI) symptoms like vomiting, nausea, epigastric pain, early fullness, and postprandial discomfort. The presentation can be acute or chronic, leading to non-specific symptoms and delaying diagnosis. In a Korean study from 2003 to 2013, the duration of symptoms before diagnosis ranged from 1 to 730 days (median 68 days), and the age at diagnosis ranged from 8.5 to 16.2 years (median 11.9 years).[2] The wide range of symptom manifestation duration for SMA syndrome is likely due to its non-specific symptoms, leading to many patients receiving OGDS for common UGI symptoms. While OGDS helps differentiate UGI diseases, it cannot diagnose SMA syndrome. A study by Kim JY et al.in 2021 suggests that endoscopy to the third part of the duodenum provides clues for determining the need for SMAS evaluation.[4] The exam should note three signs: [1] vertical or oblique narrowing of the third part of the duodenum during air insufflation for at least 15 seconds, [2]

marked dilation of the first and second part of the duodenum, and [3] presence of a bile lake in the stomach. Zhang R et al. hypothesized that SMA syndrome leads to weak acid reflux, causing reflux symptoms and duodenitis due to compression of the duodenum.[5] Patients with SMA syndrome are thin, may suffer from gastroptosis and delayed gastric emptying, leading to increased intragastric pressure and bile reflux duodenitis. After months of anti-reflux medication, red-flag symptoms worsened, leading to persistent post-meal vomiting due to oral intolerance.

Evolution of radiological techniques from serial upper GI studies to non-invasive CT scan, now considered the gold standard for diagnosing SMA Syndrome. This advancement allows for earlier detection and prompt treatment initiation. Shin MS et al. studies in 2013 and 2021 showed consistent cutoff values for diagnosis in adults (SMA angle <22°-25°, SMA-aorta distance <8 mm).[5] However, no consensus exists for diagnosing children, as pediatric cases can have varying cutoff values. This study also proposes the utilization of aorto-mesenteric distance instead of the aorto-mesenteric angle, given the varying anatomy of the superior mesenteric artery (SMA) and the absence of consensus on angle measurement.[2]

The treatment of SMA Syndrome involves bowel rest, fluid maintenance, electrolyte balance, nutritional support, and rehabilitation to improve weight, reduce intestinal obstruction symptoms, and address precipitating factors. Nutritional support is the major component of conservative treatment for aortomesenteric angle compression. This can be done with enteral nutrition that includes taking frequent small meals of nutritious liquid and lying on the left side or prone after eating. Anti-reflux medicines with a prokinetic can help further alleviate symptoms. Naso-jejunal feeding is an enteral feeding to provide nutritional support, and parentral feeding is an option when enteral feedings are not tolerated.[1-2,5] Shin et al. achieved a remarkable outcome in conservative treatment of SMA syndrome, with 83.3% of patients showing weight gain after treatment.[2] Such treatment should be instituted for at least six weeks before considering surgical intervention. Successful surgical therapies have included duodenojejunostomy, gastrojejunostomy, or resection of the Ligament of Treitz or Strong's procedure.

CONCLUSION

SMA syndrome is a rare condition which presents as chronic abdominal pain in children. To properly diagnose this challenge, clinicians should look into OGDS and contrast-enhanced CT. This case study has revealed cases where growth spurts and duodenitis can serve as catalysts for the onset of SMA Syndrome, and as such, it should be taken into consideration when approached with recurring abdominal complaints. In recent times, the medical approach to treatment has made significant progress, favoring nutritional treatments over the traditional reliance on surgical methods.

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DECLARATION

The authors have no conflicts of interest to declare.

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Late-onset efavirenz neurotoxicity

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SUMMARY

Efavirenz is a commonly used antiretroviral drug in Malaysia. It is used to treat Human Immunodeficiency Virus infection alongside with two nucleoside reverse transcriptase inhibitors (NRTI). Efavirenz is well recognized to cause transient neuropsychiatric side effects early during the initiation. Recently, cases of delayed-onset neurotoxicity with similar clinical syndromes caused by efavirenz have been reported, primarily in the South African population. Here we present a case of a Malaysian lady living with HIV treated with an efavirenz-based ART who presented with late onset encephalopathy and ataxia, which improved significantly after the withdrawal of efavirenz.

INTRODUCTION

The number of people living with HIV in Malaysia was estimated to be at 81,942 in year 2022 and it has been reported that 66% of them were receiving antiretroviral therapy (ART).[1] Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that can inhibit HIV replication. It is widely used as part of the first line ART to treat HIV in Malaysia.[2] Acute and transient neuropsychiatric side effects were often reported after initiating efavirenz based treatment.[3] The common side effects include giddiness, attention deficit, headache, sleep disturbance, and depressed mood, but they are usually mild and resolve after few weeks of exposure.[3] However, lately there have been reports of patients who developed ataxia and encephalopathy which were attributed to efavirenz induced neurotoxicity. Ebrahim Variava et al. and Lyneshree Munsami et al. described cases of late onset efavirenz toxicity in South Africa which involves 20 patients and 40 patients respectively.[4-5] A case report from India also documented delayed-onset cerebellar ataxia and encephalopathy after 3 years of efavirenz therapy.[6] Despite efavirenz being widely used in Malaysia, there has been no similar report of ataxia or encephalopathy until now.[7] Here we report likely the first case of late onset efavirenz neurotoxicity in Malaysia.

CASE PRESENTATION

We encountered a 56-year-old lady with underlying type 2 diabetes mellitus on insulin and HIV positive on antiretroviral therapy (ART). She was first diagnosed with HIV in 2020 via contact tracing and was then started on an ART regimen of oral tenofovir 300mg, emtricitabine 200mg, and efavirenz 600mg daily. After 2 years of treatment, she presented with 2-month history of slurred speech and progressive body weakness requiring wheelchair for ambulation. She had poor appetite and weight loss (49 to 44kg). There was otherwise no history of fever, vomiting, cough, or visual disturbance. She was not on any other medication or supplement. On examination, she was emaciated, orientated with a full Glasgow Coma Scale (GCS) but was slow in responding and had a scanning speech. Neurological examination demonstrated reduced power symmetrically at all four limbs with a Medical Research Council (MRC) grading of 4/5. She had generalized hypotonia and hyporeflexia. Her coordination was also abnormal with truncal ataxia and dysdiadochokinesia. Otherwise, her sensations and cranial nerves examinations were normal. She had a Mini Mental State Examination (MMSE) score of 14/30 indicating moderate cognitive impairment.

Her full blood count, renal profile, and liver function test were unremarkable. Her repeated CD4 count was 549, and her HIV viral load remained suppressed. She had a normal C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), thyroxine (T4), thyroid stimulating hormone (TSH) and creatine kinase (CK) levels. Rapid plasma reagin and treponemal test were negative. She had a Hemoglobin A1c (HbA1c) of 7.2%. Her chest X-ray was also normal. Her MRI Brain showed old lacunar infarct within both frontal lobes, which was not consistent with her neurological findings. A provisional diagnosis of efavirenz induced encephalopathy was made. However, efavirenz level was not available in our centre. Other differential diagnosis included HIV associated neurocognitive disorder (HAND), HIV myelopathy, and paraneoplastic syndromes. Nonetheless, her efavirenz was withdrawn and switched to dolutegravir. She was offered for a lumbar puncture to further investigate but she declined.

She was seen back in the clinic 2 weeks later, showing overall improvement clinically with improved strength, speech, memory, and appetite. Her MRI cervical revealed cervical spondylosis with mild central canal stenosis at C5/C6 level but there was no cord compression. Her electroencephalogram (EEG) revealed mild generalized cerebral dysfunction, with bifrontal focal slowing which was suggestive of encephalopathic changes. Her vitamin B12 level was normal and folate level was low (3.5nmol/L). However, her symptoms had already improved prior to folate supplementation. Other workup including a paraneoplastic autoimmune profile was negative. As for her positive anti-nuclear antibody (ANA), she did not exhibit any clinical feature of connective tissue disease. Furthermore, her anti-dsDNA antibodies and extractable nuclear antigen (ENA) were negative. By applying the Naranjo Adverse Drug

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Table I: Naranjo Adverse Drug Reaction Probability Scale

Question	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
	Total Score : 5			
Interpretation: Definite ≥ 9 Probable 5-8 Possible 1-4 Doubtful ≤ 0				

Reaction Probability Scale, a score of 5 was obtained (Table 1), indicating a probable adverse drug reaction from efavirenz.8 At 3 months after withdrawal of efavirenz, her symptoms had totally resolved and she was able to resume her activities of daily living independently. Her neurological examination also demonstrated resolved encephalopathy, cerebellar sign and limb weakness.

DISCUSSION

We described a case of a Malaysian lady with HIV who was treated with an efavirenz based ART and presented 2 years later with encephalopathy and ataxia, which improved significantly after the withdrawal of efavirenz. These findings are consistent with the cases reported from other authors recently (Table II). In the case series from South Africa, which consist of 20 and 40 patients respectively, most of their patients presented with ataxia and encephalopathy after being on efavirenz treatment.[4-5] The degree of encephalopathy can vary from mild confusion and psychomotor retardation to coma. Some patients even had mood disturbances or psychotic symptoms prior to the onset of ataxia and encephalopathy.[9] Similar to the previous reports, our case also presented as late onset and had a subacute presentation.[4-5,9] The duration of efavirenz treatment prior to the presentation of encephalopathy or ataxia can vary from 5 months to more than 5 years.[4-5,9] All those patients had supratherapeutic plasma efavirenz level.[4-5,9] Unfortunately, we were unable to measure efavirenz level in our patient because the test is not available in our centre. Similar to our case, further investigations did not yield any other aetiology to explain the presentation, and most of the patients showed improvement after efavirenz was withdrawn. Despite that, mortality has been reported to be as high as 15% due to complications from efavirenz neurotoxicity in the South Africa cohort.[5-6]

Efavirenz has been known to cause CNS toxicity, resulting in neuropsychiatric symptoms. However, the exact mechanism of efavirenz causing neurotoxicity is still unclear and some studies suggested that the neurotoxicity is mediated by oxidative stress and mitochondrial dysfunction.[3] Based on the case series in Africa, several risk factors for late onset neurotoxicity have been suggested, including concomitant isoniazid use, low body weight, and female gender.[4-5] This association is also supported by a recent study which also found that slower metabolism of efavirenz due to mutations in CYP2B6 gene is strongly associated with late onset efavirenz neurotoxicity.[10] Efavirenz is primarily metabolised through the CYP2B6 enzymes, which contribute to more than 90% of efavirenz metabolism whereas less than 8% of efavirenz is metabolised by the CYP2A6 enzyme.[3] CYP2B6 slow metabolizer due to genetic polymorphism is associated with a higher plasma efavirenz level, and these slow metabolizer are more frequently found in the African, Hispanics and Indian populations.[3] Hence CYP2A6 enzyme became an important role to metabolise efavirenz in those with impaired CYP2B6. Isoniazid use can inhibit the CYP2A6 enzyme, which causes raised plasma efavirenz level in those with genetically slow metabolizer. Our patient did share some risk factors for late onset efavirenz neurotoxicity which is low body weight (49kg) and female gender. She did have concomitant isoniazid use for tuberculosis preventive therapy, but the last usage was one year prior to the symptom onset. We were also unable to establish if our patient has genetic mutation in the CYP2B6 gene nor ancestry link to Africa or India.

This case report highlights a significant yet underrecognized issue of late-onset efavirenz neurotoxicity, which has not been previously documented in Malaysia. As efavirenz remains a commonly used antiretroviral medication, this study underscores the importance of monitoring for delayed neurotoxic effects even after prolonged period of treatment. This report provides valuable insights that may prompt clinicians to consider efavirenz-induced neurotoxicity in their differential diagnosis for patients presenting with late-onset neurological symptoms. Furthermore, it emphasizes the need for further research into the risk factors and mechanisms behind efavirenz neurotoxicity, particularly in diverse populations.

Table II: Reported cases of Late-onset efavirenz neurotoxicity

Author, Country	Age, Sex	Weight (Kg)	Duration of efavirenz treatment	CD4 count/ HIV Viral Load (VL)	Clinical features	Efavirenz level (mg/L) *normal range 1-4	Investigations	Outcome
Variava, E. et al. 2017.[4] 20 patients. South Africa.	Age: 24-36, all female	34.1-42.6	12-66 months	Median CD4: 299, 17 patients had supressed VL	Ataxia: all patients Encephalopathy: 11 out of 20 patients	Supratherapeutic in all patients	Brain imaging : 9: normal 7:generalized atrophy, 1: cerebellar atrophy, 1: pineal cyst, 1:encephalitis CSF: 19 – normal, 1 - clotted	Improved once efavirenz withdrawn. 2 had recurrence when rechallenged. 3 died.
Lyneshree Munsami et al. 2023.[5] 40 patients. South Africa.	Mean age: 42.1 3 male, 37 female	Not available	17 patients: <12 months 17 patients: >12 months 6 patients: unknown	26 out of 40 CD4>200, 34 out of 40 VL suppressed	Ataxia: 33 patients Encephalopathy: 19 patients	Supratherapeutic in all patients (8-96)	33 Brain imaging: normal/ non-specific 34 lumbar puncture: 28: normal, 3 : non-specific abnormalities, 2: pleocytosis and elevated protein 1: treponema pallidum positive 8 out of 9 EEG: diffuse slowing	32: recovered on average 2 weeks after efavirenz was withdrawn. 1: remained severely ataxic 4: passed away
GRK Sarma et al. 2022.[6] India.	23, female	28	>24 months	CD4: 193 VL: not detected	Psychosis: 4 patients Ataxia with encephalopathy	Not available	Brain imaging: Normal CSF: normal	Improved 4 weeks after efavirenz was withdrawn
HM Cross et al. 2018.[9] 7 patients. South Africa.	Age: 36-47 All female	55-62	17-48 months	CD4: 324-462 All VL supressed	Ataxia with psychomotor slowing. 2 patients had mood and psychotic symptoms.	Supratherapeutic (>20)	Brain imaging: Normal/non-specific CSF: normal EEG: generalised (predominantly theta) slowing	Improved after a median of 14 days after efavirenz withdrawal
Our patient (Malaysia)	56, female	49	24 months	CD4: 549 VL: supressed	Ataxia Psychomotor retardation	Not available	MRI : non-specific CSF: not done EEG: mild generalised cerebral dysfunction	Improved 2 weeks after efavirenz was withdrawn

CONCLUSION

This case report presents the first documented instance of late-onset efavirenz neurotoxicity in Malaysia, adding to the growing body of evidence highlighting this condition. Our findings emphasize the necessity for clinicians to be vigilant for late-onset neurological symptoms in patients on long-term efavirenz therapy. Early recognition and prompt discontinuation of the drug can lead to significant clinical improvement, as demonstrated in this case.

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DECLARATION

The authors declare no conflicts of interest related to this publication.

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Diagnostic challenges: Concomitant dengue fever with mycoplasma pneumonia in an adolescent

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SUMMARY

Dengue fever is a mosquito-borne viral infection that is endemic in more than 100 countries and has the highest incidence among infectious diseases in Malaysia. While the dengue virus typically causes dengue fever, bacterial and fungal co-infections are relatively rare, often complicating diagnosis. We report an unusual case of a 13-year-old boy with dengue fever, presenting with acute respiratory symptoms, later diagnosed as co-infection of Mycoplasma pneumoniae. The diagnostic challenge in this case arose due to the overlapping clinical features of dengue and viral upper respiratory tract infection (URTI), including persistent high-grade fever, cough, and headache, which initially led to a misdiagnosis of viral URTI. This delayed the performance of specific dengue diagnostics, such as NS1 antigen testing and resulted in the progression of respiratory symptoms. Resolution of the diagnostic dilemma was achieved through chest X-ray (CXR) imaging, which revealed lobar pneumonia and the subsequent confirmation of Mycoplasma pneumoniae co-infection alongside dengue through serological testing. This case highlights the importance of maintaining a high index of suspicion for co-infections in febrile patients presenting with atypical respiratory symptoms. Early and combined use of serological testing and imaging can help avoid delays in diagnosis and improve patient outcomes, particularly in dengue-endemic regions where concurrent infections may be under-recognized.

INTRODUCTION

Dengue is a mosquito-borne viral disease caused by the dengue virus (DENV), primarily transmitted by Aedes aegypti mosquitoes.[1] The disease can range from mild febrile illnesses to severe complications, particularly in cases of secondary infection. Early symptoms of dengue, such as fever and headache, often overlap with those of other viral infections, leading to potential diagnostic delays or misdiagnoses.[2] Although bacterial co-infections in dengue are relatively uncommon, they can significantly complicate the clinical course and delay appropriate treatment. Timely recognition and management of such co-infections are crucial, as antibiotics may improve outcomes and prevent further complications.

Bacterial co-infections, while underreported, pose notable diagnostic challenges. Cases involving Mycoplasma pneumoniae have illustrated these difficulties, as symptoms of *Mycoplasma pneumoniae* infection can overlap with those of dengue.[3] For example, an 8-year-old girl in Thailand with dual infections of Mycoplasma pneumoniae and dengue hemorrhagic fever exhibited liver failure, demonstrating significant diagnostic challenges in pediatric cases. Another study reported a tourist from Thailand who developed dengue hemorrhagic fever and Mycoplasma pneumoniae pneumonia, further complicated by clostridial colitis.[4-5] These cases highlight the complexity of diagnosing concurrent infections and underscore the importance of integrating clinical, laboratory, and radiological assessments.

This report presents a rare case of a teenager whose initial presentation of respiratory symptoms and viral-like features led to a delayed diagnosis of dengue fever. The subsequent identification of a Mycoplasma pneumoniae co-infection further complicated the clinical picture and delayed appropriate treatment. This case underscores the need for heightened awareness and comprehensive diagnostic approaches in managing dengue, particularly in the presence of co-infections.

CASE PRESENTATION

A 13-year-old boy presented to our primary care clinic on his third day of illness with persistent fever, cough, and headache consistent with a viral infection. He has a recent travel history to Taiping, Bentong, and Thailand; however, he has no history of visiting recreational parks or jungle trekking. Despite the initial clinical presentation supporting the diagnosis of viral URTI, there is a concern about the decreasing trend of low normal platelet counts. The decision to repeat the full blood count was carried out till day 5 of the illness, in which the platelet count still showed within low normal range values. Even though the suspicion of dengue fever grew due to the absence of typical symptoms such as rash or severe thrombocytopaenia, dengue serology was still not prioritised. His vital signs remained stable during his follow-up, and systemic examinations were unremarkable. By the sixth day of illness, with the persistent fever, headache and further reduction of platelet counts, dengue serology (IgM) was finally conducted, revealing evidence of dengue infection. Interestingly, respiratory symptoms remained subtle throughout this period until the eighth day of illness, when he presented to the emergency department (ED) with worsening shortness of breath in two days. At a presentation to the ED, he appeared to have tachypnea with a respiratory rate of 20 per minute and an oxygen saturation rate of 95% in room air. Respiratory examination revealed crepitation

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Table I: Laboratory findings in the case of Mycoplasma Pneumonia and Dengue Fever

Day of illness	Day 3	Day 4	Day 6	Day 8
RBC count	15.3	15.1	13.9	
Platelet	146	140	132	
Hematocrit	47.6	47.1	44.5	
WBC	6.0	6.5	4.9	4.5
Total bilirubin				6.8
ALT				59
AST				58
Urea				2.6
Creatinine				59.3
CRP				3.3
Dengue IgM			Positive	
Dengue IgG			Negative	
NS1			Negative	
Mycoplasma				Positive
Mycoplasma Pneumoniae Total Antibody				1 : 1280
COVID-19				Negative
BFMP				No parasite seen
HSV 1 and 2				Negative
Leptospira				Negative
Blood Culture and Sensitivity (Aerobes and Anaerobes)				No growth for 5 days

Table II: Summary of laboratory findings and its interpretations

Test	Patient's results	Normal values	Interpretation
White blood cell count	6.5 → 4.9 → 4.5	4.0- 11.0 x10³/µL	Reduction in WBC count consistent with viral infection, likely dengue.
Platelet count	146 → 140 → 132	150 -450 x10³/µL	Persistent low normal trend, indicative of potential dengue-related thrombocytopenia.
Dengue IgM Serology	Positive	Negative	Confirmed dengue infection.
Chest X-ray (CXR) imaging	Right Upper Lobe Consolidation	Normal	Revealed pneumonia, indicating co-infection.
Mycoplasama Serology	Positive 1 : 1280	Negative	Confirmed co-infection with Mycoplasma pneumoniae.
Liver Function Test	Elevated (Transaminitis)	Normal: ALT < 40 U/L, AST < 40 U/L	Elevated liver enzymes, consistent with dengue and/or bacterial infection and complications.
COVID-19 test	Negative	Negative	Ruled out COVID-19 as a cause of respiratory symptoms.

over the right upper chest. The sudden manifestation of respiratory distress triggered the concern of dengue-related respiratory complications; hence, a chest X-ray (CXR) and some blood parameters were arranged. His CXR findings showed right upper lobe lobar pneumonia changes, and his liver function tests revealed transaminitis, prompting immediate reevaluation and subsequent hospital admission.

Given the atypical respiratory symptoms alongside confirmed dengue fever, a secondary bacterial infection was suspected, with Mycoplasma pneumoniae being a common cause of atypical pneumonia in children. Mycoplasma serology was ordered to confirm this, and the positive result guided the initiation of appropriate antibiotic (Augmentin and Azithromycin) therapy, resulting in significant clinical improvement. He was discharged on day 4 of admission with follow-up as an outpatient. His repeat CXR improved, and his liver function test normalised

DISCUSSION

Dengue cases surged globally over the past two decades, with reported instances increasing tenfold from 2000 to 2019, reaching 5.2 million. Despite a slight decline during 2020-2022 due to the COVID-19 pandemic, a significant upsurge occurred in 2023, marked by outbreaks spreading into previously unaffected regions.[1] In Malaysia, a tropical country, dengue cases in 2024 are rising sharply compared to the same period last year, based on alarming data from the Ministry of Health.[6]

Dengue typically manifests as an acute febrile illness. Early recognition is crucial for prompt management and prevention of complications like severe dengue and dengue shock syndrome. Our case highlights the complexities of diagnosing dengue when initial symptoms mimic those of a viral respiratory infection. Although fever and headache are well-documented primary symptoms of dengue, this case is unique due to the atypical progression and concurrent Mycoplasma pneumoniae infection.[7]

Previous studies, such as those by Wilder et al. (2005) and Castilho et al. (2022), document that typical dengue cases present with leukopenia and thrombocytopenia, hallmark features of the disease.[8-9] However, in our case, lab results deviated from the usual dengue profile, likely due to

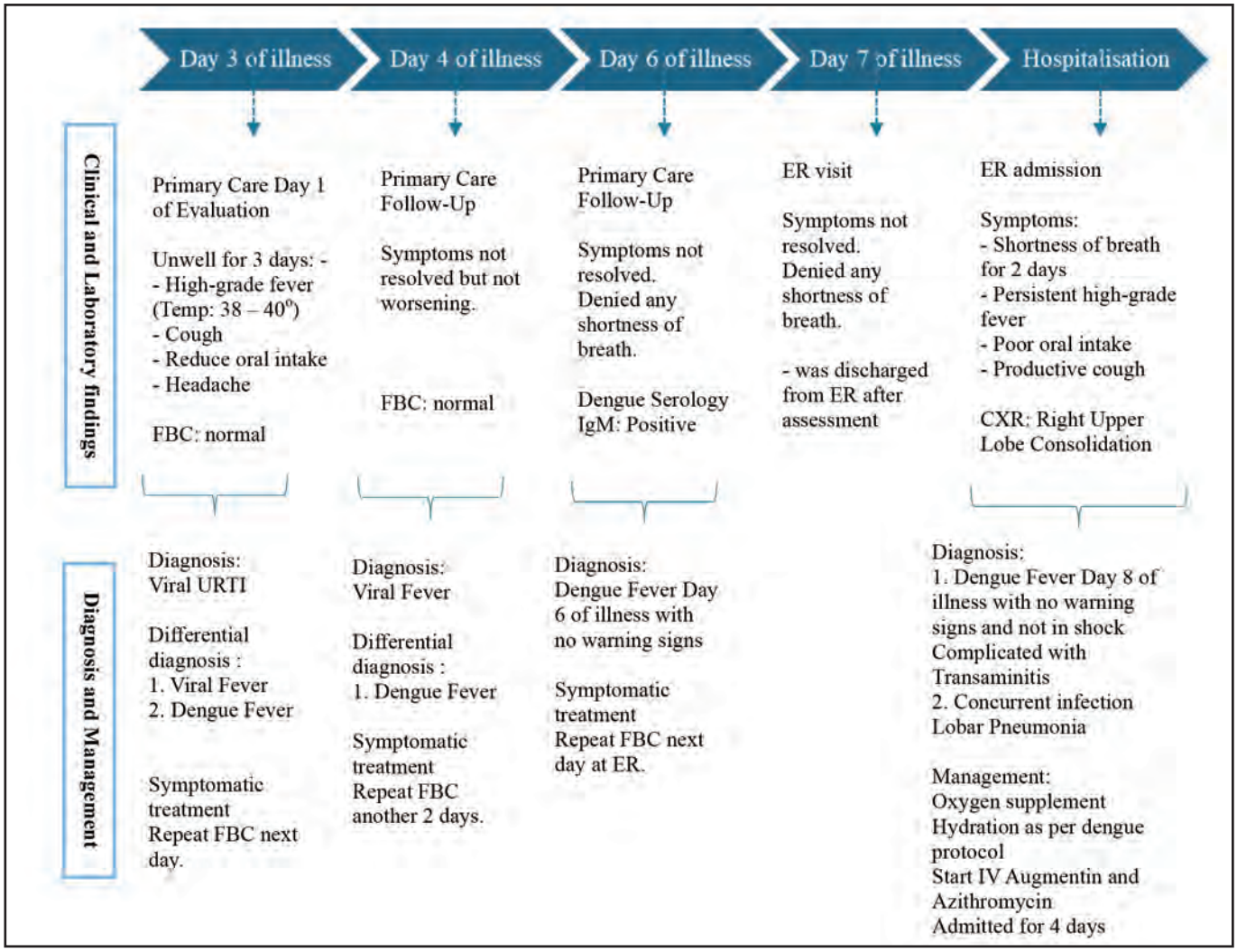

Fig. 1: Timeline of disease course

concurrent bacterial infection. This emphasizes the need for heightened clinical suspicion in endemic areas, especially when symptoms do not fit the classic dengue pattern. Typically, when evaluating suspected dengue fever, a reduction in platelet counts warrants testing for dengue serology, namely the NS1 antigen, which is most effective within the first five days of illness. However, its sensitivity decreases as the illness progresses, as seen in this case, where the NS1 antigen test was negative on day 6.[10]

Rapid combo dengue tests, including NS1 antigen and IgM/IgG antibody tests, are valuable tools in primary care settings for early detection. The NS1 antigen test, effective in the first 1-5 days, aids early diagnosis. In this case, the NS1 test was negative on day 6, contributing to the delayed diagnosis. Using combination tests that detect both NS1 antigen and IgM/IgG antibodies could provide more comprehensive diagnostic information, facilitating timely treatment. Establishing protocols or algorithm approach that recommend such combination tests in primary care settings may help clinicians make timely and accurate diagnoses, particularly in cases where the initial presentation is atypical or symptoms appear late in the disease course.

The patient's extensive travel history to endemic areas added further complexity, underscoring the need for heightened suspicion of co-infections in such contexts. Travelers returning from regions where dengue is prevalent present an increased risk of local transmission, and overlooking this history may lead to underestimation of the true incidence due to varying reporting standards. This highlights the importance of incorporating travel history into diagnostic protocols, especially in areas where dengue is endemic.

After a diagnosis of dengue fever was confirmed, the patient returned to the emergency department with worsening respiratory symptoms. A dengue-related complication, likely dengue pneumonia, was suspected. Given the potential for rapid progression and severe respiratory compromise, it is important to remain vigilant for concurrent infections that can occur alongside dengue. Chest X-rays and clinical assessments are vital for diagnosing pneumonia and detecting lobar involvement. Introducing protocols that include the use of chest imaging and Mycoplasma serology for patients with persistent respiratory symptoms, despite initial dengue diagnosis, could enhance early detection of co-infections and improve patient outcomes.[11]

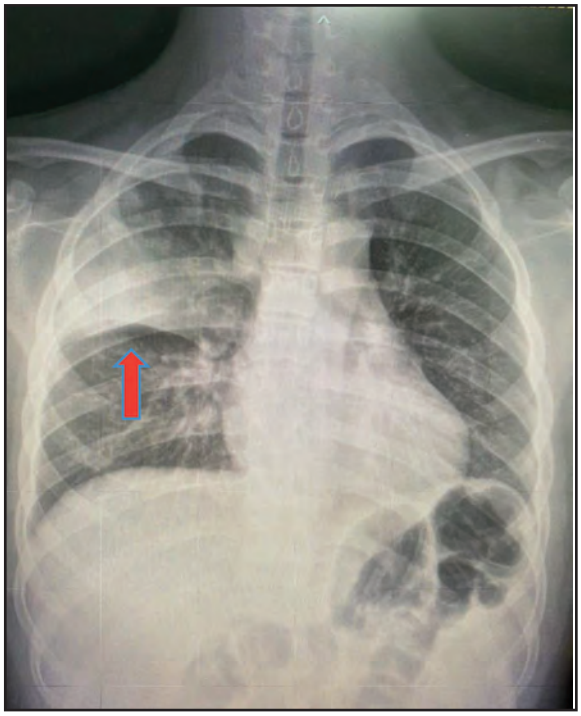

Fig. 2: Chest radiography showing an ill-defined area of increased density in the right upper lobe without volume loss

Diagnosing lobar pneumonia can be challenging as initial symptoms such as fever and cough overlap with many respiratory and viral infections. Lobar pneumonia, also known as atypical pneumonia, can present subtly at first, making it difficult to differentiate from other respiratory conditions. Pediatric patients, who may not always exhibit classic signs and symptoms, add to diagnostic uncertainty, often delaying pneumonia diagnosis in primary care. A persistent high-grade fever for six days despite regular paracetamol should warrant referral to secondary care for further evaluation. Recognizing the complexities and uncertainties of such cases in primary care settings is essential, especially given limited diagnostic resources.

Mycoplasma pneumoniae is a common cause of atypical pneumonia, particularly in children and adolescents. While macrolide antibiotics are recommended for treatment, diagnosing *M. pneumoniae* can be difficult based on clinical symptoms alone due to its variable presentation.[12] Dual infections of *M. pneumoniae* and dengue fever in pediatric cases are especially challenging, potentially leading to severe complications, such as dengue hemorrhagic fever, liver failure, and clostridial colitis.[4] In our case, the patient developed transaminitis but fortunately did not progress to liver failure due to prompt treatment. A similar case of concurrent *M. pneumoniae* and dengue hemorrhagic fever in a tourist from Thailand was reported in Russia in 2022, showing similar clinical presentations to our case.[5]

The association between *M. pneumoniae* and dengue fever is an emerging area of interest in infectious disease research. Both conditions pose significant health concerns in tropical and subtropical regions. Understanding their potential co-occurrence is crucial for improving patient outcomes. Recognizing a patient's epidemiological history is key to identifying not only the primary diagnosis but also the potential coexistence of other equally severe infectious diseases.

Clinicians should remain vigilant, identifying early warning signs, utilizing diagnostic tools effectively, and initiating prompt antibiotic treatment to prevent worsening morbidity and mortality. Establishing standardized protocols that recommend early screening for co-infections in patients with atypical symptoms and ensuring access to rapid combo dengue tests can enhance diagnostic accuracy. Furthermore, reinforcing the importance of referral to secondary care for persistent or worsening symptoms will ensure appropriate management. Our patient's positive response to combined dengue management and antibiotic treatment for *Mycoplasma pneumoniae*, without severe complications such as liver failure, further underscores the uniqueness of this case.

By integrating our findings with existing literature, we highlight a novel aspect of this case—the identification of Mycoplasma pneumoniae amidst dengue fever. This rare scenario contributes to the growing understanding of how co-infections can complicate the clinical and diagnostic landscape. The positive Mycoplasma serology, alongside the development of lobar pneumonia, emphasizes the need for a high index of suspicion and a multi-faceted diagnostic approach in such cases. Our case underscores the growing importance of co-infections due to global travel and changing epidemiology, emphasizing the need for updated pediatric care protocols that integrate broader diagnostic strategies to ensure timely and effective treatment.

CONCLUSION

This case highlights the underappreciated occurrence of co-infection by the dengue virus and bacteria, emphasizing the need for heightened clinical awareness. Particularly in pediatric patients, atypical presentations or prolonged symptoms should prompt consideration of bacterial co-infection, as seen here with *Mycoplasma pneumoniae*. This case underscores the critical role of thorough diagnostic testing, including serology for potential co-infections, to guide appropriate treatment and improve patient outcomes.

Beyond individual cases, this finding has broader implications for public health in dengue-endemic areas. It suggests that clinical guidelines may need to evolve to incorporate routine consideration of co-infections in febrile patients, especially those with unusual or persistent symptoms. Raising awareness of co-infections could lead to earlier diagnosis and prevent life-threatening complications, ultimately improving patient care in endemic regions.

ACKNOWLEDGMENT

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DECLARATION

The authors declare no conflicts of interest.

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CASE REPORT

A puzzling paradox: Congenital bowel malrotation masquerading as duodenal atresia in a case of non-bilious emesis

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SUMMARY

Intestinal malrotation is a congenital abnormal bowel position within the peritoneal cavity, usually involving small and large bowels. It is considered primarily a disease of infancy with infrequent occurrence beyond the first year of life. The twisting and malposition of the intestine can cut off the blood supply. If undiagnosed for a prolonged duration, it can be fatal. Diagnosing malrotation of the gastrointestinal (GI) tract in newborn babies in primary care settings can be challenging, where it needs a structured approach with supportive clinical findings and examinations. Although it can be a straightforward diagnosis, approximately 15% of upper GI (UGI) studies result in equivocal findings, leading to false-positive and false-negative interpretations.[1] We report a case of a five-day-old infant presenting with non-bilious vomiting with radiographic imaging of a double bubble sign, which was subsequently found to have bowel malrotation.

INTRODUCTION

Persistent vomiting in an infant is consequential and sometimes poses a challenge in diagnosis in primary care. An isolated episode of non-bilious vomiting in most infants can be due to milk intolerance, gastro-oesophageal reflux, or gastroenteritis. However, continuous emesis can be due to multifactorial life-threatening conditions such as duodenal atresia, annular pancreas, duodenal stenosis, and bowel malrotation. The diagnosis should be made based on the particular onset, age of presentation, nature of clinical conditions, and proper investigations. A simple reassurance or waiting for the vomiting to be self-limiting is not a wise choice to be made, especially in primary care.

Despite various aetiologies that can cause vomiting in an infant, intestinal malrotation should not be missed. Under one year of age, malrotation presents in around 1 in 2500 live-born infants and is more common in males than females. It can cause an infant to be more likely to develop a midgut volvulus in the first few weeks of life, subsequently causing vascular compromise in the intestines.[2] The cardinal features of intestinal malrotation are bilious vomiting and abdominal distension. However, it can be non-bilious, especially for young children and infants.[3] The clinical manifestations may develop quickly and are generally dramatic enough, especially for infants. They may be in shock, and the conditions are critical for survival.[4]

The management of such cases is a mandatory early surgical intervention. The prognosis is good if there is no midgut volvulus, intestinal necrosis, prematurity, or other abnormalities. This case report aims to increase medical practitioners' suspicion towards congenital malrotation upon seeing cases of infants solely presented with vomiting and the importance of early recognition, preventing delay in diagnosis and treatment.

CASE PRESENTATION

A day-five-of-life newborn baby boy was brought by his mother to the primary care clinic for sudden, frequent vomiting, which was non-projectile and associated with abdominal distension for one day. The vomitus contained milk and saliva. There was no bile, mucus or blood. It was not associated with fever, loose stool, upper respiratory tract infection or head trauma. During the first visit to a primary care clinic, the baby was discharged home, and reassurance was given to the parents. However, he was brought to our clinic the next day because of persistent vomiting. He was born full-term with a birth weight of 3.65kg and was exclusively breastfed. The perinatal and antenatal histories were uneventful.

On examination, the baby was afebrile and active on handling. The anterior fontanelle was normotensive. His vital signs were normal, with good pulse volume, and his capillary refill time was less than 2 seconds with warm peripheries. The abdomen was not distended and was soft on palpation. There was no mass palpable, and the bowel sound was normal. Other systems examinations were unremarkable. He was then subsequently referred to the hospital for further management, given the possible diagnosis of intestinal obstruction.

An abdominal radiograph was done, and normal findings were noted. He was then admitted for observation and hydration maintenance. However, while in the ward, the vomiting persisted, and abdominal distension was observed.

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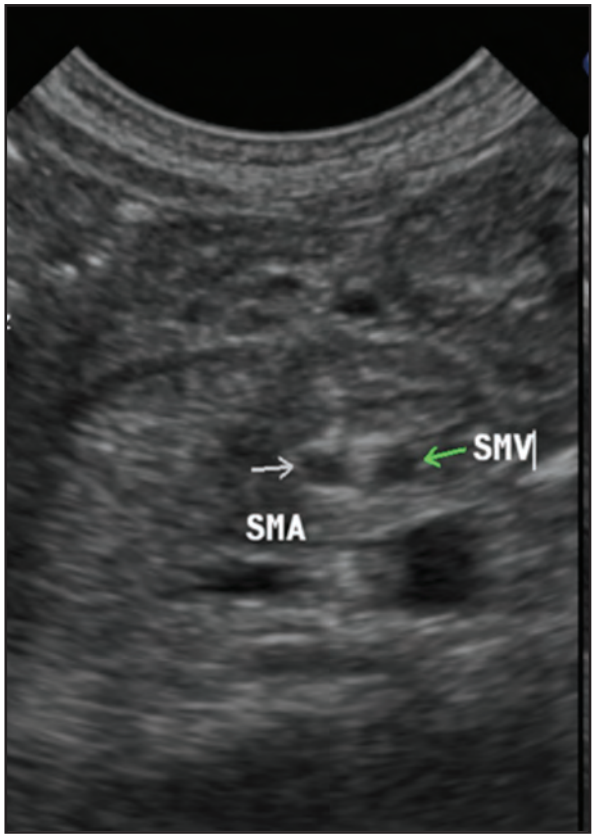

Fig. 1: Ultrasound in axial plane showing the reverse superior mesenteric artery (SMA) and superior mesenteric vein (SMV) orientation

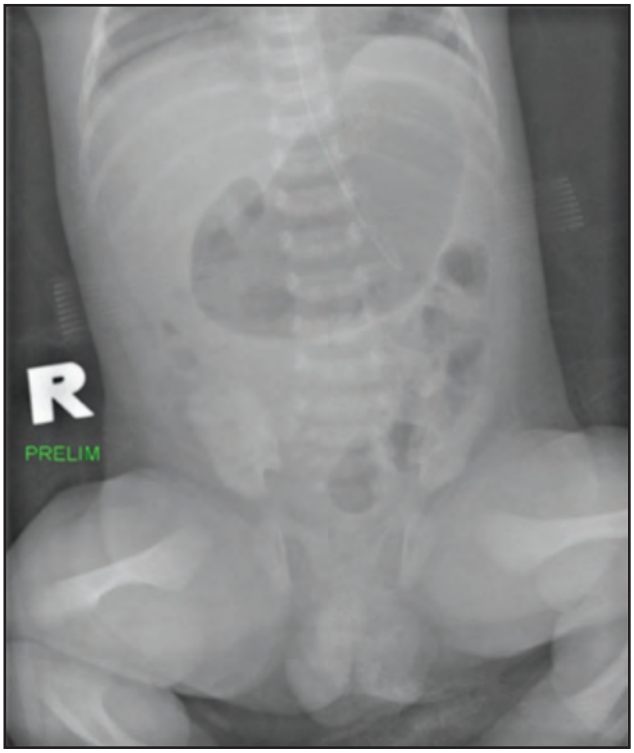

Fig. 2a: A preliminary abdominal radiograph shows air-filled distended stomach with minimal gas distally

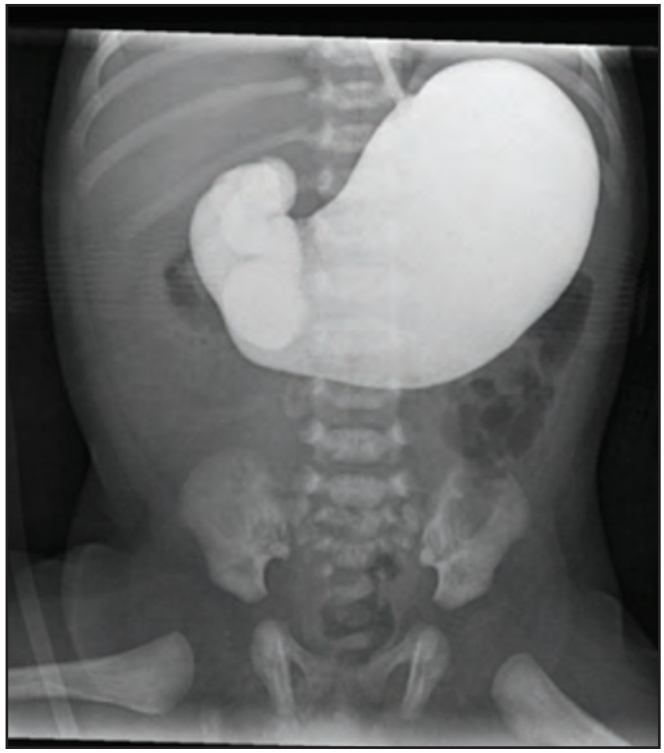

Fig. 2b: Contrast is seen within the distended stomach. Features are suggestive of subtotal duodenal stenosis with presence of distal gas observed

A subsequent ultrasound of the abdomen was performed, showing a suspicious superior mesenteric artery (SMA) and superior mesenteric vein (SMV) relationship inversion (Figure 1). However, no apparent sonographic features suggest midgut volvulus with malrotation. Another abdominal radiograph was done that showed distended stomach with air in distal bowel loops which otherwise, were not dilated. After that, a UGI contrast study was performed, which confirmed malrotation. Other biochemical markers, blood and urine cultures were normal.

He was then referred to the pediatric surgeon for further management. A Ladd's procedure was performed. Intraoperative findings showed that the duodenojejunal (DJ) flexure is on the right side of the vertebra, with no volvulus but narrowed mesentery. Otherwise, other intraoperative findings, such as the location of the small bowel, large bowel and caecum in this patient, cannot be described further. He was discharged well post operatively. During the follow-up at the age of one month, the baby tolerated feeding well and had satisfactory weight gain. There have been no more vomiting episodes since then.

DISCUSSION

A newborn baby with vomiting is worrisome, and parents will seek immediate medical advice. Vomiting in newborn babies should not be taken lightly. It can happen due to multiple pathologies such as intestinal obstructions, viral gastroenteritis, gastroesophageal reflux disease, pyloric stenosis, Hirschsprung disease and sepsis.[5] In addition, vomiting may result from congenital atresia or an error in embryonic rotation, resulting in malrotation with or without volvulus.[6]

Depending on the onset, quality, frequency, and associated symptoms, medical practitioners must determine whether the infant needs further investigation or sufficient reassurance only. In this case, the healthcare provider attending to the patient during the first visit to the primary care clinic must take a thorough history to rule out all the differential diagnoses mentioned above. This is crucial so that delayed diagnosis can be avoided and the patient can be managed accordingly promptly. In this case, after the second visit to the primary care clinic, the infant was immediately referred to the nearest tertiary centre for further management.

The most significant complication of intestinal malrotation is midgut volvulus, which is life-threatening and may lead to short-bowel syndrome.[6] In addition, a higher rate of complications such as bowel ischemia occur in children, including infants, given a larger fraction of patients in this age group are brought to the primary care clinics with acute presentations. Thus, a physician must have a high index of suspicion based on age, symptoms, and physical examinations before proceeding to perform the necessary investigations.

As mentioned earlier, malrotation diagnosis can pose a challenge in the primary care setting. Clinical presentations for malrotation can occasionally be confused with duodenal atresia (DA).[7] Nevertheless, in DA, infants will present with bilious vomiting in the first 48 hours of life. Clues to differentiating malrotation and DA include antenatal history and radiographic features such as a smooth outline to the most distal point of a double bubble (DA) rather than the 'bird's beak', which suggests malrotation.

In addition, the inversion of the superior mesenteric artery and vein relationship may indicate intestinal malrotation. From the axial plane, at the level of the junction of the superior mesenteric vein (SMV) with the portal vein, the SMV is usually located to the right of the superior mesenteric artery (SMA). Thus, an SMV not lying to the right of the SMA is highly sensitive to intestinal malrotation (Daneman, 2009). As in our case, the reverse orientation of SMV and SMA was suggestive towards intestinal malrotation. Also, an upper gastrointestinal contrast study is 93-100% sensitive and will show a corkscrew appearance when a volvulus is present. The contrast study also helps to define the position of the duodenal-jejunal flexure, the cecum and the proximal colon.[8] However, any suspicion of malrotation warrants emergency investigation and/or operative intervention.[9] Direct visualization of a whirlpool sign helps to establish the diagnosis.[8] In this case, even though it was non-bilious vomiting, the symptom was persistent, followed by abdominal distension after day five of life, which led towards the diagnosis of intestinal malrotation. The management would remain the same.

Ultrasound (US) is crucial in the diagnostic imaging workup for infantile vomiting.[7] Workup for intestinal malrotation should be considered in all patients with bilious emesis, abdominal pain or distention. As in our case, the US abdomen had been done during admission, after the initial abdominal radiograph at the emergency department which showed normal findings. However, malrotation could not be ruled out; thus, a UGI contrast study was performed before surgery was decided upon. An abdominal radiograph was also repeated prior to the UGI contrast study. This also shows that other alarming pathologies still need to be ruled out, even with normal radiographic findings during the first visit. For this condition, the management focuses on avoiding intestinal necrosis and reversing ischemia if it already happens. This is achieved with Ladd's procedure, named after Dr William Edward Ladd, the pioneer pediatric surgeon of North America who first performed the procedure in 1936. Instead of correcting the malrotation, it helps to open the narrow mesenteric pedicle to prevent volvulus from recurring.[5] There is also a debate on whether to choose laparoscopic or open surgery. However, laparoscopic exploration is the procedure of choice compared to open surgery in that it shortens hospital stays and increases the recovery rate.[9] Nevertheless, it will be converted to an open procedure if there is evidence of intestinal necrosis present or difficult local anatomy. The mean hospital stay was 4 days (range 3-12days).[10] In this case, the baby was discharged well.

One of the most common complications that can happen post-operatively is intestinal obstruction. There are also cases of readmission within six months after Ladd's procedure for different problems such as wound infection, feeding difficulties, ascites, pneumonitis, constipation, and abdominal pain. Cases of failure to thrive or

gastroesophageal reflux disease (GERD) also need to be given attention. As for this case, parental satisfaction was high, and no long-term morbidity was observed during the subsequent follow-up with the paediatric surgery department. These complications also need to be highlighted during routine check-ups at primary care.

CONCLUSION

A definitive diagnosis of malrotation can be challenging in the primary care setting with limited resources. For primary care providers, an accurate clinical judgment for a case of vomiting in an infant is a must. Any infant with symptoms and signs of acute intestinal obstruction must be investigated further. Reassurance does not suffice. Although this case presented with non-bilious vomiting, intestinal malrotation remained one of the differential diagnoses. Intestinal malrotation must be considered, even though it is rarely found in daily practice, as the final diagnosis is commonly established at the tertiary centre. In a primary care setting, one should never rely only on plain radiograph findings to diagnose or exclude intestinal malrotation. Appropriate referrals should be made to prevent diagnosis delay and complications.

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DECLARATION

The authors have no conflict of interest to disclose.

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CASE REPORT

Thymoma-associated paraneoplastic syndromes: A case series unveiling diagnostic challenges and therapeutic outcomes

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SUMMARY

This study aims to explore the association between thymoma and various paraneoplastic syndromes (PNS), focusing on diagnostic challenges and treatment responses. We retrospectively analysed four cases diagnosed with thymoma and associated PNS, managed via uniportal video assisted thymomectomy and subsequent clinical follow-up. The cases presented with nephrotic syndrome, Good's syndrome, and two instances of pure red cell aplasia (PRCA). Surgical intervention resulted in varying outcomes among the paraneoplastic conditions. The Good's syndrome case showed improvement post-thymectomy with the patient remaining infection-free at the last follow-up. One of the PRCA cases achieved complete remission post-thymectomy without further adjuvant therapy. Nephrotic syndrome presented alongside thymoma contributed to a more challenging course, with the patient's renal function deteriorating postoperatively. This case series underlines the importance of a personalized approach in managing PNS associated with thymomas due to the unpredictable therapeutic outcomes. It also highlights the necessity for multi-disciplinary involvement in care and the urgent need for further research to establish a standardized treatment protocol. This study contributes valuable insights into the natural history and management of these complex syndromes in the context of thymoma.

INTRODUCTION

The landscape of thymomas and their associated paraneoplastic syndromes (PNS) represents a confluence of oncological and immunological intricacies. The pioneering observation by Weigert et al. in 1901, identifying a thymoma in conjunction with myasthenia gravis (MG), marked the inception of our investigation into this complex interplay.[1] The International Thymic Malignancy Interest Group (ITMIG) has refined our understanding of the epidemiological and clinical dimensions of these associations.[2]

Transitioning from historical theories of "bad humours" to contemporary autoimmune paradigms has been pivotal. Thymoma cells can secrete cytokines and peptides, instigating aberrant immune responses.[3] These molecules can trigger the activation of autoreactive T cells or the production of autoantibodies targeting distant organ systems, leading to a spectrum of PNS.[4] The disruption of thymic architecture inherent in thymomas derails the T-cell maturation process, compromising central immune tolerance and paving the way for autoimmunity.[5]

In this series, we delve into four case studies, each presenting a unique facet of thymoma-associated PNS, including nephrotic syndrome, Good's syndrome, and 2 cases of pure red cell aplasia (PRCA). These cases highlight the heterogeneity in clinical presentations and therapeutic responses, underscoring the imperative for individualized management strategies.

CASE PRESENTATION

Case 1

A 61-year-old lady was referred for an incidental finding of a mediastinal mass during a routine chest X-ray. She had chronic kidney impairment (stage 4), diabetes mellitus type 2, and hypertension. Over the past year, she developed bilateral lower limb swelling and significant proteinuria (5611 mg/litre). A CT scan revealed a well-defined mass in the mediastinum. An image-guided biopsy suggested a Thymoma Type AB. She underwent a right uniportal video assisted thoracoscopic thymomectomy in September 2023. Postoperatively, upon follow up, there was no recurrence detected in surveillance CT of the Thorax. Her urine protein readings however remained static, and she refused a renal biopsy despite multiple counselling efforts. Her renal function deteriorated, and she was ultimately counselled for long-term renal replacement therapy.

Case 2

A patient presented with breathlessness and reduced effort tolerance for three weeks in February 2019. Diagnosed with PRCA in January 2019, she had been managed with immunosuppressants and zinc supplements. A chest radiograph revealed a right-sided pleural effusion, and a CT scan showed a large mediastinal mass suggestive of thymoma. Bronchoscopy ruled out bronchial involvement. An image-guided biopsy confirmed Thymoma Type AB. She underwent a right anterolateral thoracotomy and thymomectomy in June 2019. Postoperative recovery was uneventful, and she achieved total remission of PRCA without further treatment. She has been medication-free for four years, with no evidence of recurrence on follow-up CT scans.

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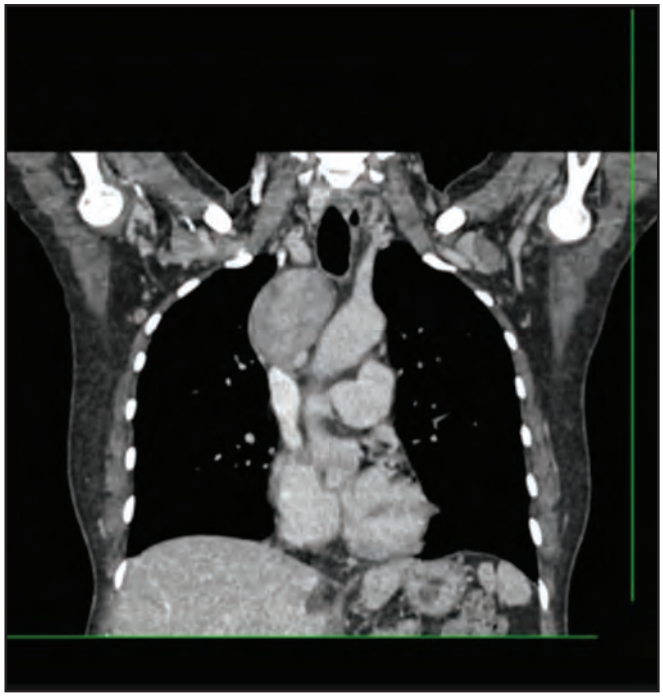

Fig. 1: Pre-operative CT Thorax for Case 4

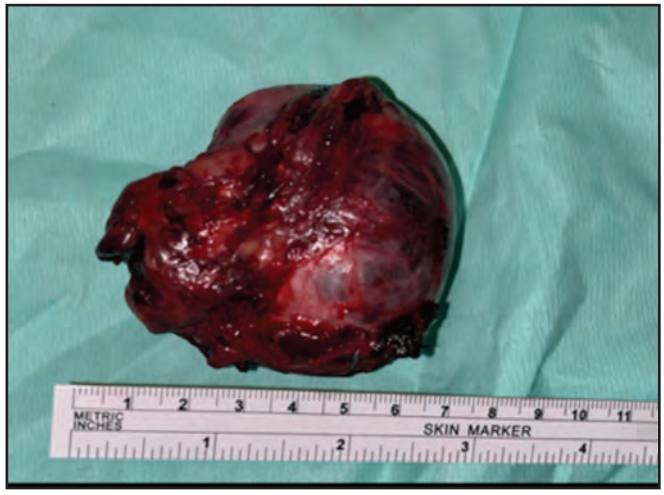

Fig. 2: Thymoma specimen

Case 3

A 58-year-old gentleman with hypertension and oral lichen planus presented with reduced effort tolerance and palpitations in November 2022. He was found to be severely anaemic (Hb 4.9 g/dl) and required immediate transfusion of four units of packed cells. A chest X-ray revealed a right hilar opacity, and a subsequent CT scan showed a large anterior mediastinal mass. An image-guided biopsy confirmed a Thymoma Type AB. He underwent a uniportal right video assisted thoracoscopic thymomectomy in January 2023. Postoperative recovery was uneventful. Follow-up histopathological examination confirmed the thymoma. Surveillance CT thorax in August 2023 showed no recurrence, but the patient remains on ciclosporin therapy for PRCA control.

Case 4

A 58-year-old ex-smoker with recurrent lung infections from March to June 2023 had a thymoma with hypogammaglobulinemia. She was repeatedly admitted for respiratory infections caused by pathogens like Extended Spectrum Beta Lactamase Klebsiella and Pseudomonas Aeruginosa. A chest radiograph showed a widened mediastinum, and a CT scan revealed a mediastinal mass as shown in Figure 1. An image-guided biopsy confirmed a Thymoma B2 subtype. She underwent a uniportal right video assisted thoracoscopic thymomectomy in August 2023. Postoperatively, she remained free from infections with regular IVIg therapy. Follow-up CT scans showed no recurruence, but her serum immunoglobulin levels remained low, with her IgA, IgG and IgM results being <0.10g/L, 5.07 g/L and <0.20 g/L respectively, necessitating continued IVIg therapy.

DISCUSSION

Thymomas are unique tumours that have a significant impact on the immune system, often leading to paraneoplastic syndromes (PNS). These syndromes, such as nephrotic syndrome, pure red cell aplasia (PRCA), and Good's syndrome, present distinct clinical challenges and require tailored management approaches.

Nephrotic Syndrome

Nephrotic syndrome associated with thymoma is rare and poses a significant treatment challenge. The disruption of T-cell maturation and the release of cytokines by thymoma cells contribute to renal impairment. Our patient's refusal of a renal biopsy limited our ability to confirm the exact type of nephropathy, complicating the treatment strategy. Studies suggest that while some patients respond well to thymectomy, others may experience persistent or worsening renal dysfunction. This variability underscores the need for comprehensive preoperative evaluation and long-term renal monitoring post-thymectomy. Further research is needed to understand the mechanisms driving nephrotic syndrome in thymoma patients and to develop targeted therapies.[6]

Several studies have suggested a link between thymoma and various renal pathologies, such as minimal change disease, membranous nephropathy, and focal segmental glomerulosclerosis (FSGS). These conditions often manifest after the initial treatment of the thymoma. The largest case series by Karras et al. reported that 47% of thymoma-associated nephropathy cases occurred post-thymoma treatment, with a significant proportion progressing to end-stage renal failure.[7] This highlights the importance of vigilant monitoring and potential adjunctive therapies to manage renal complications effectively.

Summary of Case Discussions

Case	Symptoms	PNS association	Co-morbidities	Treatment	Follow up	Outcome
Thymoma AB	Bilateral Lower Limb swelling. Frothy Urine.	Nephrotic Syndrome.	Hypertension. Diabetes Mellitus Type II.	Right Video Assisted Thoracoscopic Thymomectomy.	Refusal of renal biopsy, unable to confirm subtype. Further deterioration of renal function.	Long term consideration of Renal Replacement Therapy.
Thymoma AB	Breathlessness. Reduced effort tolerance.	Pure Red Cell Aplasia.	None.	Right Anterolateral Thoracotomy and Thymomectomy.	Resolution of anemia.	Remission of PRCA and medication free.
Thymoma AB	Reduced effort tolerance. Palpitations.	Pure Red Cell Aplasia.	Hypertension.	Right Video Assisted Thoracoscopic Excision of Mediastinal Mass.	Persistence of anemia	PRCA control with ciclosporins.
Thymoma AB	Recurrent respiratory tract infections.	Good's Syndrome	None	Right Video Assisted Thoracoscopic Thymomectomy.	Cessation of recurrent respiratory tract infections.	3 weekly administrations of Intravenous Immunoglobulins.

The variability in outcomes for nephrotic syndrome patients post-thymectomy highlights the complexity of these cases. It suggests that while thymectomy can help manage the underlying tumour, additional treatments may be necessary to address renal complications. The involvement of nephrologists in the care team can help optimize treatment plans and monitor renal function closely, ensuring timely interventions when necessary.

Pure Red Cell Aplasia (PRCA)

PRCA is characterized by severe anaemia and a low reticulocyte count. The pathogenesis of PRCA in thymoma patients involves the secretion of inhibitory cytokines by thymoma cells, which suppress erythroid precursors.[8] Our two cases of PRCA demonstrated different outcomes post-thymectomy. One patient achieved complete remission without additional treatment, while the other required ongoing immunosuppressive therapy. This variability is reflected in the literature, where some patients achieve remission post-thymectomy, while others require additional interventions such as immunosuppressants, steroids, or splenectomy. The Mayo Clinic's 50-year study highlighted the need for adjuvant therapies in most cases.[9] These findings indicate that thymectomy alone may not be sufficient for PRCA management, and a personalized treatment plan should be developed for each patient.

The literature on PRCA suggests that while thymectomy can lead to remission in some cases, the response is highly variable. Schmid et al. reported that some patients did not achieve remission even with additional steroid therapy post-thymectomy, necessitating further interventions such as blood transfusions.[9] This underscores the need for a comprehensive treatment plan that includes both surgical and medical management to address the underlying autoimmune dysfunction.

The management of PRCA requires a multidisciplinary approach, involving haematologists to guide immunosuppressive therapy and monitor for potential side effects. Regular follow-up and blood tests are crucial to ensure that the patient's anaemia remains under control and to adjust treatment plans as needed. Additionally, patient education on the importance of adherence to therapy and regular monitoring can improve outcomes.

Good's Syndrome

Good's syndrome, a rare combination of thymoma and immunodeficiency, presents significant clinical challenges. The syndrome is characterized by hypogammaglobulinemia and recurrent infections, as seen in our patient. The management of Good's syndrome requires a multidisciplinary approach involving oncologists, immunologists, and infectious disease specialists. Thymectomy can reduce the tumour burden, but its impact on immunodeficiency is variable. Our patient showed improvement in infection rates post-thymectomy with regular IVIg therapy, but long-term immune function monitoring is necessary. The literature emphasizes early diagnosis and treatment of immunodeficiency to prevent severe infections. Further research is needed to understand the long-term outcomes of thymectomy and the best management strategies for the immunodeficiency component of Good's syndrome.[10]

Good's syndrome is particularly challenging due to its impact on both humoral and cellular immunity. Patients often present with recurrent infections caused by opportunistic pathogens, highlighting the need for ongoing immunoglobulin replacement therapy. The literature suggests that while thymectomy can help reduce tumour burden, it may not fully restore immune function. Long-term follow-up and management of immunodeficiency are critical to improving patient outcomes,[10] Additionally, patients with Good's syndrome are at an increased risk for developing other autoimmune conditions, necessitating regular monitoring and comprehensive care.[10]

The management of Good's syndrome should involve regular follow-ups with immunologists to monitor immunoglobulin levels and adjust IVIg therapy as needed. Patients should be educated on infection prevention measures, and prompt treatment of infections is crucial to avoid complications. A comprehensive care plan that addresses both the thymoma

and the immunodeficiency can help improve the patient's quality of life.

Key Insights and Future Directions

The cases presented in this series highlight the heterogeneous nature of PNS associated with thymoma and the importance of a personalized approach in their management. Thymectomy remains a cornerstone treatment for thymoma, but its efficacy in resolving associated PNS varies significantly. The unpredictable nature of these syndromes necessitates a multidisciplinary approach involving various specialists to manage both the tumour and its systemic effects.

Additionally, there is a critical need for more extensive studies to elucidate the underlying mechanisms of PNS in thymoma patients. Understanding the specific cytokines, autoantibodies, and genetic factors involved can pave the way for the development of targeted therapies. Collaborative efforts combining clinical expertise with basic and translational research are essential to improve diagnostic and therapeutic strategies.

The variability in patient responses to treatment also underscores the importance of patient education and counselling. Patients should be informed about the potential outcomes and the necessity for long-term follow-up and adjunct therapies. Establishing standardized treatment protocols based on robust clinical evidence will enhance patient care and improve prognoses.

CONCLUSION

This case series provides critical insights into the varied presentations and treatment outcomes of paraneoplastic syndromes (PNS) associated with thymoma, revealing a spectrum of clinical challenges and the importance of individualized therapeutic strategies. Our findings affirm that while thymectomy remains a pivotal treatment for myasthenia gravis and offers potential remission for conditions like PRCA, the management of PNS such as nephrotic syndrome, particularly when occurring alongside thymoma, demands a nuanced approach due to the inherent complexity and individual variability of these diseases.

The study also highlights the need for a multidisciplinary approach that extends beyond surgical intervention, emphasizing the role of ongoing monitoring and adjunct therapies in addressing the autoimmune dysregulation characteristic of these conditions. Notably, for disorders like Good's syndrome, thymectomy may serve as an initial step in management, but the overarching goal is to restore immune homeostasis, necessitating long-term immunological support and surveillance.

The outcomes detailed in this series underscore the critical need for a more substantial evidence base to guide clinical decision-making. As such, there is an urgent call for further research to deepen our understanding of the pathophysiological mechanisms underlying PNS associated with thymoma and to develop standardized treatment protocols that can enhance patient prognosis and quality of life.

Ultimately, the complexity of thymoma-associated PNS challenges us to look beyond one-size-fits-all solutions, advocating for personalized medicine backed by rigorous research and collaborative care strategies. Our continued commitment to investigating these syndromes will pave the way for innovative treatments and improved outcomes for patients grappling with the dual burden of thymoma and its paraneoplastic manifestations.

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DECLARATION

The authors declare no conflicts of interest.

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CASE REPORT

Eye sign points to ancient diagnosis: A case report of neurosyphilis

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SUMMARY

A 50-year-old gentleman first presented with worsening motor disturbances, psychosis, and cognitive deterioration; he was initially misdiagnosed with schizophrenia and substance-induced psychosis. Computed tomography of the brain showing widening of sylvian fissures, atrophy of the temporal lobe and cerebellum as well as atrophy of the basal ganglia. After further evaluation, neurosyphilis was identified, with Argyll Robertson pupils serving as the key diagnostic finding. This case emphasizes the importance of performing a complete eye examination in neuropsychiatric assessment and considering infectious aetiologies in atypical presentations.

INTRODUCTION

There has been a resurgence of syphilis, beginning in the 1970s, with changes in sexual practices.[1] Neurosyphilis causes a variety of neuropsychiatric signs and symptoms. Argyll Robertson pupils are characterized by small, irregular pupils that accommodate but do not react to light, and are indicative of neurosyphilis. This case study centers on the patient's initial misdiagnosis with psychiatric diagnosis, which led to the identification Argyll Robertson pupils, and the existence of tertiary neurosyphilis.

CASE PRESENTATION

We present a case of a 50-year-old Malay man without any notable medical history who arrived with a steady decline in memory, disorientation, and motor impairments over two and a half years. The patient had progressive cognitive decline, characterized by forgetfulness, misplacing personal belongings, and having trouble navigating when operating a vehicle. In addition, he displayed disorientation when driving and could not successfully carry out basic activities like cooking simple meals. Despite these cognitive difficulties, he still managed to function independently.

After failed traditional treatment for 6 months, the patient sought the advice of a psychiatrist. A urine drug test indicated the presence of morphine, leading to the diagnosis of substance-induced psychosis. As part of the treatment, he was prescribed risperidone 1 mg to be taken twice daily. The patient's condition progressively worsened, as evidenced by increased social withdrawal, preoccupation, incoherent speech, and exacerbated sleep difficulties. His ability to perform the basic tasks required for daily living was compromised, necessitating the need for monitoring.

The patient was admitted to the medical ward, citing stiffness and tremors in both upper limbs, fever, and severe gastroenteritis symptoms. His cognitive decline had advanced, limiting his ability to identify only immediate relatives. His everyday living activities become completely dependent on his family members. The neurological examination of the patient revealed increased muscle tone in both upper and lower limbs, bilaterally. In the upper limbs, muscle power was reduced to 4/5 on both sides, and reflexes were brisk bilaterally. Similarly, in the lower limbs, muscle power was also 4/5 on both the right and left sides; however, reflexes were noted to be normal. The initial investigations consisted of a computed tomography brain scan, which revealed widening of sylvian fissures (Figure 2), atrophy of the temporal lobe and cerebellum as well as atrophy of the basal ganglia (Figure 1), and a lumbar puncture, which indicated increased cerebrospinal fluid protein levels of 1.38, cerebrospinal fluid glucose 3.37, and no acid-fast bacillus seen. Encephalitis autoimmune receptor profile was conducted on the cerebrospinal fluid, testing for several antibodies; contactin-associated protein 2 antibody, leucine-rich glioma-inactivated protein 1 antibody, dipeptidyl aminopeptidase-like protein 6 antibody, gamma-aminobutyric acid receptor antibody, and N-methyl-D-aspartate receptor antibody. All results were negative. The patient underwent treatment for probable meningoencephalitis and successfully finished a two-week regimen of antibiotics. During this hospitalization, the administration of risperidone was stopped because of the occurrence of extrapyramidal side effects and hyperactive delirium. The patient's creatine kinase levels initially increased to 29,000, then decreased to 4,000.

After discharge, the patient displayed increased social isolation, a lack of organization, and a disregard for personal cleanliness. His motor function began to decline, as indicated by his broad-based gait, muffled voice, slurred speech, and positive Romberg sign. He failed to attend follow-up appointments, but he returned 15 months later with increased irritability and disorganized behaviour. The patient was diagnosed with schizophrenia and prescribed olanzapine 10mg to be taken at night. Additionally, he received a monthly intramuscular injection of Fluanxol 20mg.

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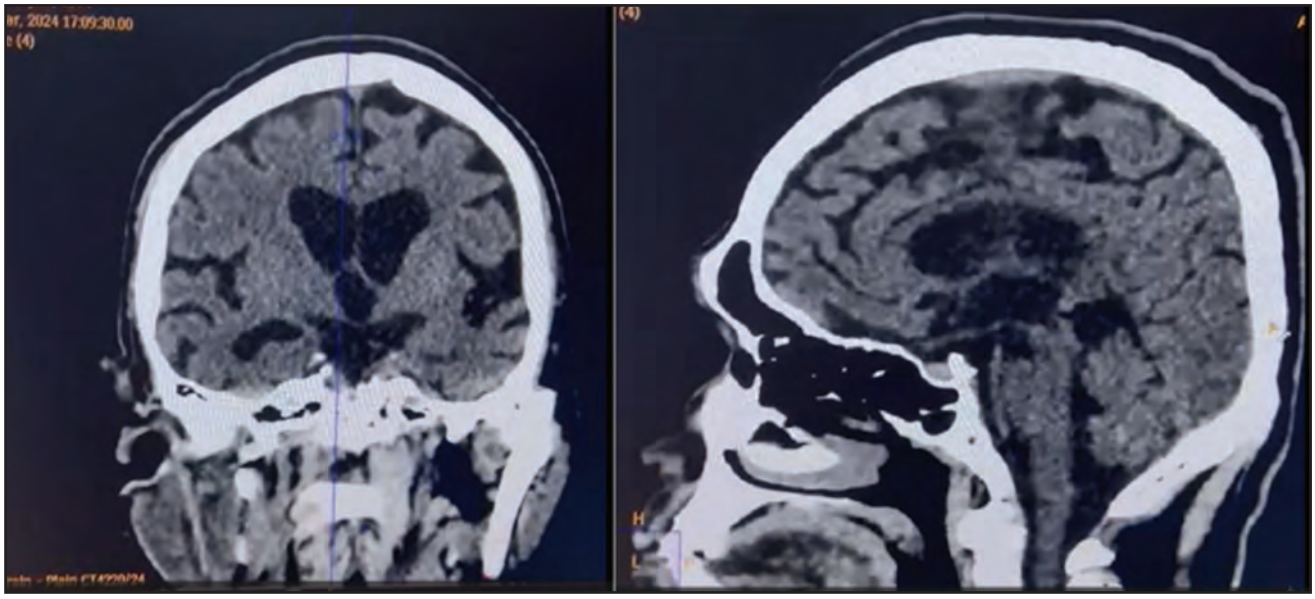

Fig. 1: Coronal view reveals atrophy involving basal ganglia. Parietal lobe relatively more affected, sagittal view, cerebellar atrophy also seen, thinning of corpus callosum seen

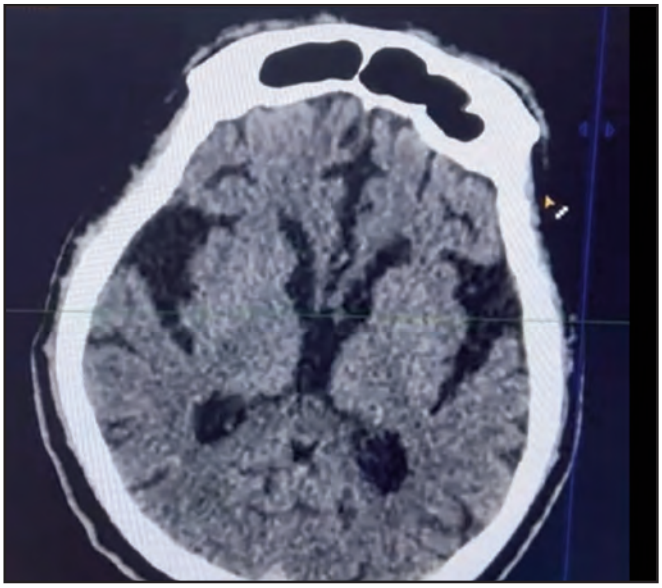

Fig. 2: The axial view shows widening of the Sylvian fissures

Five months later, the patient exhibited heightened irritability, verbal abuse, irrelevant speech, and disorganized behaviour, which included aggression toward family members. The urine drug test yielded negative results, while the basic laboratory tests (Full Blood Count, Renal Profile, Liver Function Test) showed no abnormalities. He received intramuscular Haloperidol and intravenous Valium and was subsequently transported to hospital. The psychiatric impression was relapsed schizophrenia. Nevertheless, upon admission, he experienced rigidity of bilateral upper limb, and creatine kinase levels rose to 1,542. The administration of antipsychotic medication was stopped because of the occurrence of extrapyramidal adverse effects.

His cognitive state fluctuated throughout his hospitalization. Computed tomography of the brain was repeated; it did not show any additional changes from the first scan. On the eighth day, blood testing indicated a positive Treponema pallidum particle agglutination test and reactive rapid plasma reagin test with a titre of 1:32, resulting in a diagnosis of neurosyphilis. The patient has no previous history of syphilis. Infectious disease specialists administered intravenous penicillin 4 million units every 4 hour for 14 days. Most notably, he exhibited Argyll Robertson pupils, which were small, irregular, and unresponsive to light but responsive to near accommodation.

DISCUSSION

Argyll Robertson pupils, named after Scottish ophthalmologist Dr. Douglas Argyll Robertson, are a distinct indicator of advanced tertiary neurosyphilis. Characterized by small bilateral pupils that fail to constrict in bright light but do constrict when focusing on a nearby object. This finding is highly specific to late-stage syphilis.[2]

Widespread use of penicillin had reduced the prevalence of Argyll Robertson pupils. However, this trend has reversed, particularly among men who have sex with men and individuals with human immunodeficiency virus. In 2016, the Centers for Disease Control and Prevention reported 30,676 cases of late and latent neurosyphilis in the United States, with many falling within the men who have sex with men population.[3]

The precise mechanism underlying Argyll Robertson's pupils is not well understood. Syphilis could be inducing lesions in the dorsal midbrain area. This affects the pupillary light reflex but does not affect the accommodation reflex.[2,4] The syphilitic lesion is the dorsal part of the midbrain, close to the Sylvian aqueduct. Damage to the Edinger-Westphal nucleus would impact the efferent pupillary fibers situated on its dorsal side. These fibers have a crucial function in the light reflex. The fibers associated with the accommodation reflex,

situated nearer to the ventral aspect of the Edinger-Westphal nucleus, remain unchanged.[4]

Argyll Robertson pupils were identified in this patient by small bilateral pupils that fail to constrict in bright light but do constrict when focusing on a nearby object. The symptoms typically occur bilaterally and develop slowly over months to years.[5] The patient's other neuropsychiatric symptoms, such as cognitive deterioration, motor abnormalities (e.g., broad-based gait), and behavioural alterations, were indicative of neurosyphilis.[6]

Other potential causes of light-near dissociation, such as Adie's pupil, diabetic neuropathy, and specific optic nerve lesions, should be considered as differentials. Argyll Robertson pupils are small and irregular in shape, and these correlate with other advanced syphilis symptoms such as tabes dorsalis and general paresis of insane.[6]

Tabes dorsalis is a late stage of neurosyphilis, distinguished by the degeneration of the nerves in the dorsal columns of the spinal cord. Apart from Argyll Robertson pupils, ataxia and proprioception loss are associated with the condition.[7] Patients frequently exhibit a wide-based walking pattern and a positive Romberg sign due to defective proprioception, as seen in this case.

General paresis of the insane is a condition characterized by the widespread and long-lasting inflammation of the brain caused by the invasion of Treponema pallidum. PARESIS is an abbreviation for Personality, Affect, Reflexes, Eye, Sensorium, Intellect, and Speech. These are the primary aspects of the disease, which exhibits a wide range of symptoms including cognitive impairment, behavioural changes, psychiatric features, as well as neurological signs such as dysarthria, myoclonus, intention tremors, seizures, hyperreflexia, and Argyll Robertson pupils.[8] This is corroborated by the most recent computed tomography of the brain results, which revealed brain atrophy. This is in line with the symptoms exhibited by the patient, including personality changes and delusions. Magnetic resonance imaging and computed tomography scans help identify causes of neurodegenerative dementia. Comprehensive cognitive evaluation would be necessary as well. Neurosyphilis should be considered even in human immunodeficiency virus negative heterosexual individuals when they experience rapid progressive dementia or any atypical form of dementia.[8]

Usually in neurosyphilis there are small, isodense focal nodules near the meninges which suggest the presence of syphilitic gummas. Syphilitic gummas usually appear as tiny nodules next to the meninges that have the same density as surrounding tissues on computed tomography scans. On magnetic resonance imaging scan, the objects appear dark on T1-weighted pictures, bright on T2-weighted images, and show a strong signal indicating movement on diffusion-weighted imaging. In addition, they exhibit homogeneous contrast enhancement on T1-weighted magnetic resonance imaging or contrast-enhanced computed tomography images.[9] Based on computed tomography scan findings in this case, it also suggest a differential diagnosis of frontotemporal dementia, as the bacteria has a predilection towards the frontal and temporal lobes.[10]

The existence of Argyll Robertson pupils is a diagnostic sign for neurosyphilis. In this instance, the detection of Argyll Robertson pupils redirected the diagnostic attention from other psychiatric and inflammatory diseases to an underlying infectious disease. This emphasizes the importance of comprehensive neuropsychiatric and ocular evaluations in individuals exhibiting atypical psychiatric symptoms, as ocular manifestations may offer essential diagnostic insights.

CONCLUSION

This case study emphasizes the importance of conducting thorough neuropsychiatric assessments and investigating viral causes in patients with unusual psychiatric symptoms. Argyll Robertson pupils are an important diagnostic sign for tertiary neurosyphilis, highlighting the importance for medical practitioners to be attentive in identifying these pathognomic signs which might guide the diagnostic workup and swiftly starting the necessary treatment.

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DECLARATION

The authors declare no conflicts of interest related to this publication.

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ANCA- associated vasculitis with pulmonary-renal syndrome in the elderly: A case report and review

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SUMMARY

We present a case of a 67-year-old Chinese male who presented with acute kidney injury and nephrotic syndrome. The patient subsequently developed pulmonary hemorrhage, and his serum myeloperoxidase and proteinase 3 tests were positive, indicating ANCA-associated vasculitis. Due to the rapid progression of his clinical condition, treatment was initiated with plasma exchange and intravenous immunoglobulin, alongside induction therapy with high-dose glucocorticoids. Renal biopsy was not performed due to multiple challenges. During his two-month hospital stay, the patient required hemodialysis at least twice a week and received standard treatment of care. Despite the aggressive treatment approach, the patient continued to exhibit signs of renal insufficiency, necessitating ongoing supportive care and monitoring.

INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) represents a group of rare, potentially life-threatening autoimmune diseases characterized by inflammation and destruction of small to medium-sized blood vessels. The primary subtypes of AAV include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). These conditions are hallmarked by the presence of ANCA, which target components of neutrophil cytoplasm, most commonly myeloperoxidase (MPO) and proteinase 3 (PR3).[1]

In elderly patients, AAV presents unique challenges. The pathogenesis remains complex and multifactorial, involving genetic predisposition, environmental factors, and dysregulation of the immune system. Clinical manifestations in this population can be particularly diverse and may be confounded by age-related comorbidities. Symptoms can range from mild manifestations such as fatigue and arthralgia to severe, life-threatening conditions like rapidly progressive glomerulonephritis and pulmonary haemorrhage. Moreover, the elderly are more susceptible to the adverse effects of immunosuppressive therapy, complicating treatment strategies.

This case report aims to present a detailed account of an elderly patient diagnosed with ANCA vasculitis, highlighting the clinical presentation, diagnostic challenges, therapeutic interventions, and outcomes. Through this case, we seek to contribute to the growing body of literature on AAV in the elderly and underscore the importance of a tailored, multidisciplinary approach in the management of this complex disease in older adults.

CASE PRESENTATION

A 67-year-old Chinese man with no prior medical history or known drug allergies presented with a one-month history of frothy urine, increased frequency of micturition, incomplete voiding, epigastric discomfort, and intermittent bilateral lower limb cramping. He had been using traditional medicine for abdominal discomfort during this period. He denied dysuria, haematuria, fever, joint pain, malar rash, oral ulcers, skin rash, sore throat, cough, altered bowel habits and no constitutional symptoms. He is a non-smoker and does not consume alcohol. He weighed about 66 kg.

His investigations during his early admission is tabulated on Table I.

Urinalysis showed proteinuria (3+) and haematuria (3+). Renal ultrasound showed mild right hydronephrosis without evidence of calculi. He was managed as acute kidney injury (AKI) with nephrotic syndrome and started on intravenous hydrocortisone 50 mg three times a day as we were cautious in view of his age together with his anaemia and complaint of epigastric discomfort. Additional workups for glomerulonephritis were sent, including C3, C4, serum electrophoresis, urine free light chain, serum ANA, serum ANCA, serum PLA2R antibody, and serum anti-GBM came back negative. On May 21, 2024, he had a two-hour haemodialysis via the right internal jugular catheter (IJC) in preparation for renal biopsy.

Unfortunately, his condition deteriorated with the development of fever, desaturation, and significant haemoptysis. He was electively intubated for airway protection and urgent CTA of the thorax revealed diffuse pulmonary haemorrhage (see Figure 1). Biochemical investigations showed positive ANA (titre 1:160, speckled pattern), MPO (titre >221.94 IU/ml), and PR3 (titre 23.5 IU/ml). He was treated for ANCA-associated vasculitis with pulmonary and renal involvement, hence underwent seven sessions of plasma exchange with fresh frozen plasma as the

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Table I: Investigations during early admission

	10 Nov 2022	9 May 2024	10 May 2024
Haemoglobin (12-15 g/dL)		7.1	
Urea (3.5- 8.5 mmol/L)	3.4	25.4	25.5
Sodium (136-145 mmol/L)	137	137	137
Potassium (3.5-5.1 mmol/L)	3.9	4.3	4.0
Creatinine (62-115µmol)	84	527	560
Albumin (32-48 g/L)		30	
Total Cholesterol (<5.2 mmol/L)		5.8	
Calcium (2.18-2.6 mmol/L)		1.82	
Phosphate (0.78-1.65 mmol/L)		0.75	
24-hour urine PCR (<15 mg/mmol)		284.21	
Random blood sugar (<6.7 mmol/L)		5.1	

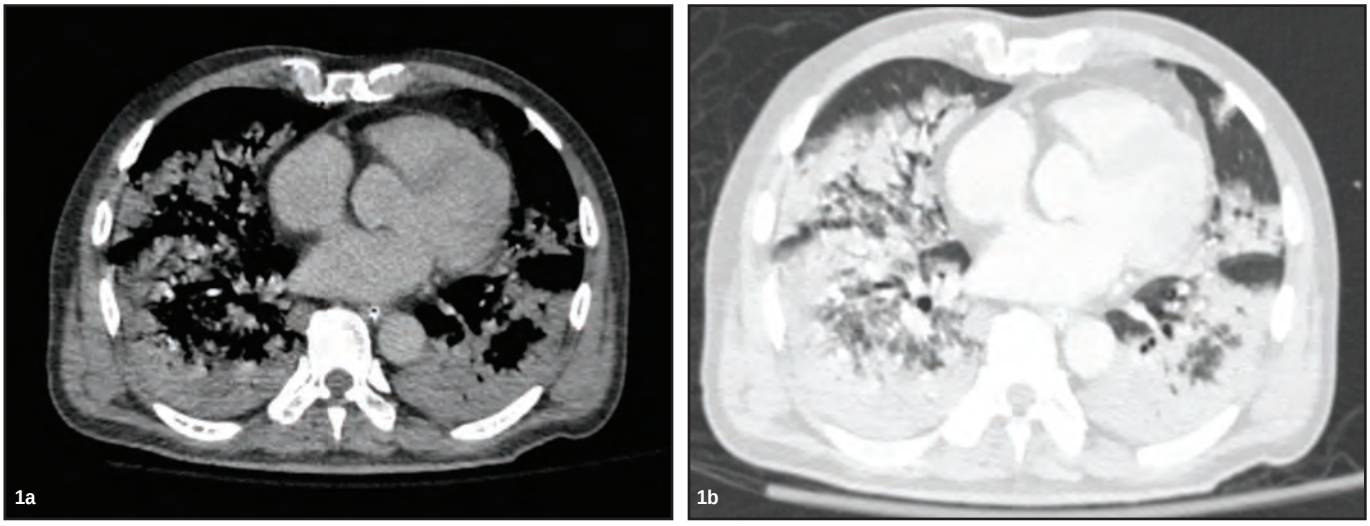

Fig. 1: CTA Thorax; axial images in soft tissue window (1a) and lung window (1b) respectively showed diffuse consolidative changes at both lung fields, predominantly at the dependent aspect associated with surrounding ground glass changes, likely to represent diffuse pulmonary haemorrhages in this case. Other differential diagnosis could be diffuse pulmonary infection / diffuse pneumonia No evidence of active bleeding (not shown in these images).

replacement fluid. He was also given 0.4 mg/kg intravenous immunoglobulin (IVIG) for five days and had his intravenous hydrocortisone increased to 100 mg three times a day. His stay in ICU was complicated with Methicillin-Resistant Staphylococcus Aureus (MRSA) bacteraemia, needing his IJC was removed, and a 14-day course of intravenous vancomycin. He showed clinical improvement and was extubated after 5 days.

Despite clinical improvement and good urine output of 1L-1.2L per day, his renal profile did not show much improvement. His urea ranged between 25-51 mmol/L, and creatinine persisted between 420-600 µmol/L, with blood gases showing mild metabolic acidosis (pH 7.34, HCO3 17.3 mmol/L). A renal biopsy was again planned but due to anaemia (haemoglobin ranging 6.5-7.9 g/dL) and thrombocytopenia (platelet range 90-100 x 10^9/L), this was not done. Full blood picture was sent showing functional iron deficiency anaemia with peripheral platelet consumption. Not only that, he went to develop frank haematuria needing bladder irrigation. There was positive leukocyte and nitrite in his urine analysis but negative urine cultures. A repeat ultrasound of the kidneys showed similar findings to previous imaging, and a subsequent CT urogram revealed a right ureteric calculus measuring 0.8 cm x 0.8 cm x 0.9 cm, causing mild right obstructive uropathy. He was empirically treated for a urinary tract infection , and an outpatient follow up was given for his ureteric stone.

Despite his 54-day-long stay with little improvement in his renal function, the renal biopsy was not performed as it was deemed too risky. He was then referred to rheumatology for extra-renal treatment for his AAV. Using the protocol as per EULAR guidelines, induction treatment was initiated: two-weekly cyclophosphamide for three cycles, followed by three-weekly for three cycles 2. Considering his previous history of severe infection, the initial cyclophosphamide dose was reduced by 30%, using a dose of 8.75 mg/kg. Full actual dose of 10 mg/kg was planned for subsequent cycles if he did not show any signs of infection. However, despite two cycles of induction treatment, his renal profile remained static with no improvement. His urea maintained 25-35 mmol/L and his creatinine between 450-600 µmol/L. Given this static trend, he was counselled for long-term renal replacement therapy, and he opted for haemodialysis. Upon discharge, he was planned for another four cycles of cyclophosphamide on an outpatient basis with weekly pre-haemodialysis blood monitoring. He was discharged with oral prednisolone at a dose of 1 mg/kg, with plans to taper the dose accordingly, and continued twice-weekly haemodialysis.

DISCUSSION

AAV represents a group of rare, potentially life-threatening autoimmune diseases characterized by inflammation and destruction of small to medium-sized blood vessels.[1,3,7] The kidney lesion associated with these conditions is pauci-immune, focal and segmental necrotizing crescentic glomerulonephritis (NCGN).[1] A severe manifestation of AAV is pulmonary-renal syndrome, which involves concurrent pulmonary hemorrhage and glomerulonephritis. This condition presents unique challenges in the elderly due to age-related comorbidities, altered immune responses, and potential treatment complications.[6]

The incidence of AAV increases with age, peaking in the seventh decade of life.[1,3] Elderly patients often exhibit a different ANCA profile compared to younger individuals, with a higher prevalence of MPO-ANCA positivity.[2,7] The pathogenesis involves autoantibodies targeting neutrophil components, leading to neutrophil activation, endothelial damage, and subsequent inflammation in various organs, predominantly the kidneys and lungs.[9]

In elderly patients, the clinical presentation of pulmonary-renal syndrome can be atypical and nonspecific, often delaying diagnosis. Common symptoms of renal involvement include haematuria, proteinuria, and rapidly progressive glomerulonephritis, often leading to renal insufficiency. Pulmonary involvement can include alveolar hemorrhage, presenting as hemoptysis, dyspnea, and diffuse alveolar infiltrates on imaging. Systemic symptoms such as fever, weight loss, and arthralgias are also frequent but may be attributed to other age-related conditions, complicating the clinical picture.[1,5,8]

Diagnosing AAV with pulmonary-renal syndrome in the elderly requires a high index of suspicion and a thorough workup. Laboratory tests often reveal elevated serum creatinine, active urinary sediment with red blood cell casts, and positive ANCA testing.[2] Imaging studies, such as chest radiographs or CT scans, may show diffuse pulmonary infiltration or ground-glass opacities suggestive of alveolar haemorrhage such as this patient. Renal biopsy is the gold standard for diagnosis as it is important for both the primary diagnosis and recurrent disease. However, in some patients, such as the one discussed, renal biopsy may not be feasible due to underlying issues such as anemia and thrombocytopenia, the presence of ureteric stone and its reason for hematuria. Furthermore, in the context of positive MPO or PR3-ANCA serology and clinical features compatible with small vessel vasculitis, an immediate biopsy may not be necessary and should not delay the initiation of treatment.[2]

Managing AAV with pulmonary-renal syndrome in the elderly involves balancing effective disease control with minimizing treatment-related adverse effects. The mainstays of therapy include induction therapy with high-dose corticosteroids combined with cyclophosphamide or rituximab to achieve remission.[1,2] The choice of agent depends on patient comorbidities and overall health status. Following induction therapy, maintenance therapy involves low-dose corticosteroids with azathioprine or rituximab to maintain remission and prevent relapses. Supportive management includes temporary hemodialysis in severe kidney involvement, plasma exchange for patients with rapidly increasing serum creatinine and those with diffuse alveolar hemorrhage who have hypoxemia, management of comorbid conditions, monitoring for infections, and addressing treatment-related complications such as osteoporosis or diabetes.[1,2,5-6]

The prognosis of elderly patients with AAV and pulmonary-renal syndrome is generally poorer compared to younger patients, primarily due to delayed diagnosis, treatment toxicity, and underlying comorbidities. However, the prognosis improves with immunosuppressive treatment.2,4 Atypical presentation and overlapping symptoms with other geriatric conditions can delay diagnosis and initiation of appropriate therapy. Furthermore, elderly patients are more susceptible to adverse effects of immunosuppressive therapy, requiring careful monitoring and dose adjustments.6 The presence of other chronic diseases can complicate management and worsen outcomes.[1,6] For the patient discussed, the diagnosis was fully established upon developing pulmonary hemorrhage and positive serum MPO/PR3 results. He was treated with plasma exchange and IVIG, but his condition was complicated by MRSA bacteremia, urinary tract infection and haematuria. His induction therapy was delayed due to infection and plans for renal biopsy, which ultimately could not be performed due to multiple challenges.

CONCLUSION

ANCA-associated vasculitis with pulmonary-renal syndrome in the elderly is a complex and challenging condition requiring a multidisciplinary approach for optimal management. Early recognition, appropriate therapeutic strategies, and vigilant monitoring for complications are crucial to improve outcomes in this vulnerable population. Further research is needed to develop age-specific treatment protocols and improve the quality of life for elderly patients with AAV.

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DECLARATION

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How to get out of jail: An endovascular approach to a mal-positioned central venous dialysis catheter from left subclavian artery to left ventricle

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SUMMARY

Iatrogenic vascular injuries during central venous dialysis catheter insertion can lead on to significant morbidity and mortality. The emergence of endovascular intervention has revolutionized the treatment and outcome of such injuries. Here we present a case of mal-positioned dialysis catheter inserted in the left subclavian artery and tracked into the left ventricle managed by concurrent removal and deployment of endovascular balloon expandable covered stent with minimal blood loss and good recovery.

INTRODUCTION

Haemodialysis is the most common mode of renal replacement therapy in patients with end-stage renal disease (ESRD). The ideal haemodialysis access is one that provides reliable, minimal complication access for dialysis. Native arteriovenous fistula (AVF) is the first choice of access as they are associated with lower incidence of complications when compared to arteriovenous graft (AVG) and central venous catheter (CVC).[1-2] Central venous dialysis catheterization is a common procedure for attaining an urgent haemodialysis access.

NKF-KDOQI guidelines recommends the use of image-guided CVC insertions to improve success of insertions.[3] The main complications include haematoma and inadvertent arterial puncture, with the incidence of 4-35%. Injuries involving the arterial system secondary to the procedure are known to be catastrophic and increase morbidity and mortality. Endovascular intervention for iatrogenic subclavian arterial injury is emerging as the preferred option, as opposed to open repair, as it is minimally invasive.[4] Here we present a case of one of the major complications associated with central venous catheterization and an effective non-surgical endovascular approach to mitigate it.

CASE PRESENTATION

A 62-year-old female, with established renal disease presented to the emergency department for severe sepsis with altered mental status secondary to catheter related blood stream infection (CRBSI) from an indwelling left internal jugular catheter. She has long standing hypertension and diabetes mellitus with target organ damage. She has had multiple native AVFs created- which subsequently failed, resulting in long-term usage of a CVC.

In view of the CRBSI, the infected catheter was removed for 2 days and a new 12 F catheter was inserted through a new route at the left internal jugular vein. However, this resulted in an unintentional mal-positioning of the catheter, with chest x-ray suggested the tip of catheter to be in the left ventricle (Figure 1). The patient was then, referred to the vascular team.

Computed tomography angiogram revealed the placement of the catheter into the left subclavian artery (LSA) and directed to the aortic valve into the left ventricle (Figure 1). It was also noted that she had an aberrant left vertebral artery-which arose from the aortic arch(Figure 1). The catheter was left in-situ and the patient was prepared for intervention.

Emergent concurrent removal and endovascular stenting of the LSA were performed, as opposed to open surgical repair. Left brachial and left common femoral access were obtained percutaneously under ultrasound guidance for stenting and angiography respectively. A 8x57mm balloon expandable stent covered stent (BE Graft, Bentley) was inserted in place over a Rosen wire protected by a 6F 45cm sheath via the left brachial access(Figure 2). Upon pull back of sheath to expose the stent, the dialysis catheter was removed with immediate deployment of the stent (Figure 2). Final angiography revealed no extravasation of contrast(Figure 2) and the patient showed good recovery with good left upper limb perfusion and no neurological complication.

DISCUSSION

Insertion of a central venous catheter for dialysis access is commonly carried out in our region. It is recommended that central venous catheterization to be performed under safe ultrasound guidance. However, depending at the facility, an ultrasound machine is not always readily available and there may also be inadequate competence in ultrasound guided puncture. These may have led to incidences of inadvertent iatrogenic arterial injury to the great vessels of the arch. Traditionally, these patients would be referred to the cardio-thoracic team for an emergent retrieval of catheter and open repair of the artery. These procedures runs a high risk of

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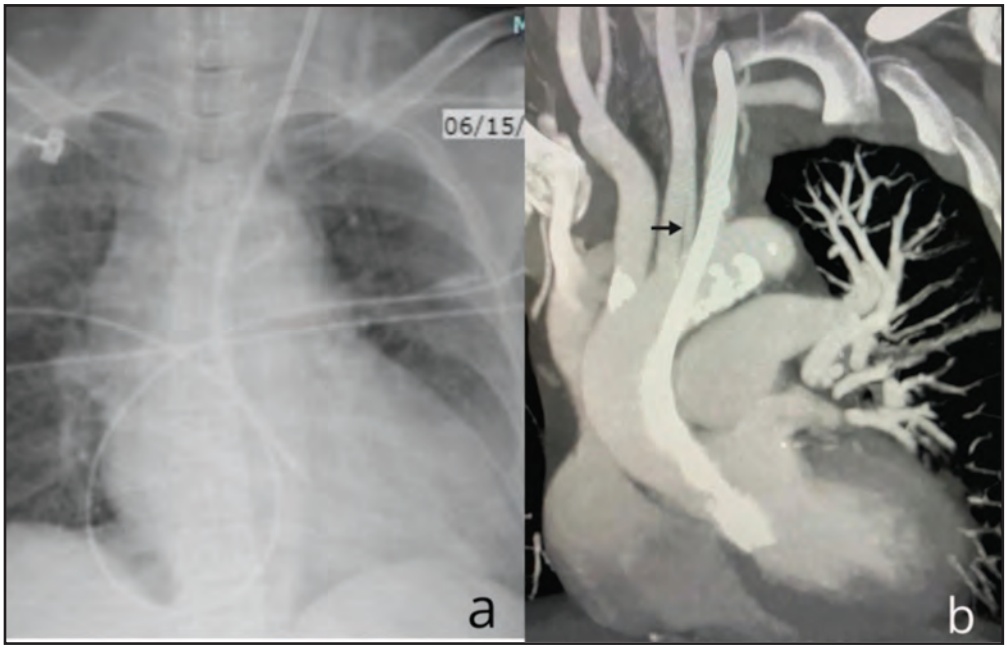

Fig. 1: Chest x-ray showing the course of CVC(a) and CTA showing CVC in left ventricle(b) with an aberrant left vertebral artery arising from arch of aorta(arrow)

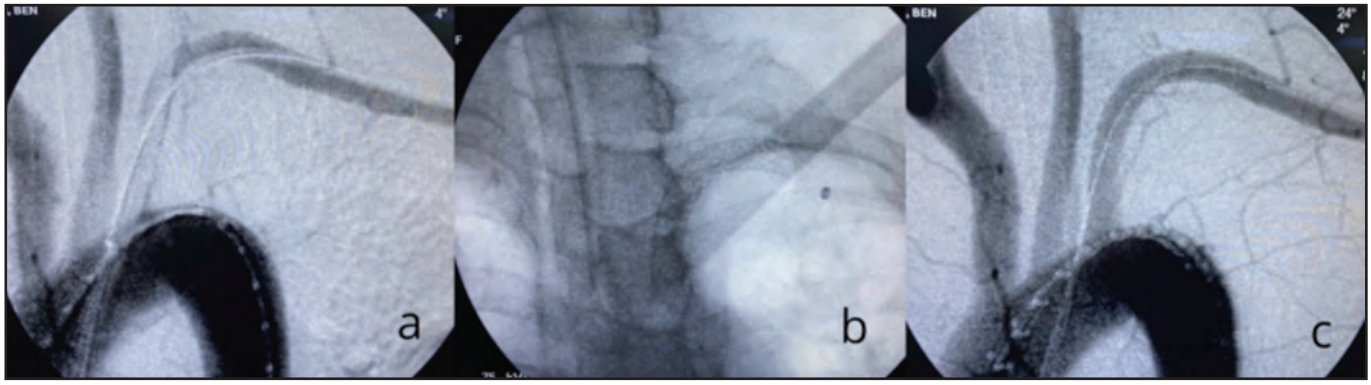

Fig. 2: Balloon expandable stent put in place with 6F sheath(a). Deployed 8mm balloon expandable stent(b) and completion angiogram(c)

morbidity especially in patients with end-stage renal disease and other co-morbidities due to the invasive operative access, long operative time and prolonged recovery. With the emergence and advancement of endovascular therapy, we now have the option of an endovascular repair of such iatrogenic injuries with good outcome.[4] Endovascular repair of this injury allows a shorter operative time and a faster recovery for the patient.

CONCLUSION

This case report describes the technical aspect and clinical decision in managing an arterial injury related to central venous haemodialysis catheter- allowing in a relatively bloodless and complication-free procedure.

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DECLARATION

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Hemihysterectomy as management of ruptured cornual pregnancy in a bicornuate uterus

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SUMMARY

A bicornuate uterus arises from incomplete fusion of the two Müllerian ducts during embryogenesis, predisposing to adverse pregnancy outcomes. Rupture of the gravid horn in a bicornuate uterus is rare yet life-threatening. A high index of suspicion among clinicians is paramount for timely detection and management of this condition. We present a case of a 34-year-old woman, gravida 3, para 1+1 at 18 weeks gestation presented with severe abdominal pain and hypovolemic shock. Emergency laparotomy confirmed rupture of the right horn in a bicornuate uterus, resulting in expulsion of the foetus and placenta. A hemihysterectomy of the gravid right horn was performed, while preserving the intact left horn. The patient was discharged home three days following surgery.

INTRODUCTION

Failure of the Müllerian ducts to fuse completely during embryogenesis resulted in a range of uterine structural abnormalities, which can be symmetrical or asymmetrical. Examples of uterine anomalies include the didelphic uterus, bicornuate uterus, septate uterus, arcuate uterus, and uterus with rudimentary horns. Often at times, these anomalies remain undetected until difficulties arise, such as infertility, repeated miscarriages, or its discovery during an early prenatal ultrasound screening or during abdominal surgery. Our patient had a successful term pregnancy 15 years ago, and her current pregnancy had advanced to 18 weeks before a complication of uterine rupture happened. Pregnancy in a bicornuate uterus poses a risk of uterine rupture; even though the risk is small, it can potentially be fatal. Surgery is the mainstay treatment in managing the ruptured cornual of a bicornuate pregnancy, and hemihysterectomy was performed to remove the ruptured horn.

CASE PRESENTATION

A 34-year-old woman, G3P1+1 at 18 weeks gestation, was referred to our hospital due to severe abdominal pain persisting for one day and a history of presyncope. There was no reported vaginal bleeding, gastrointestinal symptoms, or trauma to her abdomen. The patient had a successful term pregnancy 15 years ago, delivered via caesarean section due to breech presentation, and experienced a miscarriage 13 years ago. The current pregnancy was spontaneously conceived, and she attended regular antenatal care from 8 weeks gestation. An early ultrasound examination revealed a suspicious mass adjacent to the gestational sac, initially thought to be a fibroid (Figure 1).

Upon presentation to the Emergency Department, the patient exhibited severe pain, pallor, and signs of hypovolemic shock, including a heart rate of 140 and a blood pressure of 90/60 mmHg. Her abdomen was tense with diffuse tenderness and guarding. Speculum examination revealed a single cervix with no evidence of vaginal bleeding or septum. Ultrasound examination confirmed a viable foetus consistent with 18 weeks of gestation but also showed a discontinuity of the uterine lining and massive free fluid up to Morrison's pouch, raising suspicion of uterine rupture. A diagnosis of hypovolemic shock secondary to suspected uterine rupture was promptly made, and the patient was expediently taken to the operating theatre.

Intraoperatively, 2 litres of hemoperitoneum were drained. The uterus appeared to be bicornuate, with both horns having similar dimensions and connected cavities. Each horn was connected to normal ipsilateral Fallopian tube and Ovary. The right gravid horn had ruptured, resulting in both the foetus and placenta expelled out of the uterus. To reduce the bleeding, clamps were applied between the two horns and the right uterine pedicle. It was decided to preserve the intact left horn and proceed with hemihysterectomy of the right horn. The ruptured right horn was separated medially by dissecting the attachment between the two horns which was clamped earlier, followed by suturing the connection with Vicryl 1. Laterally, the right horn was detached by dissection of the right round ligament. Retroperitoneal space was opened to identify the ureter and the blood vessels. The right ovarian ligament was dissected preserving the right ovary. The parametrium was dissected along the uterine horn and the right uterine artery was dissected and ligated with Vicryl 1. The uterovesical fold was separated and the bladder was gently displaced. The inferior attachment of the right horn was detached by placing a straight clamp horizontally above the cervix and cutting above it. The areas were sutured with Vicryl 1.

The patient received a massive blood transfusion, including a disseminated intravascular coagulation (DIC) regimen. Postoperatively, she exhibited rapid recovery and was discharged home after 3 days. She was counselled for long-acting reversible contraception and advised for caesarean section in the future pregnancies.

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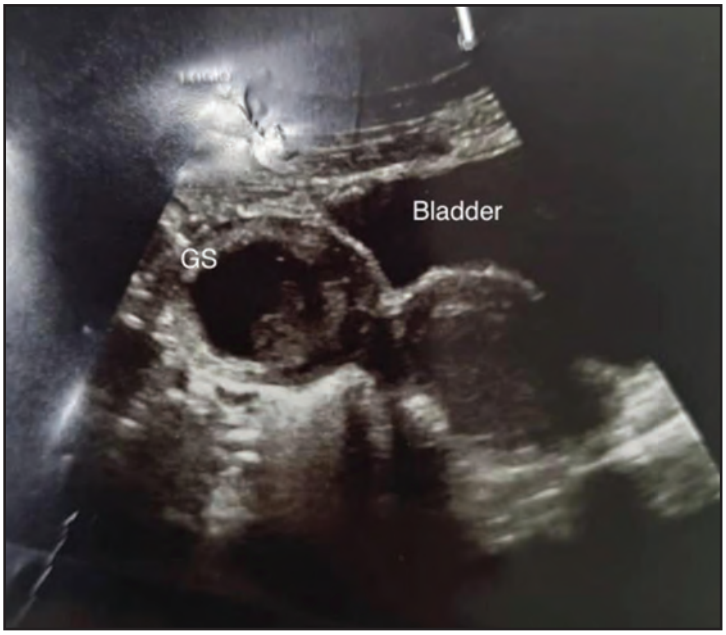

Fig. 1: First ultrasound report showing the gestational sac (GS) and the uterus which was mistakenly thought as fibroid

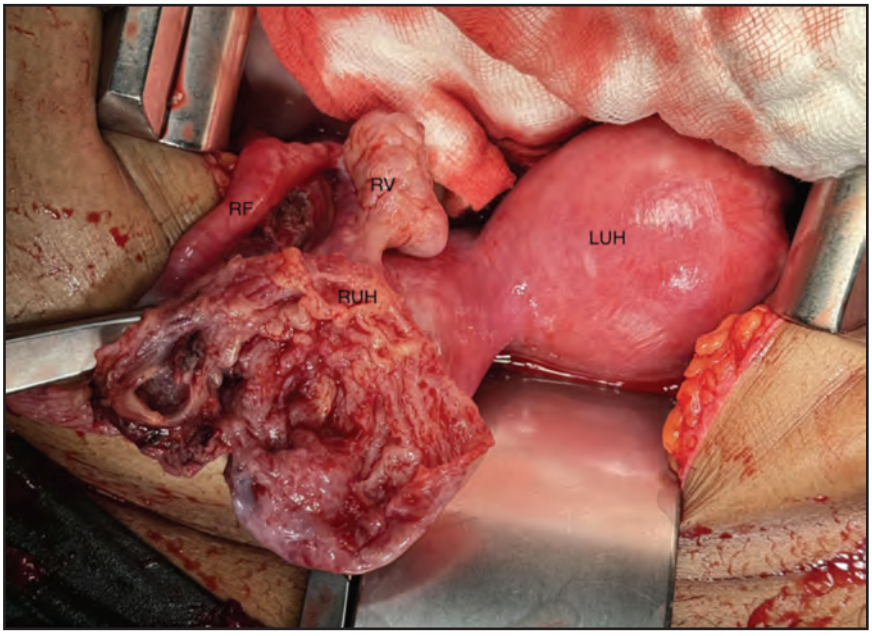

Fig. 2: Right uterine horn (RUH), Right Ovary (RV), Right Fallopian Tube (RF) and Left Uterine Horn (LUH)

DISCUSSION

Pregnancy with Müllerian anomalies are rare but can impose a significant danger to women's life. The frequency of major structural anomalies of the uterus in the general population is difficult to determine with certainty but it is estimated that the prevalence is 4 in 1000.[1] Bicornuate uterus is an anomaly caused by incomplete fusion of the two Müllerian ducts during embryogenesis and it is characterised by two separate but communicating endometrial cavities and a single uterine cervix. Failed fusion may extend to the cervix, resulting in a complete bicornuate uterus, or may be partial, causing a milder abnormality.[2] This patient has a partial bicornuate uterus and each uterus has a horn which is connected to ipsilateral Fallopian tube and ovary. The cavities of the two horns are connected and based on ESHRE/ESGE classification of female genital tract congenital anomalies, this patient is classified as V0C0U3c.[3]

Live birth rate of pregnancy in the bicornuate uterus is approximately 60% and this is evident in this patient as she had a successful term pregnancy 15 years ago. However, this condition also predisposes women to adverse pregnancy outcome such as early pregnancy loss, preterm labour, malpresentation and rarely uterine rupture.[2,4] The abnormal

uterine horn failed to expand as the pregnancy advances due to uneven thickness in the myometrium and abnormal placentation. Therefore, rarely the pregnancy can go beyond the second trimester before rupturing.[5] Ultrasound features of a cornual pregnancy will show an empty uterus with laterally located gestational sac surrounded by thin myometrium but in tubal pregnancy, the ring of myometrium will be absent.[6] Tsafrir et al. suggested the following criteria for diagnosing a pregnancy in the rudimentary horn: (1) a pseudo pattern of asymmetrical bicornuate uterus; (2) absent visual continuity between the cervical canal and the lumen of the pregnant horn, and (3) the presence of myometrial tissue surrounding the gestational sac.[6] In this case, there is no continuity of the uterine cavity containing the gestational sac and the cervix and the left horn was wrongly identified as fibroid.

The mainstay of management strategy for a ruptured cornual pregnancy is excision of the rudimentary horn and repair of the defect. Cornual wedge resection is the most commonly used technique in unicornuate uterus but in a bicornuate uterus, resection of the affected horn following the hysterectomy steps should be done. The reasons are because it significantly reduced bleeding and prevented future pregnancy in the abnormal uterine horn. A midtrimester rupture generally occurs at the fundus as opposed to lower-segment rupture during labour hence causing a more massive haemorrhage.[7] Hemihysterectomy of the affected horn can be performed via laparotomy or laparoscopic approach. In this case, laparotomy was chosen due to the patient's hemodynamic instability. The steps are similar to the standard hysterectomy procedure. The defect on the unaffected horn should be closed in two layers. Ravasia et al has reported the incidence of uterine rupture significantly increased in women with Müllerian anomalies who attempted vaginal birth after caesarean section in comparison to women with normal uterus, 8% and 0.6% respectively.[8] In this case, the patient had uterine rupture and history of previous caesarean section making her risk of uterine rupture in future pregnancy much higher. It would be wise to avoid pregnancy for at least a year and provide her with reliable contraception. The patient should be properly counselled regarding the risks involved if she decides to embark on another pregnancy.

CONCLUSION

Both horns of the bicornuate uterus may exhibit differing levels of myometrial strength and distensibility. Implantation of pregnancy in the abnormal, weaker horn can lead to a catastrophic consequence. Performing a hemihysterectomy on the aberrant horn is advised to prevent the occurrence of future pregnancies in the same location.

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DECLARATION

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CASE REPORT

Neurolisteriosis in an immunocompromised patient

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SUMMARY

Neurolisteriosis is a rare but severe manifestation of Listeria monocytogenes infection, particularly affecting immunocompromised individuals. We present the case of a 33 year-old female with systemic lupus erythematosus (SLE) who developed left-sided hemiparesis with pneumonia. Despite initial treatment with antibiotics and corticosteroids, her condition worsened, requiring neurosurgical intervention. Brain biopsy revealed Listeria monocytogenes, confirming the diagnosis of neurolisteriosis. She received prolonged antibiotic therapy and supportive care, leading to clinical improvement. This case highlights the challenges in diagnosing and managing neurolisteriosis in immunocompromised patients and underscores the importance of early recognition and intervention for optimal outcomes.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs. A dysregulated immune response, the severity of the disease, and immunomodulatory agents used significantly increase the susceptibility to infection in individuals with SLE.

CASE PRESENTATION

We describe a 33 years old lady with underlying SLE with Lupus Nephritis. She presented with worsening left-sided hemiparesis for 3 days, associated with fever and productive cough. Notably, her prednisolone was increased to 1mg/kg/day for a recent lupus nephritis flare, which increases her risk for opportunistic infection.

On examination, her Glasgow Coma Scale (GCS) was 15/15 with equal and reactive pupils. She was febrile but saturating well under room air. Neurologically, she had evidence of left hemiparesis with Medical Research Counsil (MRC) power of 4/5 over the upper limb and 3/5 over the lower limb, associated with increased muscle tone and hyperreflexia over the left upper and lower limbs, which progressed to dense hemiplegia within 2 weeks. Her sensation was intact throughout. Other systemic examination was unremarkable. She had no clinical features suggestive of active SLE.

Upon presentation, laboratory examination revealed raised WBC (13.5 x 10^3/UL) and CRP (23.2mg/L) with mild renal derangement (creatinine 124umol/L) .Other blood parameters were unremarkable. A contrasted CT brain revealed right frontal and posterior parietal enhancing hypodense lesions (4.7 × 2.3 x 5cm), causing mass effect to adjacent sulci with another small peripherally enhancing lesion seen at the right frontal region, 0.8 x 1cm.There was no abnormal leptomeningeal enhancement. Her MRI brain revealed multiple irregular peripherally enhancing intra-axial lesions with vasogenic oedema and mass effect.

She was started on intravenous (IV) Ceftriaxone 2gm BD for 4 days, then escalated to IV Meropenem 2gm TDS due to persistent fever. She was also started on dexamethasone to reduce the mass effect. Lumbar puncture was contraindicated in view of serial imaging showing lesions causing mass effect.

She was intubated for airway protection after 2 weeks of admission in view of drop in GCS (E2V1M1). A repeated CT brain showed worsening white matter oedema at right frontal and posterior parietal lobe, with worsening hypodensity at right basal ganglia with increasing mass effect which have contributed to her drop in GCS. She had no documented seizure.

A right decompressive craniectomy, image-guided stereotactic biopsy and fasciduroplasty was done on her. Intra-operatively, the dura was thinned out with clear, high-pressure cerebrospinal fluid (CSF). Brain biopsy HPE revealed rod-shaped bacterial colonies consistent with Listeria monocytogenes, which was also identified from the CSF cultures and blood cultures done via conventional method.

She was given IV Ampicillin 2gm 4 hourly for a total of 6 weeks. Dexamethasone was tapered off and maintenance IV Hydrocortisone was given to control her SLE. A repeated CT brain after 6 weeks of antibiotic showed resolving right frontal and posterior parietal lesions. Upon discharge, she was bedbound with improving left hemiparesis (MRC power 2/5) and full GCS level.

A repeated CT brain 6 months later showed reduced hypodensity over right frontal and parietal vasogenic oedema with no significant enhancement suggestive of residual vasogenic oedema.

DISCUSSION

Neurolisteriosis is an uncommon but severe manifestation of Listeriosis, caused by the bacterium Listeria monocytogenes.1 Listeria monocytogenes is prevalent in the environment, with a widespread presence in soil, water and the digestive tracts

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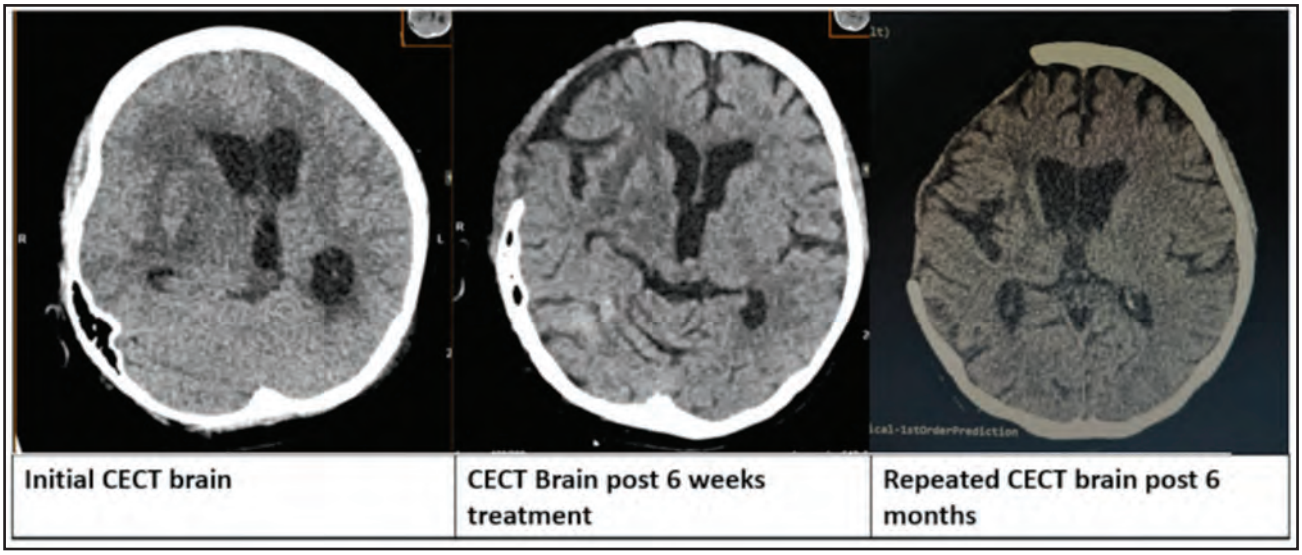

Fig. 1: Serial Contrasted Enhanced CT Brain.

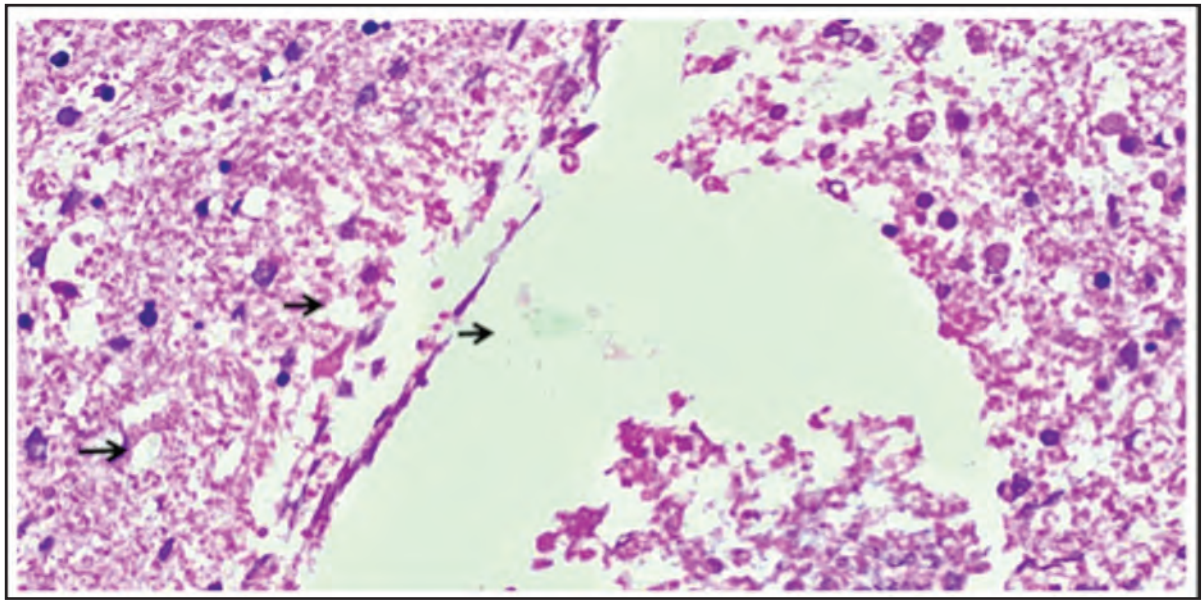

Fig. 2: Multiple foci of rod-shaped bacterial colonies are seen within the glial tissue (black arrow) from the brain tissue biopsy.(Images provided by Pathologist- in- charge Dr Ang Yee Ping (Anatomic Pathologist)).

of animals. Contamination of vegetables can occur through contact with contaminated soil or the application of manure as a fertilizer.[1] Moreover, ready-to-eat foods are susceptible to contamination at the processing stage, and the bacteria have the potential to proliferate to hazardous levels during both distribution and storage.[1]

In contrast to numerous other prevalent foodborne bacteria, L. monocytogenes exhibits the ability to endure and replicate at the low temperatures typically present in refrigerators.[1] Consuming contaminated food with high numbers of L. monocytogenes is the main route of infection.[1] There are two types of infection: non-invasive, like febrile enteritis, and the invasive type that usually affects immunocompromised patients, pregnant women and their newborns.[2] While listeriosis typically manifests as a foodborne illness with symptoms like fever, muscle aches, and gastrointestinal issues, neurolisteriosis specifically involves the central nervous system, leading to neurological symptoms.[3]

Neurolisteriosis typically manifests in three forms: meningitis/meningoencephalitis, rhombencephalitis, and cerebritis, often progressing to the development of cerebral abscesses.[4] The examination of cerebrospinal fluid yields limited information and exhibiting a low success rate in isolating the pathogen through fluid cultures. Listeria is more frequently detected in blood culture.[2] For assessment of lesions and accurately evaluate the extent of the disease, as well as to monitor treatment, a cranial magnetic resonance imaging (C-MRI) should be conducted.[2]

Treatment for Neurolisteriosis is Ampicillin 2g IV every 4 hours (or penicillin G 4 million units IV every 4 hours) with or without gentamicin 5mg/kg/day IV in three divided doses for a duration of at least 1 week.[5]

However, close monitoring of renal function is essential when using gentamicin. It is advised to avoid the use of dexamethasone due to its association with worse outcomes. For cerebral abscess, treatment duration of 4-6 weeks is recommended based on clinical response.[6]

CONCLUSION

This case report sheds light on the complexities and challenges associated with neurolisteriosis. Through the detailed analysis of the patient's presentation, diagnostic procedures, and treatment course, we emphasize the importance of early recognition and intervention in managing this rare but serious neurological infection especially in immunocompromised patients.

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The authors would like to thank the patient for agreeing to publish this case.

DECLARATION

The authors have no conflict of interest to disclose.

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CASE REPORT

Acute myocarditis with accelerated junctional rhythm and cardiogenic shock as a complication of influenza A (H1N1)

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SUMMARY

Respiratory infection is usually manifested as fever, cough, and sore throat, which are the common presentations to health care facilities. It is caused mainly by viruses such as influenza and parainfluenza viruses with seasonal epidemics. Most viral respiratory infections are mild in nature and only require supportive treatment with adequate hydration and rest. However, some may develop complications such as acute respiratory failure requiring ventilatory support and heart failure due to myocarditis and pericarditis. Acute viral myocarditis can manifest with different severity from subtle non-specific changes in the electrocardiogram to life-threatening cardiogenic shock. We report a case of influenza A infection in a young lady complicated with cardiogenic shock due to acute myocarditis with accelerated junctional rhythm and isorhythmic atrioventricular dissociation.

INTRODUCTION

Viral respiratory tract infection is one of the most common acute illnesses worldwide. It has a typical presentation of fever with respiratory symptoms such as cough, sore throat, and nasal discharge. The infection often follows a self-limiting course and can be treated outpatient with symptomatic relief such as adequate hydration and antipyretic medication. However, in some cases, the infection can be life-threatening leading to respiratory failure requiring mechanical ventilatory support as well as multiorgan failures resulting in cardiogenic shock, and severe renal and hepatic failures.

Cardiac complications in viral respiratory tract infections such as myocarditis and pericarditis are not uncommon, and may manifest as chest pain, dyspnoea, palpitation, or syncope. Apart from non-specific ST segment changes and pathological Q wave seen on an electrocardiogram in an acute myocarditis, ventricular tachyarrhythmias and conduction blocks are also commonly seen. Accelerated junctional rhythm is rare and seldomly reported in adult with acute viral myocarditis.[1-2]

CASE PRESENTATION

A 28-year-old woman presented with a 4-day duration of fever, productive cough with yellowish sputum, and diarrhoea. She has no notable past medical history, particularly no history of any cardiac disease. Her physical examination upon presentation revealed a clinically stable young woman with blood pressure of 112/68 mmHg, heart rate of 68 beats per minute, temperature of 36.8˚c, and oxygen saturation 98% on room air. Her systemic examinations were otherwise unremarkable. Her blood investigations showed a low C-reactive protein level of 0.6 mg/dL and leukopenia, lymphopenia, and mild thrombocytopenia of 2.62 $x10^9$/L, 0.79 $x10^9$/L, and 147 $x10^9$/L respectively. Other investigations including renal and liver function tests were unremarkable.

She was initially admitted to the ward for observation while waiting for further investigation. As she was living in the dengue endemic area and had probable dengue sign of fever, diarrhoea, and leukopenia, a dengue serology was tested which turned out to be negative. On the second day of admission, she developed an episode of dizziness and chest discomfort with a blood pressure of 80/52 mmHg and heart rate of 60 beats per minute. An electrocardiogram revealed an accelerated junctional rhythm with ST depressions over the lead II, III, and aVF (Figure 1). She required inotropic support with intravenous infusion of noradrenaline after a cautious fluid resuscitation. A serial high-sensitivity troponin I showed a significant rise in a three-hour-interval from 5.7 ng/L to 701.[3] ng/L. A nasopharyngeal swab later confirmed the diagnosis of influenza A viral infection with subtype H1N1/2009 complicated with acute viral myocarditis with accelerated junctional rhythm.

DISCUSSION

Influenza infection is an acute febrile illness of global importance due to its capability of causing a worldwide pandemic.[3] A seasonal influenza is able to cause up to five million infections per year, with an annual mortality rate of 300,000.[4] Its main routes of human transmission are via air droplets, aerosols, and contact transmission which often leads to upper respiratory tract infections manifested as acute febrile illness with respiratory symptoms of cough, sore throat and nasal discharge, and non-specific symptoms such as headache, myalgia, malaise, and anorexia.[5] In severe cases, influenza infections involve lower respiratory tract and manifest as pneumonia and acute bronchitis and can be complicated with extra-pulmonary manifestations such as acute renal and hepatic impairments, myocarditis, pericarditis, and other neurological disorders such as

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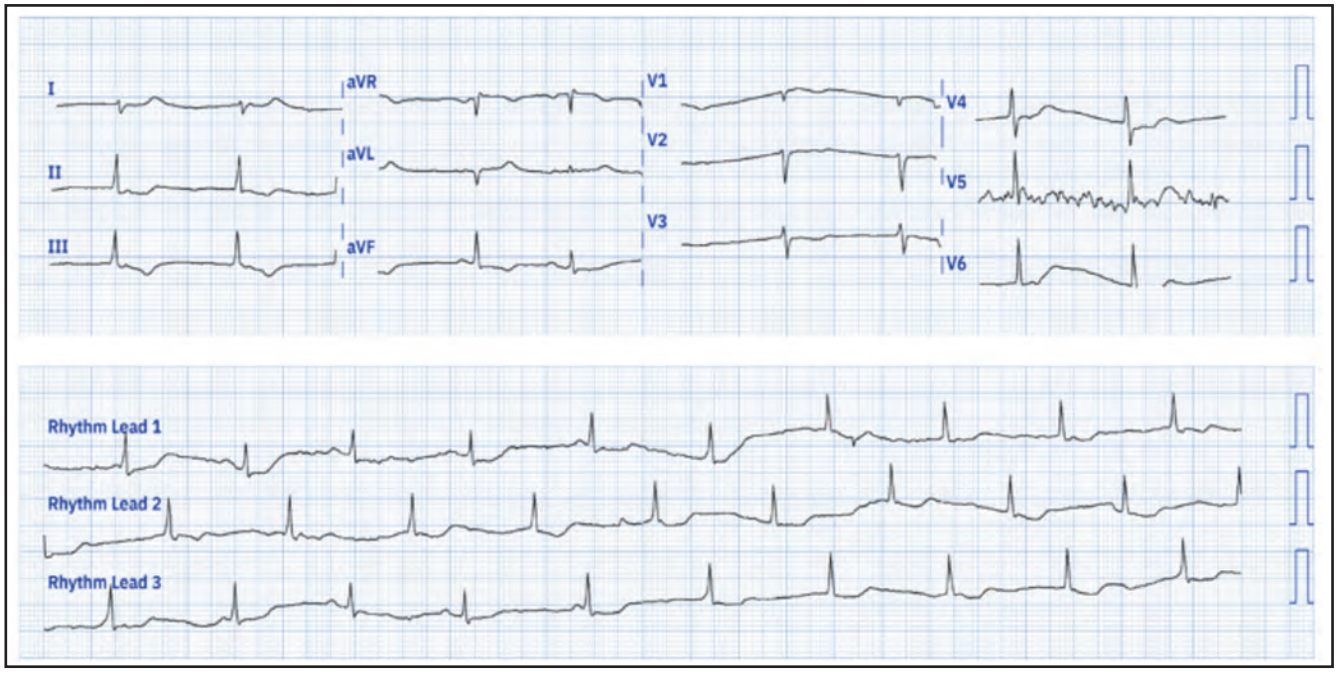

Fig. 1: Electrocardiogram showed atrioventricular dissociation with a ventricular rate of more than 60 beats per minute suggesting an accelerated junctional rhythm. There were ST segments depression in the inferior lead and T waves were flattened in most leads

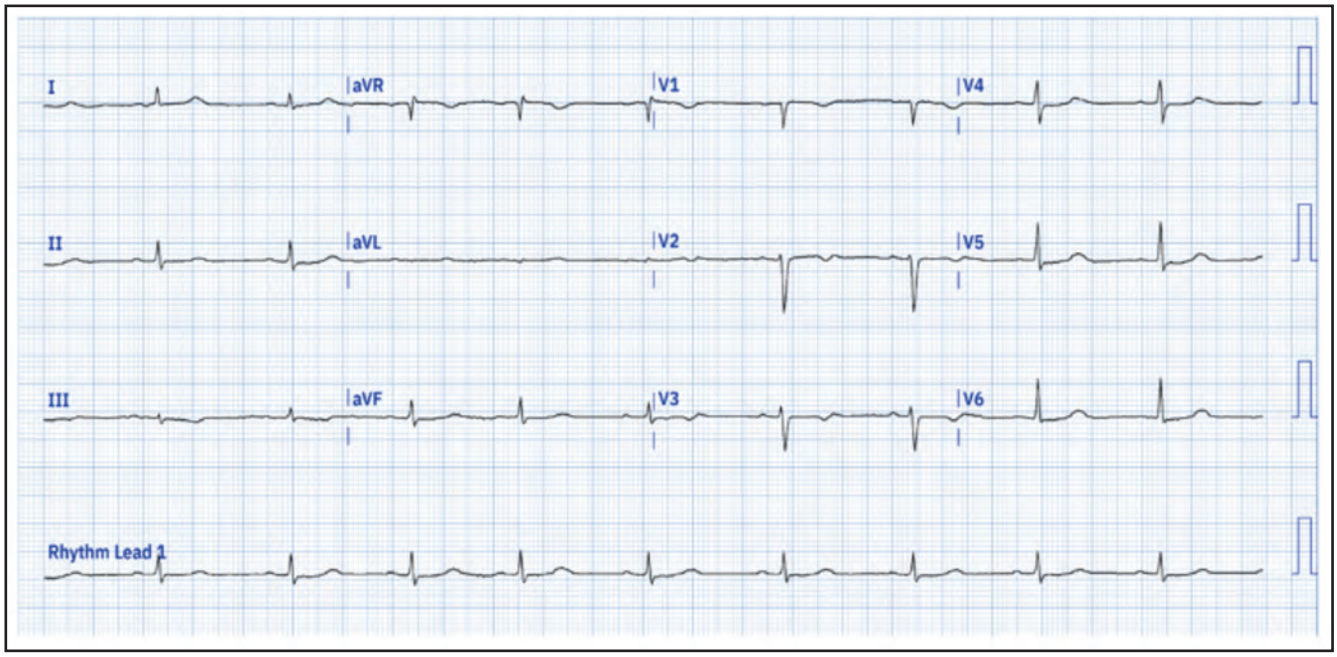

Fig. 2: Electrocardiogram showed reversion to sinus rhythm with non-specific ST segments and T waves changes

Guillain-Barre syndrome, transverse myelitis, and encephalomyelitis.[3]

Myocarditis is an inflammatory injury of the cardiac muscle, which can be caused by infections of different origins as well as non-infectious causes such as toxins, drugs, and autoimmune.6 Viral myocarditis remains the most common cause of myocarditis, predominantly due to picornaviruses such as Coxsackie A and B.[7] The exact mechanism of myocarditis due to viral infections remains uncertain but myocarditis resulted from influenza infections is postulated to be a result of immune-mediated myocardial injury.[8] Acute influenza-related myocarditis usually develops within first three days of symptoms of influenza in 51% of patients,[1] manifests with a range of severity from subtle asymptomatic non-specific changes in electrocardiogram to sudden cardiac death which accounts for approximately 10% of young patients below 35 years old.[9]

The diagnosis of myocarditis is difficult due to its heterogenous manifestations. Physical examination may reveal signs of cardiogenic shock or heart failure while electrocardiogram may show non-specific T-wave changes with elevated cardiac enzyme such as high sensitivity troponin I or T in approximately 64% of patients.[10] Accelerated junctional rhythm is reported in children and rarely reported in adults with acute myocarditis.[11] Echocardiography may reveal changes such as increased myocardial wall thickness and abnormal myocardial echogenicity. Nonetheless, left ventricular ejection fraction is preserved in approximately 75% of patients in early course of myocarditis, and may decline rapidly later.[10] The viral myocarditis in our case manifested as acute chest pain with dizziness due to accelerated junctional rhythm with cardiogenic shock, her echocardiography was normal with elevated cardiac enzyme and cardiac arrhythmia as the only positive findings in her investigations for myocarditis.

The majority of cases of acute myocarditis are mild and self-limiting, however some cases may be fulminant.[4] Treatment of myocarditis is mainly supportive, however, the association between myocarditis and viral infection suggests the potential benefits of antiviral strategies and antiviral vaccines in the treatment of viral myocarditis.[12] Antiviral medications would be effective in the early stages of viral myocarditis, despite most adult patients present in the chronic phrases of disease.[6] High-dose steroids are not recommended due to unproven benefit and potential harmful effect on the infection.[1] Our case managed to recover in terms of resolution of cardiac arrhythmia and hemodynamic stabilization after a day of manifestation with supportive treatment without long-term sequel or complication.

CONCLUSION

Viral myocarditis is not an uncommon complication of viral infections. It can lead to hemodynamic instability and increase morbidity and mortality of viral infections. Accelerated junctional rhythm is rarely reported but can be a manifestation of cardiac arrhythmia in H1N1 myocarditis. Although the mainstay treatment of myocarditis is supportive, early recognition of the condition is crucial to ensure appropriate monitoring and support before its recovery.

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DECLARATION

The authors have no conflict of interest to disclose.

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CASE REPORT

SIADH caused by immature ovarian teratoma with gliomatosis peritonei: A case report

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INTRODUCTION

Immature ovarian teratoma causing SIADH with gliomatosis peritonei (GP) is a rare clinical entity. Immature ovarian teratoma comprises of less than 1% of all ovarian tumours and is made of all 3 germ cell layers (ectoderm, endoderm and mesoderm). This is the only tumour that is graded according to immature neural elements and determines the prognosis as well as treatment plan. GP is defined as benign peritoneal deposits of matured glial tissues. SIADH is a constellation of hyponatremia, hypotonicity and increased sodium loss in the urine. We report a case of a 30-year-old female with a right immature ovarian teratoma with SIADH and GP. To the best of our knowledge, this is the first immature ovarian teratoma with SIADH and GP ever published.

CASE PRESENTATION

A 30-year-old, para 1 female presented with a lower abdominal pain and distension for one week duration. Physical examination revealed a huge mobile right lower abdominal mass that crosses the umbilicus and was firm in consistency measuring 20 x 20cm. Contrast-enhanced computerized tomography scan(CECT) of the abdomen and pelvis showed a large, well demarcated, encapsulated lobulated heterogeneous enhancing solid cystic mass with coarse calcification measuring 8.9cm x 15cm x 15cm (APXWXCC) with clear plane with surrounding organs (Figure 1A and 1B). Her tumour markers that were raised were AFP which was 19.6 IU/ml, CA 125 which was 223 U/ml and CA 19-9 which was 197 U/ml. Her LDH was 253 U/L with sodium of 125, hypotonic serum osmolarity and high urine sodium.

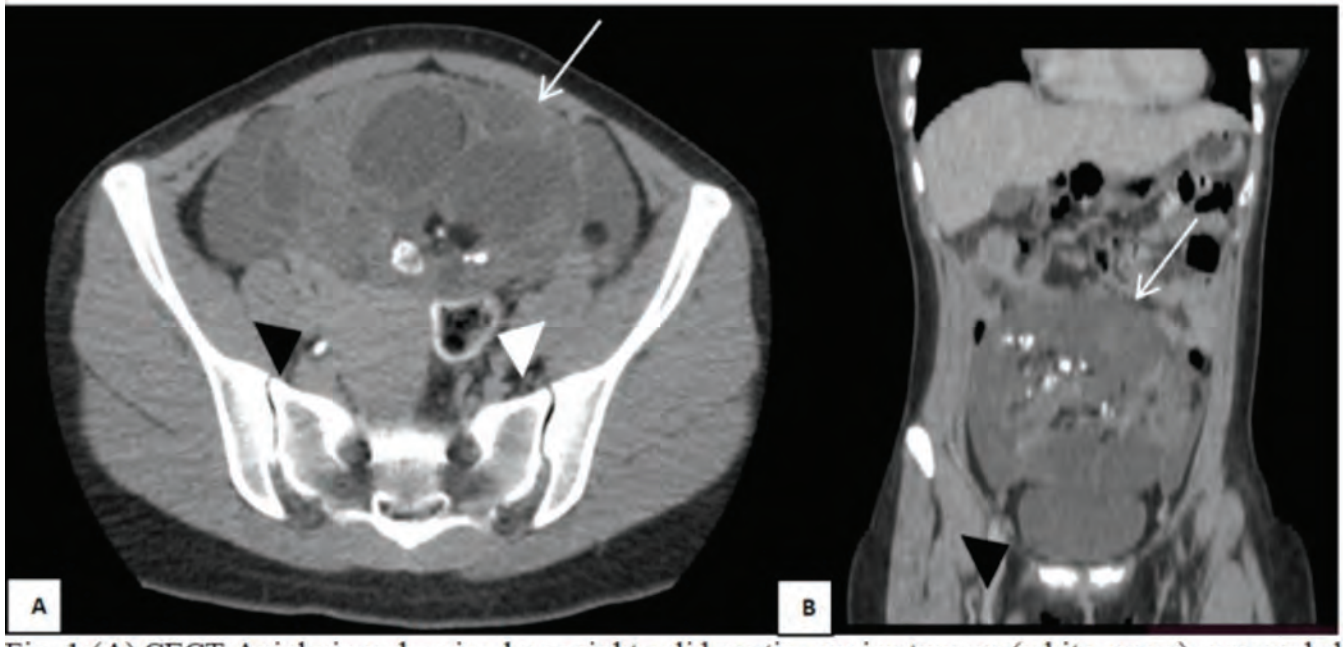

Fig. 1:(A) CECT Axial view showing large right solid-cystic ovarian tumour (white arrow) surrounded by uterus (black arrow head) and sigmoid colon (white arrow head) posteriorly. (B) CECT Coronal view showing a large right solid-cystic ovarian tumour displacing the bladder inferiorly.

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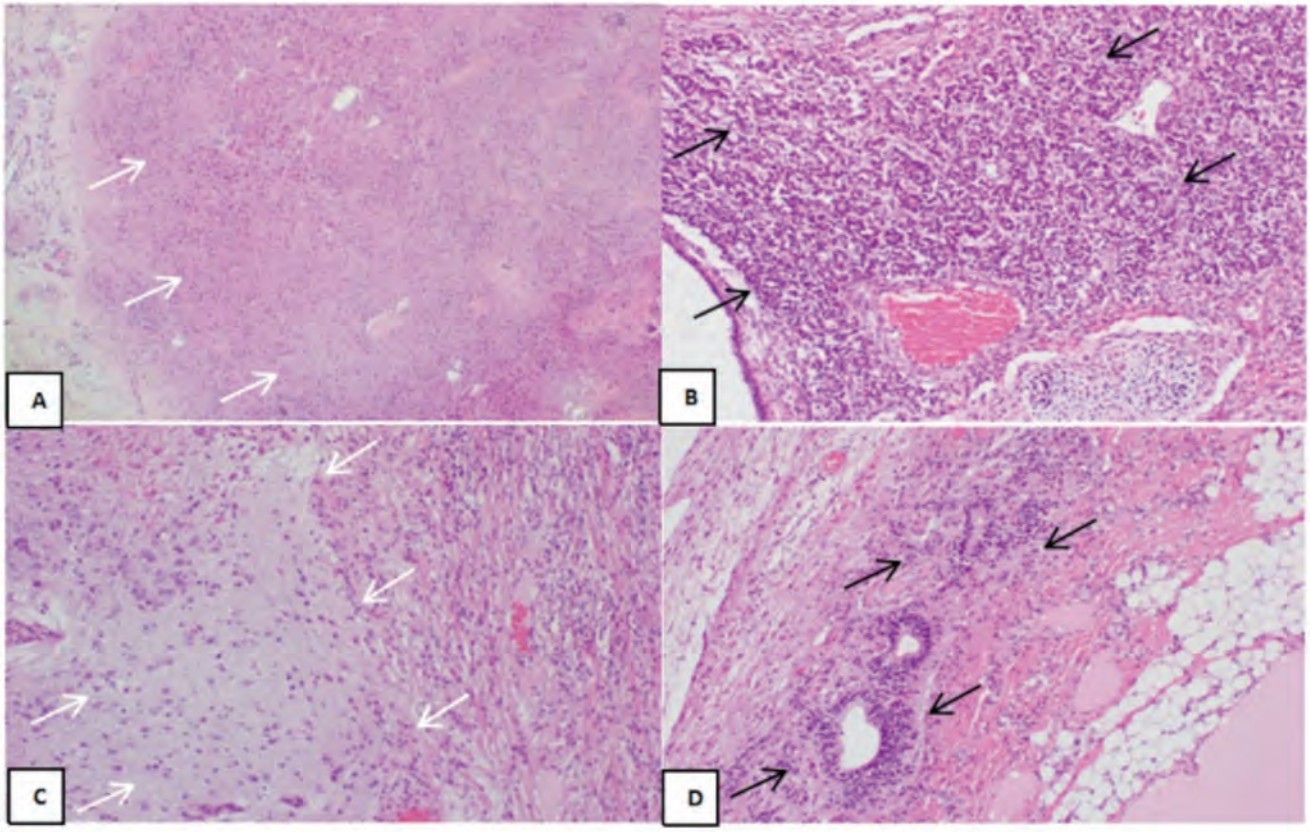

Fig. 2: (A) Peritoneal nodule HPE, 40x magnification. Compact nodules of mature glial tissue surrounded by fibrocollagenous and fibrovascular stroma (white arrows). (B) Ovarian Tumour HPE, 100x magnification. Immature neuroectodermal tissue comprises tubules and rosettes of primitive, mitotically active cells with increased nuclear:cytoplasmic ratio, hyperchromatic nuclei and scant cytoplasm (black arrows). (C) Ovarian Tumour HPE, 100x magnification. Glial tissue is seen in this field (white arrows). (D) Ovarian Tumour HPE, 100x magnification. Admixture of immature and mature teratoma components. Glial tissue, adipose tissue, and immature neuroectodermal tissue are present in this field (black arrows).

She was first electively admitted for right salpingo-oopherectomy, omentectomy and appendicectomy with keep in view pelvic lymph node dissection. However, as her sodium was reported to be low and her surgery was postponed to the following week while optimizing her sodium by restricting her fluid as her blood results was suggestive of SIADH. When her bloods were optimized she underwent a midline laparotomy for right salpingo-oopherectomy, omentum biopsy and appendicectomy with pelvic lymph node harvest. Intra operatively we noticed multiple peritoneal nodules at anterior abdominal wall and the pelvis as well as 800 cc of straw colour ascitic fluid which we biopsied as well as aspirated to send for histopathological examination (HPE) and cytological examination. The right ovary measured 25 x 25cm intraoperatively with nodules on the surface of the right ovary while the left ovary appears to be normal. Uterus and other bowels were normal. There was also omental caking and enlarged right pelvic lymph nodes and hence we proceeded with omentectomy and right pelvic lymph node dissection.

The post-operative course was uneventful and her sodium normalized and she was discharged at post operative day 6. HPE showed grade 1 immature right ovarian teratoma which is low grade (Grade 1)with focal capsular breach (Figure 2B, 2C and 2D). Her lymph nodes showed nodal gliomatosis while her peritoneum and omentum showed gliomatosis peritonei (Figure 2A) and lastly appendix was normal. The ascitic fluid showed loose cohesive cells, reactive mesothelial cells, lymphocytes and histocytes. At follow up review of 3 months, she was well and undergoing adjuvant chemotherapy - BEP regime (Bleomycin, Etoposide and Carboplatin) planned for 4 cycles.

DISCUSSION

GP was first reported by Benirschke in 1960 while SIADH due to immature ovarian teratoma was first reported by Lam in 1996.[1-2] Based on Pubmed search engine there are only 118 cases that reported immature ovarian teratoma with GP and only 8 cases with SIADH. However, there were no reported cases on immature ovarian teratoma with SIADH and GP.

There are 2 main theories that spurred the development of GP. The first theory being via angiolymphatic spread or via capsular breach of the ovarian tumour like our case based on the histopathology.[3] The second theory is that glial foci are not genetically associated with the ovarian tumour but arises from normal cells from the pluripotent Mullerian stem cells. These cells gets differentiated into glial cells by the ovarian teratoma secreting some stimulation factors.[4]

SIADH is postulated by the immature cells of ovarian teratoma being pluripotent in nature. There have been previous publications in regards to pituitary component present in ovarian teratoma.[5] The definitive diagnosis can only be made via histopathology. Immature ovarian teratomas are germ cell tumours. For immature ovarian teratoma with gliomatosis peritonei based on the WHO grading system it is graded 0 however due to the certain areas having rare foci of immature cells it is histologically grade 1.

Salpingo-oopherectomy, omentectomy, appendicectomy, peritoneal biopsy and pelvic lymph node dissection has always been advocated as the treatment of ovarian tumours. While the mainstay of SIADH treatment is fluid restriction and surgical resection. Prognosis or overall survival of immature ovarian teratoma is not affected by presence of GP however the recurrence rates were higher in those with GP. Prognosis is based on the quantity of immature cells in the ovarian tumour and this will decide the grade of the tumour and treatment plan. Adjuvant chemotherapy with BEP is the chemotherapy of choice mainly for high grade tumours (Grade 2 and 3). However, the role of adjuvant chemotherapy is debatable in grade 1 immature ovarian tumours as some centres suggest only close observation while others advocate adjuvant chemotherapy based on the age, GP spread, and tumour burden. For our case, we suggested 4 cycles of chemotherapy with BEP regime because the patient was young, there was wide GP spread and huge tumour burden. We also discussed with the patient in regards to fertility preservation as she was still young and had a baseline lung function and ECHO in view that the chemotherapy can lead to adverse effects affecting her lung and heart.

CONCLUSION

Immature ovarian teratoma can present with SIADH. GP although rare is a differential diagnosis in the event of intraoperative wide spread peritoneal dissemination. Immature ovarian teratomas with GP have a good prognosis with equivalent overall survival with those without peritoneal disease but have a higher recurrence rate. Adjuvant chemotherapy in grade 1 tumours are uncertain and it all depends on few factors. However, in our patient we believe the surgery we performed and adjuvant chemotherapy we offered was the best option and effective method to treat her and reduce risk of recurrence.

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DECLARATION

The authors declare no potential conflict of interest with respect to the research, authorship, and publication of this article.

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Baby's bottom bump: A case report of perianal swelling in a 6-month-old infant

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SUMMARY

Infantile perianal pyramidal protrusion (IPPP) is an uncommon benign pyramidal shaped protrusion of perineal tissue from the midline raphe of the perineum. Here we present a case of IPPP in a 6-month-old girl with a perianal swelling which resembles perianal excoriation with skin tag. She had a spontaneous, painful perianal bulge with erythema for two weeks in duration, that gradually increased in size. She had constipation for two weeks prior to the onset of symptoms, despite being fully breastfed. Her medical history was unremarkable. There were no concerns regarding sexual abuse or any history of local infections. Her pain improved with conservative treatment and the swelling regressed spontaneously by more than 50% after three months without further intervention. This case report points out that IPPP is an uncommon benign perianal protrusion which could be easily diagnosed via clinical evaluation. Histopathological findings include acanthosis, upper dermal oedema, and a mild inflammatory infiltrate. It is more prevalent in pre-pubertal females, and is believed caused by congenital, acquired mainly due to mechanical friction, or inflammatory changes due to genital lichen sclerosus et atrophicus (LSA). Treatment primarily involves conservative management, as most lesions will spontaneously resolve or with the treatment of underlying causes. Awareness of IPPP helps prevent overtreatment and unnecessary evaluation, thereby avoiding incorrect assumptions regarding sexual abuse or other anogenital disorders.

INTRODUCTION

Infantile perianal pyramidal protrusion (IPPP) is an uncommon benign pyramidal shaped protrusion of perineal tissue originating from the perineal midline raphe. Here we report a case of IPPP involving a six-month-old girl with a perianal mass mimicking perianal excoriation with skin tag. Lack of recognition may result in overtreatment and causing excessive concerns among clinicians and parents.

Hence, this case report underlines the necessity of recognizing IPPP, via thorough clinical evaluation and identifying its classic morphology. It is crucial to prevent unnecessary investigations for sexual abuse or other anogenital conditions, as the clinical evaluations can have medicolegal implications and may be very distressing for both the patient and the family.

CASE PRESENTATION

A six-month-old girl was brought to the Primary Care Clinic due to a noticeable spontaneous, painful perianal bulge with erythema that was gradually increasing in size over two weeks in duration. Crying episodes became more frequent upon defaecation and when the swelling was touched. She was subsequently treated for perianal excoriation and skin tag with local analgesia, Topical Lignocaine 2% gel and Zinc oxide cream. Although the perianal pain improved over the following weeks, the swelling persisted despite ongoing treatment.

The child had a two-week history of constipation despite being fully breastfed. The mother expressed concern about her child's bowel habits, as she was regularly changing diapers three times a day, with stools consistent with Bristol Stool Scale type 6. However, the frequency has now reduced to once daily, with stools consistent with Bristol Stool Scale type 4, and this change is associated with increased crying episodes upon defaecation. The medical history was otherwise unremarkable. There was no history of sexual abuse and no maternal history of cervical dysplasia, human papilloma virus infection, or condyloma acuminata.

Clinical evaluation revealed normal pre-pubertal genitalia. Upon perineal inspection, we noticed a flesh-coloured elongated, pyramidal lesion, measuring 4mm x 2mm, extending from below the vaginal vestibule to the superior aspect of anal verge. The surrounding perianal skin appeared excoriated and erythematous, as shown in Figure 1. No bleeding or skin cracks were noted. The child was diagnosed as IPPP based on clinical diagnosis, and the parents were given reassurance. The child continued to receive Topical Lignocaine 2% gel and Zinc oxide cream. The constipation subsided after the parents were advised to maintain adequate hydration via on-demand breastfeeding. After three months, the swelling spontaneously regressed by more than 50% without further intervention, and she was discharged from the clinic.

DISCUSSION

Infantile perianal pyramidal protrusion (IPPP) was first described by Kashiyama et al (1996) and has since only been studied through case reports and observational studies.[1-4] It presents in a variety of shapes, but it is commonly described as pyramidal, papular, leaf-like, peanut-shaped, tongue-like, and hen's crest-shaped projection mimicking morphology of

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Table I: Differential Diagnosis of Infantile perianal pyramidal protrusion[7-10]

Condition	Clinical Features
Infantile perianal pyramidal protrusion	• Pyramidal, smooth surface, perianal protrusion, non-tender • Arising from the midline raphe of the perineum
Skin tags	• Asymptomatic, round, soft, skin-coloured, pedunculated with a stalk
Rectal prolapse	• Bright or dark red, non-tender mass protruding from the anus • Arising from the anal region
Haemorrhoids	• Mass protruding from anus • May present with painful or painless rectal bleeding, or tenesmus
Granulomatous perineal lesions of Crohn's disease	• Perineal plaques, papules, and nodules • May be associated with perineal ulceration, fistula, or abscess • Arising from anogenital region
Sexual abuse	• Painful perianal bruising or laceration with exposure of tissues beneath the dermis • May be associated with bruising, abrasions, scarring, or residual healing injuries to the surrounding anogenital structures
Haemangiomas and other vascular malformations	• Deep lesions appear bluish, while superficial lesions are bright red • May be associated with bleeding, ulceration, or infection • May involve more than one anatomical site
Condyloma acuminata	• Multiple flesh-coloured, velvety plaques, discrete warty papules, or cauliflower-like growth, non-tender • Arising from perineal region • More common in sexually active individual • Caused by the HPV virus
Molluscum contagiosum	• Discrete, firm, dome-shaped, smooth surface, pearly white or flesh-coloured, waxy papules with characteristic central umbilication • Arising from moist regions and areas where the skin rubs

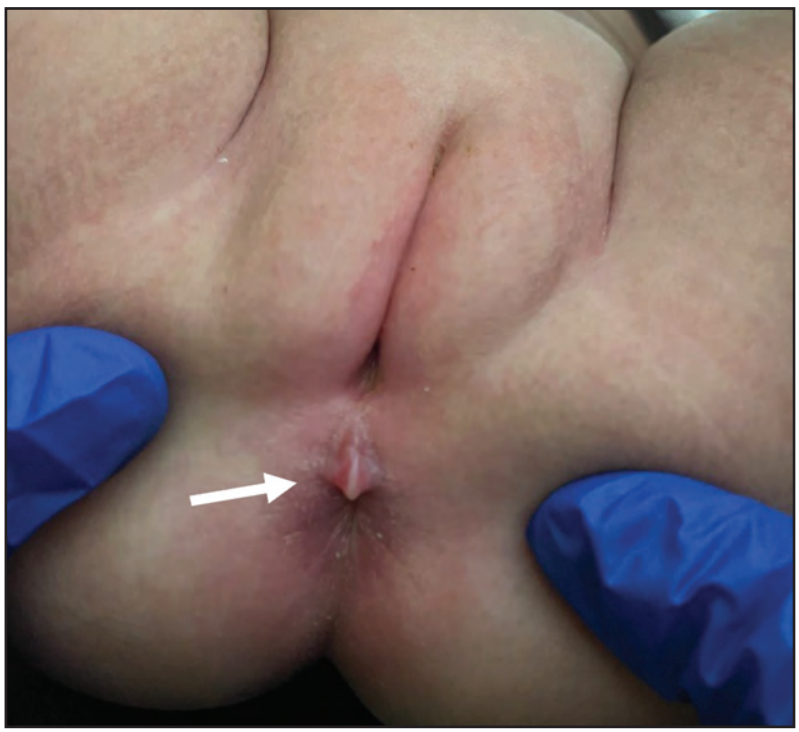

Fig. 1: A pyramidal-shaped protrusion on the anterior to the anus, measuring 4mm x2mm (white arrow) with smooth and slightly erythematous perineal skin surface. (The above photograph was consented by the patient's parents)

a skin tag.[2-3] A recent observational study from United States described IPPP as a benign condition that predominantly occurs in pre-pubertal females, aged ranging Day 1 of life to 4 years.[4] IPPP is relatively uncommon, and the most recent nearby cases were reported in Japan.[1,5] To our knowledge, this is the first case reported in Malaysia.

The colour of the lesion may vary from flesh-coloured to red or pale depending on the perineal condition. Dermatological conditions such as diaper dermatitis or perianal excoriation may contribute to the skin changes.[2-3] IPPP is typically located anterior to the anus, on the midline raphe of the perineum.[2] Histopathological studies shown relatively nonspecific findings, including acanthosis, upper dermal oedema, and

mild inflammatory infiltrate.[1] The differential diagnoses includes, skin tag, rectal prolapse, rectal polyp, external haemorrhoids, granulomatous perineal lesions of Crohn's disease, sexual abuse, haemangiomas and other vascular malformations, condyloma, and molluscum contagiosum.[2-3] The clinical features of these anogenital conditions are summarized in Table I.

Various theories explained the mechanisms of IPPP formation: (1) Congenital anatomic weakness of median raphe or a remnant of urogenital septum, as there were cases reported with new onset of perianal lesions after constipation episodes supporting the Valsalva manoeuvre theory, (2) Acquired lesion from diarrhoea, fistulas and anal fissures; likely secondary to mechanical irritation and (3) Inflammatory changes related to genital lichen sclerosus et atrophicus (LSA).[2-3] In this case study, the lesion may have arisen from either a congenital cause or an acquired cause, such as constipation, which contributed to the painful perianal excoriation.

Many studies indicate that IPPP decreases in size or resolves spontaneously over time.[2-5] In acquired cases, serial follow-up is required to manage precipitating factors, including supportive therapies such as analgesia and laxatives, along with dietary modifications like adequate hydration, are recommended to address constipation if present.[2-3] Topical corticosteroids may be prescribed for the presence of LSA.[2-3]

This case report underlines that lack of recognition of IPPP may result in overtreatment and causing excessive concerns among clinicians and parents. It is crucial to prevent unnecessary investigations for sexual abuse or other anogenital conditions, as the clinical evaluations can have medicolegal implications and may be very distressing for both the patient and the family. A previous case presentation by Margulies et al. (2024) reported that most clinicians would opt against invasive procedures such as biopsies, especially in sensitive regions, as these procedures can cause discomfort for both the patient and the parents.[6] Furthermore, a misdiagnosis of sexual abuse can potentially lead to significant emotionally distress for the family.[6]

CONCLUSION

IPPP is an uncommon benign perianal protrusion that can be easily diagnosed via thorough clinical evaluation. IPPP is mainly treated conservatively as they are mostly self-limiting or by treating underlying causes. Awareness of IPPP and accurate identification of its clinical features may aid in prevention of overtreatment and unnecessary evaluation in the future. Unnecessary evaluations can lead to incorrect assumptions about sexual abuse or other anogenital disorders, potentially resulting in medicolegal implications and causing distress for both the patient and the family.

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DISCLOSURE

The case report is registered under National Medical Research Register (NMRR ID-24-01557-WAR). The patient's parents had given informed consent to publish the clinical details in this case report. This study does not have conflict of interest between the authors and there was no funding received for this article.

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CASE REPORT

Scrub typhus, the forgotten acute febrile illness: A case series from Negeri Sembilan, Malaysia

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SUMMARY

Scrub typhus is a zoonotic bacterial infection caused by *Orientia tsutsugamushi*. Its clinical presentation is often mistaken for other acute febrile illnesses. This case series highlights the importance of obtaining a detailed history of outdoor exposure and considering scrub typhus as a possible diagnosis in patients presenting with fever, diarrhea, thrombocytopenia, and abnormal liver function tests. Thorough history taking, a high index of suspicion, and prompt initiation of treatment are crucial to reducing the mortality and morbidity associated with scrub typhus.

INTRODUCTION

Scrub typhus is an infectious disease caused by a bacterium called *Orientia tsutsugamushi*.[1] Traditionally, it has been endemic to the 'tsutsugamushi triangle", posing a significant public health issue in the Asia-Pacific area. Globally, it threatens over one billion people and causes illness in approximately one million people annually.[2] Despite being a common cause of undifferentiated fever in Malaysia, it remains under-recognized in terms of healthcare policies, registries, and research.[3] Early recognition and treatment improve outcomes and help reduce mortality and morbidity. This paper presents four clinical cases of scrub typhus in Negeri Sembilan, Malaysia.

CASE PRESENTATION

Case 1

A 42-year-old indigenous man presented with a 3-week history of fever, vomiting and diarrhoea. Physical examination revealed tenderness in the epigastric region, but no organomegaly. He works as a farmer and resides in the deep forest of Jelebu, a district in Negeri Sembilan. Initial blood results showed white blood cells (WBC) of $9.3x10^9$/L, haemoglobin (Hb) of 85g/L, and platelet count of $239x10^9$/L. His urea level was 10.9mmol/L, and creatinine was 93umol/L. Liver function tests showed a total bilirubin 93umol/L, alanine transaminase (ALT) of 318U/L, and alkaline phosphatase (ALP) of 629U/L.

Leptospira Ig M was positive, while C-reactive protein (CRP) was elevated at 119mg/L, and procalcitonin was 1.18ng/mL. Blood cultures showed no growth and hepatitis serology was non-reactive. A computed tomography (CT) scan of abdomen revealed hepatosplenomegaly with mild ascites. Based on these findings, the patient was initially treated for leptospirosis with intravenous ceftriaxone 2g once daily. Despite 2 days of treatment, the patient remained febrile. Oral doxycycline was added to the treatment regimen, and his fever subsided 48 hours later.

Subsequent testing revealed a negative blood culture. Indirect immunoperoxidase (IIP) confirmed scrub typhus with an IgG titre of 1:800, strongly suggestive of active infection. Additionally, *Orientia tsutsugamush*i DNA was detected through serum Rickettsia polymerase chain reaction (PCR).

Case 2

A 48-year-old Indonesian man presented with a one-week history of fever, diarrhoea, and vomiting. He had multiple outpatient clinic visits prior to admission, where he was only given symptomatic treatment. He had been in Malaysia for 8 years, working as a rubber tapper, with no recent travel history before admission.

On presentation, he was tachypnoeic and confused. Abdominal examination revealed a soft abdomen without guarding. An ECG showed supraventricular tachycardia.

Laboratory investigations revealed a white blood cells of $17.9x10^9$/L, platelet count of $177x10^9$/L, and haemoglobin of 163g/L. He had severe acute kidney injury and metabolic acidosis, with deranged liver function test: ALT 111U/L, aspartate transaminase (AST) 113U/L, ALP 105U/L, and CRP 161.7mg/L. Plasma high-sensitivity troponin I was elevated at 806ng/L. He was intubated due to impending respiratory distress and severe metabolic acidosis. In view of thrombocytopenia with fever, he was initially treated as a case of severe dengue fever in the district hospital. However, dengue serology was negative, and no malarial parasites were seen on blood films. Leptospira IgM was also negative.

After consultation with infectious diseases specialists, he was empirically started on intravenous amoxicillin-clavulanate and oral doxycycline (100 mg twice daily), based on his occupational history. Unfortunately, the patient's condition deteriorated rapidly, and he passed away five hours after admission to the ICU.

Further testing revealed negative results for blood cultures, Dengue PCR, and Leptospira PCR. However, serum Rickettsia PCR detection of *O. tsutsugamushi* DNA, confirming a diagnosis of scrub typhus.

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Table I: Summary of Clinical Presentation, Investigations, and Outcomes in Four Cases of Scrub Typhus

Patient	Age, gender	Day of illness upon presentation	Clinical presentation	Eschar	White blood cell (x 10^9/L)	Platelet (x 10^9/L)	Creatinine (umol/L)	Total bilirubin (umol/L)	ALT (U/L)	AST (U/L)	ALP (U/L)	ALP (U/L)	Primary diagnosis	Rickettsia PCR (Orientia tsutsugamushi DNA)	Rickettsia IIP test (serology)	ICU admission
1	42, M	20	Fever, abdominal pain, vomiting, diarrhoea	No	9.3	239	93	93	318	-	629	119	Leptospirosis	Detected	Scrub typus Ig G 1:800	No
2	48, M	7	Fever, diarrhoea, vomiting	No	17.9	177	510	8	111	113	105	161.7	Severe dengue	Detected	Negative	Yes
3	44, M	7	Fever, diarrhoea, vomiting	Yes	20	109	88	105	165	-	419	238	Acute cholecyctitis	Detected	Negative	Yes
4	33, F	7	Fever, diarrhoea, vomiting	Yes	21	75	70	23	74	201	260	234	Viral fever	Detected	Not available	Yes

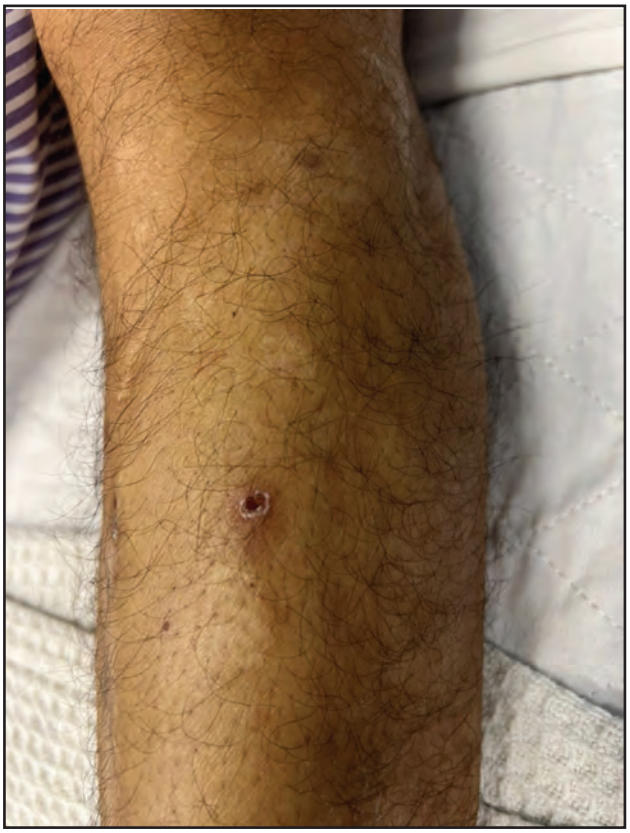

Fig. 1: Case 3- Eschar over left arm

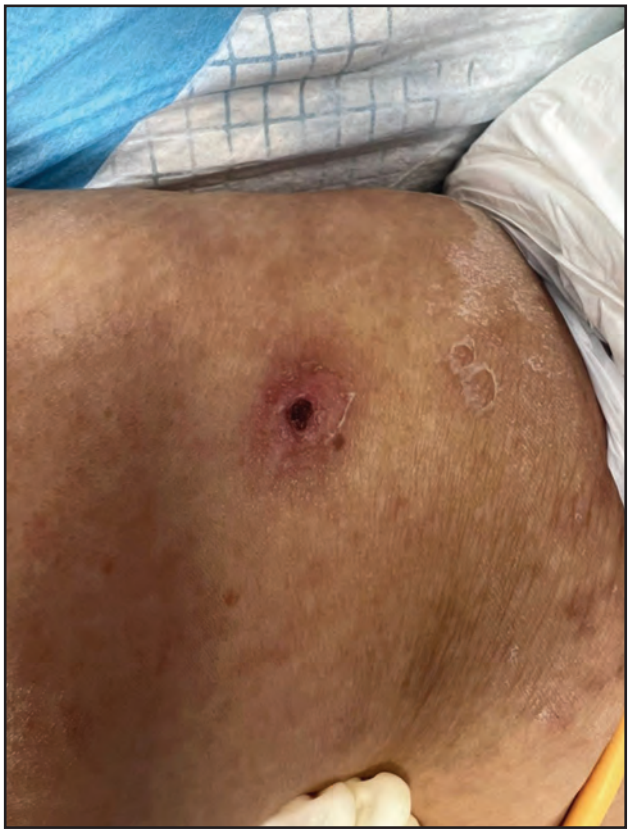

Fig. 2: Case 4 - Eschar over right inner thigh, with maculopapular rash over the surrounding skin

Case 3

A 44-year-old Bangladeshi man employed in an oil palm plantation presented with abdominal pain, fever and vomiting persisting for one week. Upon examination, he was found to be jaundiced and hypotension. He appeared septic, with abdominal pain localized to the right hypochondrium.

Laboratory tests revealed a white blood cell of $20x10^9$/L, platelet count of $109x10^9$/L, and hemoglobin level of 134g/L. His total bilirubin was measured at 105umol/L, with ALT at 165U/L and ALP at 419U/L and CRP was significantly elevated at 238mg/L.

A CT scan indicated the presence of cholelithiasis with features consistent with cholecystitis. The patient was initially treated in surgical ward with intravenous amoxicillin-clavulanate for the suspected cholecystitis. Despite initial treatment, the patient's condition worsened. His fever persisted, and he developed fast atrial fibrillation (AF). He required inotropic support and mechanical ventilation due to respiratory failure and worsening sepsis. A chest X-ray (CXR) revealed cardiomegaly with bilateral lung infiltrates. Intravenous meropenem were initiated.

During antimicrobial stewardship (AMS) round, an eschar was noted on his left arm, raising suspicion for scrub typhus. The patient was subsequently treated with intravenous azithromycin and oral doxycycline for one week. Blood cultures and hepatitis screenings were negative. He was discharged in good condition following completion of the antibiotic course. The diagnosis of scrub typhus was confirmed by a serum Rickettsia PCR, which detected *Orientia tsutsugamushi* DNA.

Case 4

A 33-year-old woman, working as a farmer in a lemongrass field, presented with a history of fever, vomiting, and loose stools for more than a week. She had initially visited a nearby clinic on day 3 of her illness, where she was treated for a suspected viral fever.

By day 7 of her illness, upon presentation to the hospital, she appeared critically ill, tachypneic, and required intubation due to severe metabolic acidosis, as well as inotropic support. On abdominal examination, there was tenderness in the right hypochondrium region. An eschar was noted on the inner aspect of her right thigh.

Laboratory investigations revealed a hemoglobin level of 173g/L, a white blood cell count of $21x10^9$/L, and a platelet count of $75x10^9$/L. Her liver function tests showed a total bilirubin of 23umol/L, ALT of 74U/L, AST of 210U/L, and ALP of 260U/L. CRP was markedly elevated at 234mg/L. The patient was diagnosed with scrub typhus and subsequently treated with intravenous azithromycin and oral doxycycline. Despite the treatment, her condition worsened, leading to severe renal injury and death on day 3 of admission. Blood cultures, leptospirosis PCR, and hepatitis serology were all negative. Serum Rickettsia PCR confirmed the presence of *Orientia tsutsugamushi* DNA, confirming the diagnosis of scrub typhus.

DISCUSSION

Orientia tsutsugamushi is an arthropod-borne, gram negative, obligate intracellular bacillus.[2] Its prevalence ranges from 9.3% to 27.9% across Asia.[4] *O. tsutsugamush*i is transmitted to humans through the larval stage of chiggers. While the exact pathogenesis remains unclear, *O. tsutsugamushi* is thought to infect the vascular endothelial cells of small and medium vessels, leading to perivascular inflammation, vascular leakage, and end-organ damage.[2]

The incubation period of scrub typhus ranges from 6 to 21 days. Symptoms like as fever, nausea, and abdominal pain, are non-specific and can resemble other febrile illnesses. If left untreated, scrub typhus can lead to severe systemic complications including myocarditis, renal failure, and acute respiratory distress syndrome.[2] Outdoor activities such as farming or plantation work, increase the risk of contracting the disease.[5] In our cases, patients presented after about 10 days of illness with non-specific gastrointestinal symptoms. Despite clear outdoor exposure, they were initially misdiagnosed with leptospirosis or dengue. This emphasizes the need for a detailed exposure history, especially for those involved in outdoor work. Although eschar is a pathognomonic sign of scrub typhus, its prevalence varies across regions, with the highest occurrence in East Asia (78.7%) and the lowest in South Asia (32.8%).[6] In the cases reported here, eschars were identified in only two out of the four patients.

Laboratory findings in our patients include mild thrombocytopenia, elevated liver enzymes, and significantly elevated C-reactive protein (CRP) levels. These findings align with a study by Yazli et al., which indicates that white blood cell count and CRP levels tend to be higher in rickettsial infections and leptospirosis compared to dengue.[3]

The diagnosis of scrub typhus can be categorised into direct and indirect methods. Polymerase chain reaction (PCR) from serum, eschar tissue, or urine is a direct method of detecting *O. tsutsugamushi* DNA, and enables earlier diagnosis, especially during the bacteraemic phase. Indirect methods, such as immunofluorescent assays (IFA) and immunoperoxidase tests, detect antibodies to *O. tsutsugamushi*, but they required seroconversion or a fourfold rise in antibody titers between acute and convalescent phases, limiting their utility for early diagnosis.[2]

In our case series, both PCR and serology testing were outsourced to the Institute for Medical Research (IMR), with a turnaround time of 2 to 3 weeks. Notably, eschar samples were not sent for testing in the two cases where eschars were present, likely due to a lack of awareness among healthcare workers about the diagnostic importance of eschar tissue in scrub typhus. This highlights a knowledge gap that could impact the prompt and accurate diagnosis of scrub typhus. Given the turnaround time for diagnostic results, it is essential to initiate treatment promptly for patients presenting with suggestive symptoms and a history of outdoor exposure.

The median mortality for patients with scrub typhus was as high as 6% but was significantly reduced to 1.4% with appropriate treatment.[4,7] According to CDC guidelines, doxycycline remains the first-line treatment and is safe for all age groups.[1] In critically ill patients, however, the absorption of oral doxycycline absorption may be impaired. In such cases, azithromycin is an alternative. Studies indicate that there is no significant difference in clinical outcomes between doxycycline and azithromycin monotherapy.[8] Varghese et al. found that combination therapy with doxycycline and azithromycin was more effective than monotherapy for severe scrub typhus.[9] In our case series, two patients received combination therapy; one recovered uneventfully, while the other succumbed to the disease on day three of treatment.

CONCLUSION

Scrub typhus is a significant tropical disease, particularly prevalent in rural populations, and can lead to serious complications if not recognized promptly. When evaluating differential diagnoses in the context of acute febrile illness, scrub typhus should always be considered. A comprehensive exposure history and thorough clinical evaluation are essential for initiating prompt treatment, which can significantly improve patient outcomes and reduce morbidity and mortality associated with this disease.

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The authors would like to thank the patient for agreeing to publish this case.

DECLARATION

The authors have no conflict of interest to disclose.

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CASE REPORT

A case of pleural mature teratoma masquerading as empyema thoracis

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SUMMARY

Mediastinal masses are diagnostically challenging due to their varied presentations. Teratomas are a rare cause. We report a case of a young woman with chronic cough and weight loss, initially treated for tuberculosis (TB) based on pleural fluid analysis. Thoracic CT revealed a large left-sided empyema. After thoracotomy and decortication, histopathology confirmed a mature teratoma. We believe this is the first report of a teratoma of the pleura which manifested as a tuberculous empyema.

INTRODUCTION

Teratoma is a unique type of tumor consisting of mature or immature cell originating from more than one germ cell layer, sometimes all three.[1] The majority of germ cell tumors develop in the gonads, with only approximately 5% being extragonadal. Among extragonadal cases, 80% are located in the mediastinum.[2] Adult patients with mediastinal teratoma usually are asymptomatic and only detected when they cause compressive symptoms. Pleural effusion is rather a rare presentation and only reported in a few cases.[3]

CASE PRESENTATION

A 19-year-old woman presented to a district hospital with a chronic cough and a 10 kg weight loss over a month. She had no fever or TB contact. Examination revealed reduced breath sounds in the left lung, and a chest X-ray showed left-sided pleural effusion. She was treated with oral antibiotics and followed up as outpatient for TB workup.

She was subsequently admitted to a tertiary hospital for persistent pleural effusion. A chest tube was inserted, and pleural fluid analysis revealed transudative fluid. TB workup was mostly negative, except for elevated pleural fluid ADA (138.73 U/L). Cytology was negative for malignancy, and she was empirically treated for TB. Intrapleural streptokinase was administered due to minimal chest drainage and persistent effusion (Figure 1A).

A CT scan two weeks later showed a large, loculated left pleural empyema with small hydropneumothoraxes in the lower part, causing subsegmental collapse of the left lung lobes, and right tracheal and mediastinal shift. Fat density lesions in the effusion suggested pleural lipomatosis (Figure 2). She was referred for decortication.

She underwent emergency left thoracotomy and decortication in our centre. Intraoperatively, a thick-walled multiloculated cortex was found at the left lung hilum, displacing and entrapping the upper and lower lobes. The loculated cortex contained clear fluid, with two cystic collection of purulent material (Figure 3C, D). Few loculations contained "cheesy" material (Figure 4), which was aspirated. Specimens were sent for culture, TB workup, and histopathology.

Postoperatively, a chest X-ray showed good lung expansion (Figure 1B), and she was discharged on day 5. She recovered without complications. Intraoperative specimens were negative for TB, so anti-TB medications were discontinued.

Histopathology confirmed a mature teratoma arising from the pleura, with no mediastinal involvement (Figure 5 A-D). It contained cysts lined by squamous and columnar epithelium, as well as adipocytes, glands, smooth muscle, and pancreatic tissue, with no signs of malignancy. The final diagnosis was mature pleural teratoma.

She was scheduled for follow-up in 3 months and pelvic imaging to rule out occult gonadal neoplasm.

DISCUSSION

The term "teratoma" was coined by Virchow in 1863, originating from the Greek word "teras," which translates to "monster." Teratomas are tumors typically comprised of various cell types derived from all three embryonic layers, namely ectoderm, mesoderm and endoderm.[1]

Teratoma commonly arise from gonads, whereas only 1 to 5% of them arise from extragonadal sites such as mediastinum, pineal area, sacrococcygeum.[4] Among the extragonadal teratoma, 80% of them are located in the mediastinum, more commonly anterior mediastinum. If the teratoma is made up of well-differentiated components, then it is a mature teratoma. A mature teratoma located in the mediastinum is typically benign, yet it harbors the potential for malignancy.[2] Benign mediastinal teratomas occur with equal frequency in both women and men, whereas malignant teratomas are more prevalent among men.[5] In this reported case, the patient is a young female who had a teratoma, which originated from pleura only, not other organs in the mediastinum. To date, there is no literature

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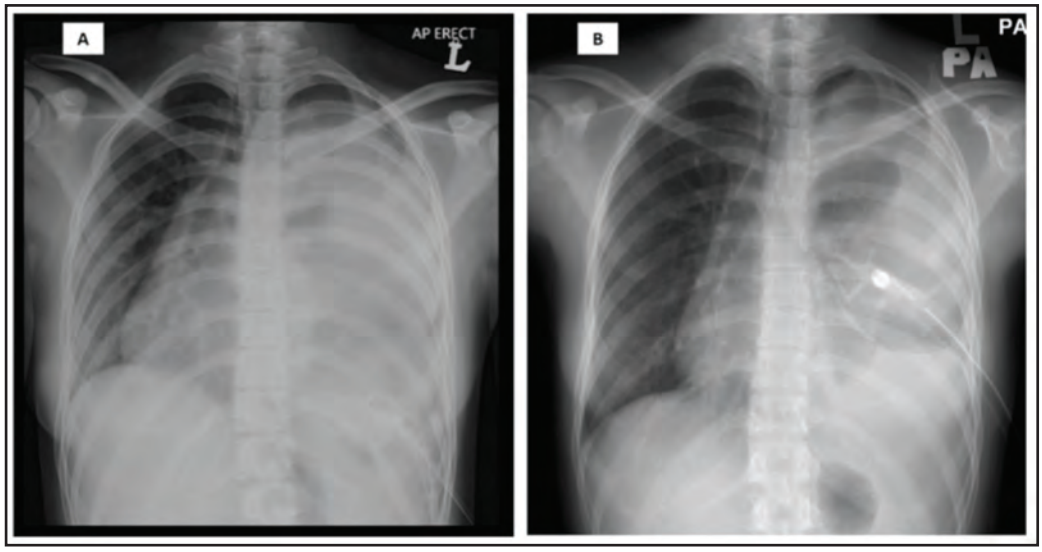

Fig. 1: CT scan coronal view, showed large loculated left pleural empyema with small locules of hydropneumothoraces at the lower part, with right tracheal and mediastinal shift

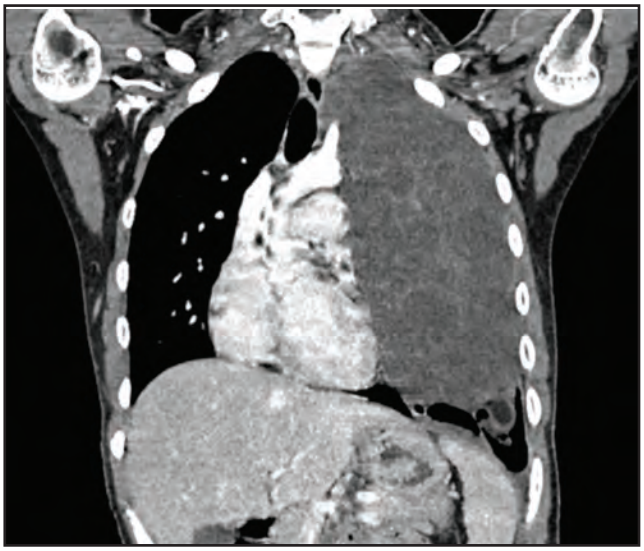

Fig. 2: CT scan coronal view, showed large loculated left pleural empyema with small locules of hydropneumothoraces at the lower part, with right tracheal and mediastinal shift

that reported on pleural teratoma manifesting as tuberculous empyema.

Benign mediastinal teratomas are usually incidentally discovered on chest radiographs during examinations. Symptomatic patients usually are due to the mass effect exerted by the mediastinal teratoma. Patient may also exhibit expectoration of hair, which is considered a pathognomonic symptom. Nevertheless, this distinctive symptom is very rare and typically a late presentation following tumor rupture into the tracheobronchial tree.6 Laboratory tests often yield normal results, and serum levels of human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) are consistently within normal ranges in patients with benign teratomas.7 Pleural effusion and empyema is considered rare presentation for mediastinal teratomas and limited to case reports only. There is also lack of data available on the its nature of pleural fluid.

The modality for assessing mediastinal teratomas is a CT scan thorax, because if offers superior evaluation of their location, extension, and vascularity. Shameem et al. highlighted that the presence of a fat-fluid level is considered pathognomonic for teratomas.[11] In the scenario of tumor rupture, pancreatic enzymes are reported to be useful, with associated findings including fat globules at the rupture site, airspace opacities, such as consolidation or atelectasis in adjacent lung parenchyma, and pleural effusion. Magnetic Resonance Imaging (MRI) is useful in cases where there is mass infiltration, demonstrating signal intensities of fat,

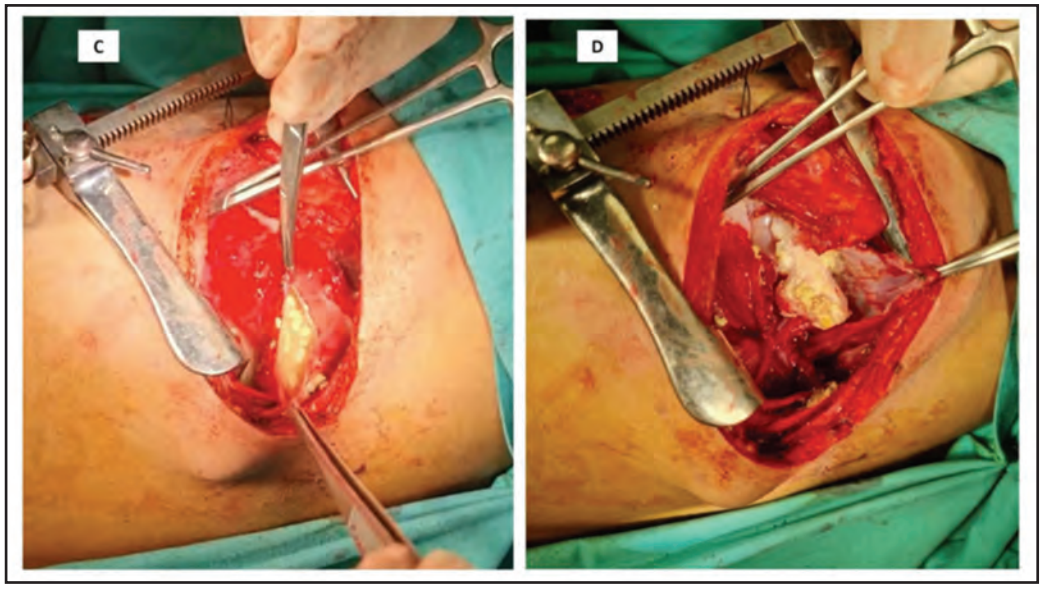

Fig. 3C & D: These figures showed intraoperatively noted purulent loculations with "cheesy" material

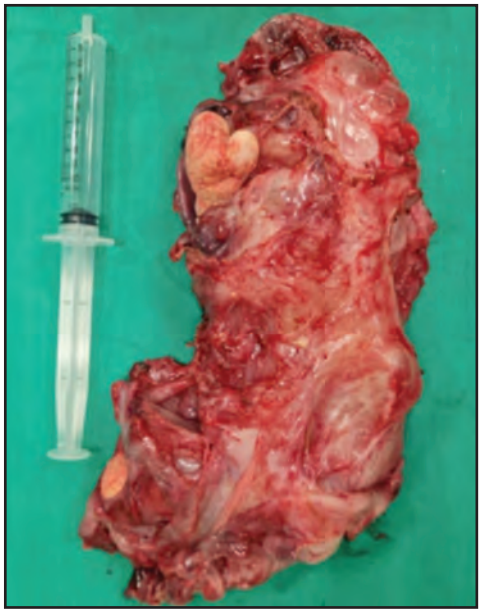

Fig. 4: This figure shows the decortication specimen, multilobulated with yellowish cheesy material seen.

fluid, and calcification. CT-guided biopsy is performed to determine the benign or malignant nature of teratomas, especially when there is pericardial involvement which warrants urgent intervention.[8]

The ideal management for benign mediastinal teratoma is always surgery aimed at complete excision of the tumor.[9] This yields an excellent prognosis, with nearly 100% survival rates. Surgery serves the benefit of both establishing the diagnosis and ensuring long-term cure, thereby reducing the likelihood of recurrence. The preferred surgical technique is median sternotomy due to its accessibility, while lateral thoracotomy is beneficial in cases involving extension into the hemithorax.[10]

CONCLUSION

Mediastinal mature teratoma represents a rare and benign disease. Patients are typically asymptomatic, but rarely may present themselves as pleural effusion. Distinctive features on CT scan and MRI aid in diagnosis and assessment of disease extent. Biopsy serves to confirm the diagnosis and exclude any immature elements suggestive of malignancy. In cases where pleural effusion lacks an evident cause, considering teratoma as a potential diagnosis, even in cases of transudative effusion, is essential. Regardless of its presentation, prompt surgical excision offers a curative approach for mature teratoma. As of date this is the first reported case of mature teratoma from pleura alone which manifests as empyema thoracis.

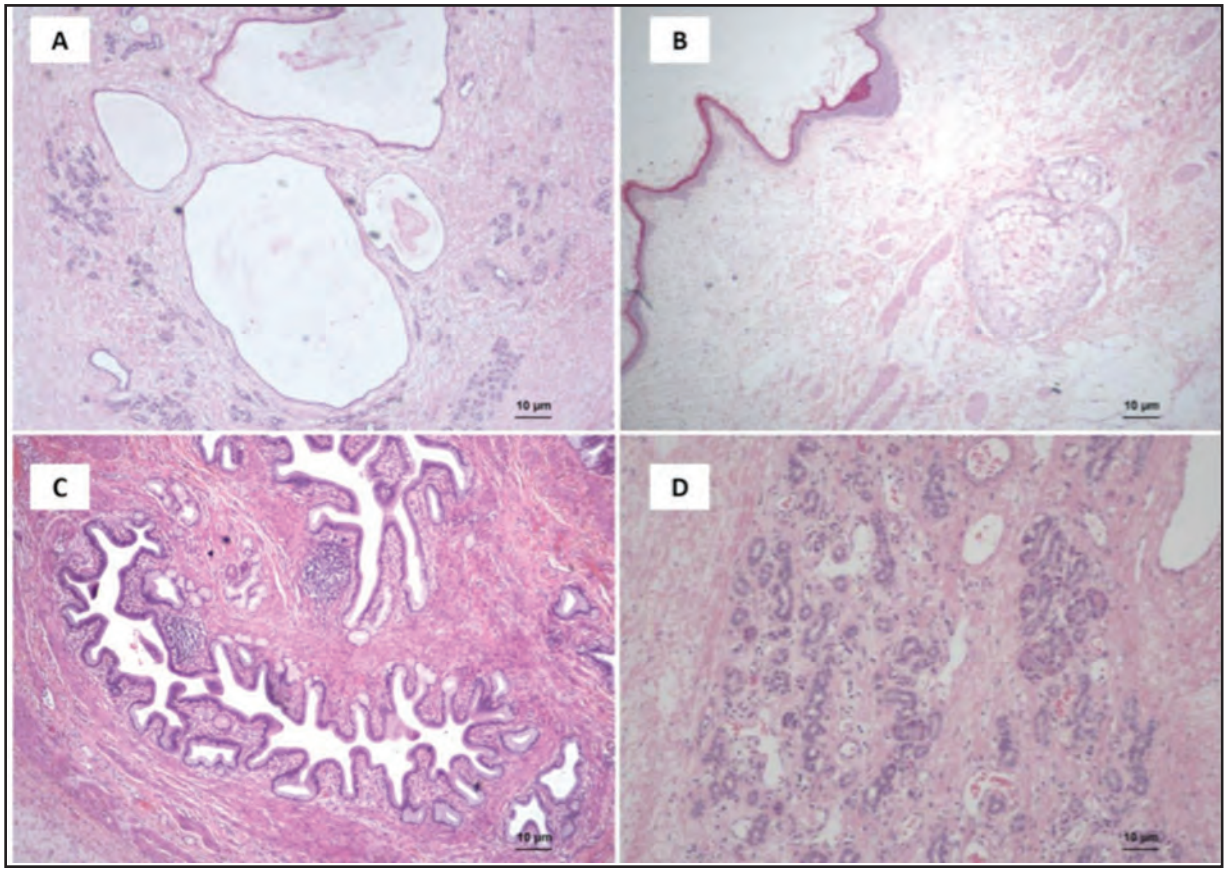

Fig. 5: Hematoxylin and eosin (H and E) stain section of the cortex showed features of mature teratoma:
(A) Multiple cystically dilated structures partly lined by squamous epithelium and columnar epithelium.
(B) Skin, pilosebaceous unit and adipocytes.
(C) Glandular epithelium and smooth muscle bundle
(D) Pancreatic ducts and acini

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The authors would like to thank the patient for agreeing to publish this case.

DECLARATION

The authors have no conflict of interest to disclose.

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CASE REPORT

‘Recurrent pharyngioma’: A rare tale of epidermoid cyst at sellar region

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SUMMARY

Epidermoid cysts (EC) arise from epithelial cells that are retained during closure of the neural tube. ECs are congenital and formed out of aberrant ectodermal cells, which become trapped during the embryogenesis between the 3rd and 5th gestational week. Craniopharyngiomas however, accounts for 6% of brain tumors in children while EC only constitutes only 1 to 2% of brain tumors. Recognizing EC early; being a rare entity and prompt intervention will be able to prevent complications and provide comfort for patients. We would like to share a case of EC in a man who was first treated as craniopharyngioma and subsequently had ‘recurrent pharyngioma’ where subsequent HPE proved to be EC.

INTRODUCTION

Epidermoid cysts (EC), also known as primary cholesteatomas, arise from epithelial cells that are retained during closure of the neural tube. ECs are congenital and formed out of aberrant ectodermal cells, which become trapped during the embryogenesis between the 3rd and 5th gestational weeks.[1] These cysts can grow by accumulating cholesterol and keratin from desquamation of the lining epithelium and potentially encases nearby nerves and arteries.

Intracranial ECs are most often located in intradural, but they can also occur extradurally in the intradiploic space in up to 10% of cases.[2] The most common intradural locations are cerebellopontine angle (60%), fourth ventricle (5%–18%), parasellar area and middle cranial fossa (15%); less frequently, within ventricles and brain parenchyma.

Here we would like to report a rare case of Epidermoid cyst masquerading as a sellar tumour in a patient seen in Hospital Tuanku Ja’afar Seremban (HTJ), Malaysia.

CASE PRESENTATION

Mr. J is a 31-year-old male who worked as a lorry driver. He complained of left eye blurring of vision since 2018. It was associated with headache and loss of weight about three kg in two months. He was referred to a neurosurgical clinic. His blood pressure was 134/89mmHg. On physical examination, his visual acuity on the left eye was 6/18 while his right vision was intact at 6/9. He did not exhibit any sign of hypogonadism. Blood investigations taken in January 2019 showed normal thyroid function test with other hormonal profile.

Magnetic Resonance Imaging (MRI) of the brain was done in July 2018 showed a sellar mass measuring 2.6cm X 2.9cm X 2.3cm. The mass has suprasellar extension and optic chiasm compression. He was advised for surgical intervention for his condition, which he declined at that point of time. He was given a neurosurgical clinic visit to review his symptoms. However, the symptoms persisted and repeated MRI was performed in January 2019 showing increasing sellar mass size measuring 2.9cm X 3.0cm X 2.4cm. The lesion appeared heterogenous, cystic and extends posteriorly which abuts the basilar artery. He was treated for craniopharyngioma, and a date was given for surgery.

He then underwent transsphenoidal excision of tumor (TSS) in March 2019 at Hospital Tuanku Ja’afar Seremban. Pre-operative blood investigations showed low FT4 and serum cortisol (as shown in Table I). Hence, Mr. J was prescribed maintenance of oral levothyroxine 50mcg daily and oral hydrocortisone 10mg in morning and 5mg in afternoon respectively. No cortisol or thyroid function test were repeated post-operatively. He was then given a 2-month endocrine clinic visit for insulin tolerance test (ITT) at medical daycare. As ITT result showed adequate cortisol response, his oral hydrocortisone was off by June 2019 and plans were given to regularly monitor his hormonal profile. Unfortunately, Mr. J did not come for any follow-up during COVID-19 pandemic. He did not take the thyroxine supplement during this period as he was asymptomatic.

In February 2023, Mr. J presented to neurosurgical team again for the complaint of headache and reduced right vision for period of 2 months since January 2023. An urgent computed tomography (CT) of brain was done and showed a well-defined lobulated isoechoic mass measuring 3.7cm X 3.0cm X 3.9cm. The mass was in the suprasellar region with mass effect (as shown in Figure 1). Again, he declined surgical intervention via open craniectomy for recurrent craniopharyngioma.

Subsequently, a new MRI brain was done on 20th April 2023 which showed larger lobulated sellar mass measuring 3.0cmX 3.3cmX 3.5cm. It was compressing to 3rd ventricles, optic chiasm and adjacent left midbrain. With the MRI brain findings and new onset of right sided body weakness for 1

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Table I: Table shows blood investigations taken prior surgery and one-week post-surgery.

	31/1/19	1/2/19	20/3/19	21/5/19	19/6/2023	29/6/23	2/7/23	3/7/23	4/7/23	11/7/23
Na (135-145)						141	150	155	148	139
K (3.5-4.5)						3.8	3.9	4.0	3.9	4.1
Urea (3.2-8.2)						4.5	4.5	3.5	3.3	3.4
Creatinine (62-115)						60	90	110	90	80
Prolactin uiu/ml (86-390)	304									
LH Iu/L (1.5-9.3)	3.7			3.2	8.1					
FSH Iu/L (1.5-12.4)	7.7			8.9	12.1					
Cortisol nmol/L	254.6	516								340.6
T4 (11.5-22.7)	11.1			12.4	12					12.9
TSH (0.55-4.78)	0.59			1.67	0.26					<0.01
Testos nmol/L (6.85-23.23)	28.64			34.25	22.9					<0.24
U. Osmo (Osm/kg)	246	550	169			618	211	106	538	
Sr Osmo (Osm/kg)		284	293			303	306	311	296	
UFEME SG						1.015	<1.005	<1.005	1.010	

Na = Sodium; mmol/L, K = Potassium; mmol/L
LH = Luteinizing Hormone, FSH = Follicle-stimulating hormone, Testos = Testosterone
T4 = Thyroxine, TSH = Thyroid Stimulating Hormone

month since May 2023, Mr. J agreed for surgical intervention during neurosurgical clinic visit on June 2023. He underwent open decompressive craniectomy surgery on 27th June 2023 for mass excision without many complications. Intra-operatively, the tumor was noted to be yellowish and has thick capsule surrounding the core. It has three main lobules which have fat-like substances in consistency. Capsulectomy was done without any major adverse event.

On 2nd July 2023, post operation day 5 (D5), Mr. J had polyuria of four liters in the span of 24 hours. Several paired serum osmolality and urine osmolality samples were taken and consistent with cranial DI (as shown in Table I). At the same time, his potassium level showed an increase from 3.8mmol/L to 4.0mmol/L. Creatinine was also noted to rise from 60 mg/L to 110mg/L. To prevent further polyuria, Mr. J was started on oral Minirin® 0.5mcg BD. He responded well to the oral Minirin®. He was discharged home well with oral Minirin® 0.5mcg BD and oral hydrocortisone 10mg BD on 11th July 2023. The Histopathology examination (HPE) result showed the sellar mass to be consistent with epidermoid cyst (as shown in Figure 2).

In following clinic visits, Mr. J recovered well. He responded well with hormone replacement oral Minirin® 0.5mcg BD and oral hydrocortisone 10mg BD. Intramuscular Testosterone replacement 250mg monthly was initiated in clinic visit as serum testosterone remained low. However, his visual field remains the same - left eye was 6/18 while his right vision was intact at 6/9. His repeated MRI Brain in September 2023 also showed no recurrence of Epidermoid Cyst. Previous right sided body weakness had also improved. He can ambulate with a walking frame and perform simple daily chores.

DISCUSSION

Epidermoid cysts (EC) account for approximately 1%-2% of all brain tumours.[3] ECs form from the accumulation of keratin and cholesterol, which desquamate into a pearly material within their walls. ECs grows in the cisternal spaces and remaining asymptomatic for years due to the absence of initial mass effect. They are commonly seen in males during the 3rd–4th decade but turn malignant predominantly in females.[4]

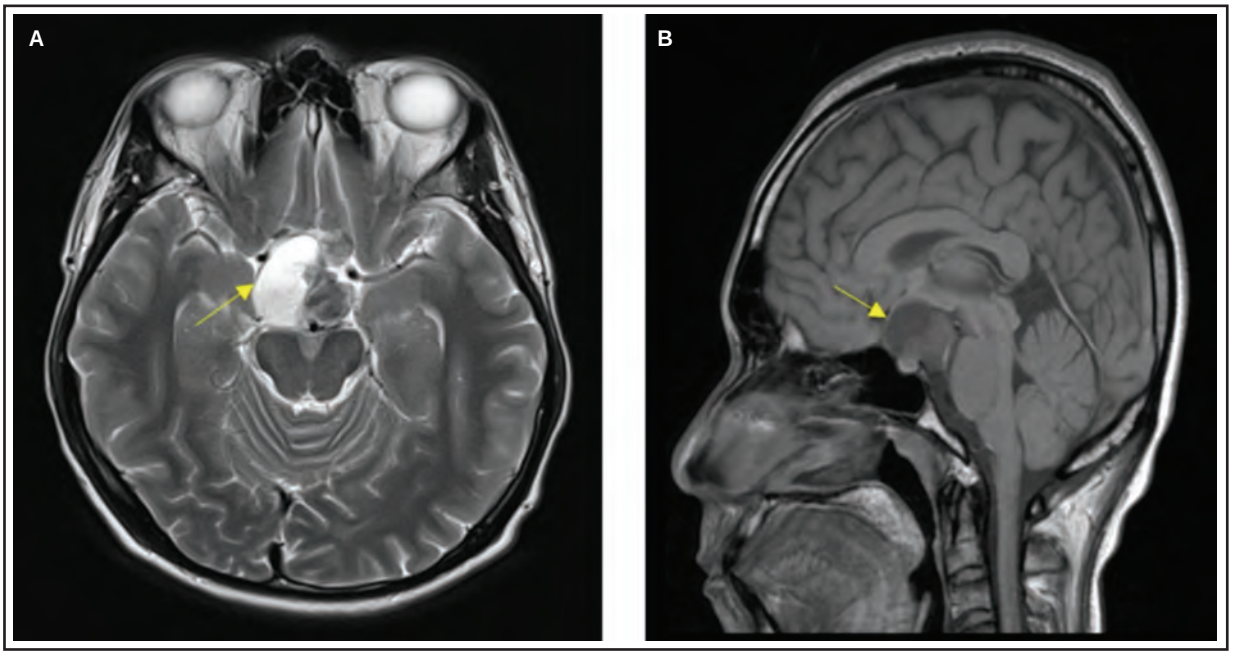

Fig. 1: Picture on the left (a) showing T2 weighted MRI brain axial view. The mass can be see via the yellow arrows. Picture on the right (b) featured MRI brain sagittal view FLAIR.

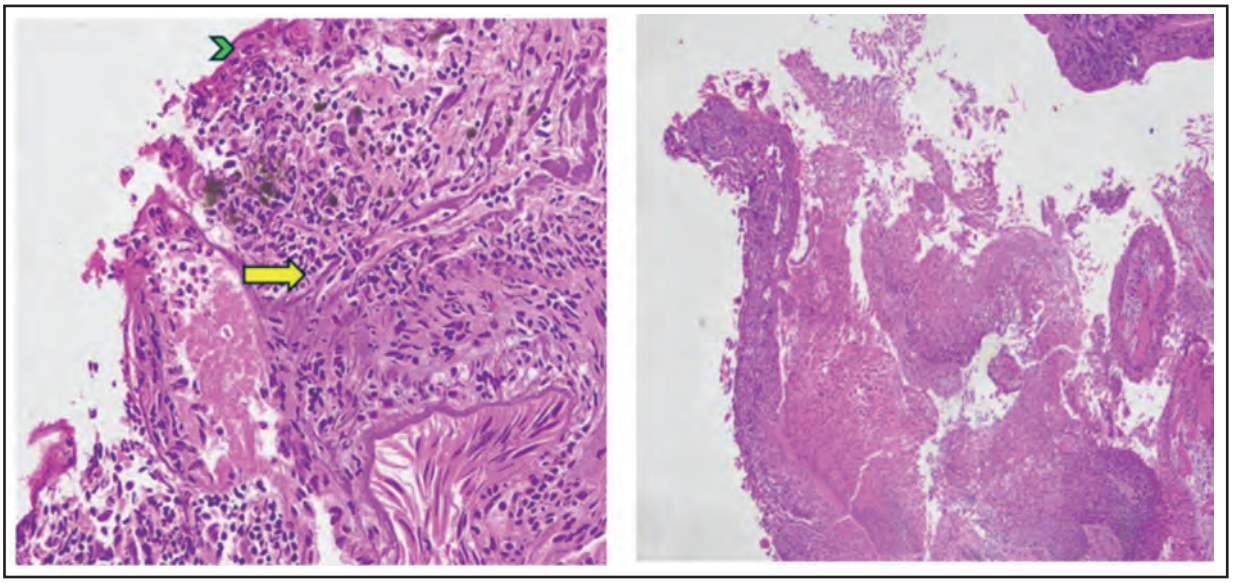

Fig. 2: Section shows severely crushed tissue composed of fibrocollagenous tissue lined by stratified squamous epithelium with granular cell layer ( ). In areas, the cyst lining is replaced by granulation tissue formation ( ). The surrounding stroma tissue show dense lymphoplasmacytic infiltrate. Some hemosiderin laden macrophages are also identified. No stellate reticulum, papillary structure or wet keratin is seen. Adjacent pituitary tissue with glial tissue is also observed.
Immunohistochemistry: The stratified squamous epithelium is positive for CK5/6 and negative for CK7, CK20, S100, GFAP, synaptophsin and chormograninA.

ECs presents similarly like the rest of intracranial space occupying lesions. Common features like headaches, cranial nerve deficits, cerebellar symptoms, seizures, raised intracranial pressure are usually seen.[5] Conventional MRI sometime cannot reliably be used to distinguish epidermoid tumours from arachnoid cysts since both lesions are very hypointense relative to brain parenchyma on T1-weighted MR. images and very hyperintense on T2- weighted images. In some literatures, ECs have been described along as cystic craniopharyngiomas.[6] Mr. J's lesion in MRI appears as suprasellar and cystic, hence initially impression was craniopharyngioma.

Histopathology examination (HPE) remains mainstay of diagnosis of ECs. The diagnosis of epidermal cyst made in this case due to presence of predominant cyst lining by stratified

squamous epithelium with prominent granular layer. The surrounding tissue shows features of foreign body granuloma possibility due to ruptured epidermal cyst. Usually there is a keratin layer within the cyst but due to long standing disease the cyst might be ruptured, and the keratin layer has been eaten up by the macrophages. No obvious stellate reticulum, papillary structure or wet keratin is identified which therefore consistent with the findings of ECs. Macroscopically epidermoid cyst appears as white caseous-like material which is like Mr. J's intraoperative findings.

Craniopharyngioma on the other hand, appears as dark 'motor-oil' fluid. Histologically, craniopharyngioma is composed of cords, lobules, nodular whorls, and trabeculae of well differentiated squamous epithelium bordered by palisading columnar epithelium cells surround looser plumper cells called stellate reticulum.

Surgical approach for ECs is generally determined by the location and the extent of the lesion.[7] Meticulous discussion and planning must be done for complete tumour resection to prevent recurrence. However, adherence of the capsule to the important neurovascular structures in and around the brain stem often leads to its incomplete removal.[8] Therefore, surgical debulking with capsule removal is a definitive treatment. Open craniotomy is the preferred choice in the case, as the lesion is large and compressing the optic chiasm and left midbrain. The surgical plane will be bigger, and lesion can be approach by the surgeon which avoiding major neurovascular structures as ECs have high capsular adherence to its' surroundings. Complications from surgery include CSF leak, aseptic meningitis, vision loss, nerve injury, diabetes insipidus (DI) and panhypopituitarism.

The risk of postoperative hypopituitarism varies according to case series and the aetiology. Surgeon's experience, the size and consistency of the tumour, the extension of surgical manipulation, and surgery for recurrent disease play a role in the occurrence of hypopituitarism. Evaluation for the anterior pituitary function should be performed approximately 4–6 weeks after pituitary surgery. Mr. J developed episodes of polyuria which prompted the screening for anterior pituitary function during postsurgical recoveries. As this is a second surgery for him, much emphasize was given to detect hypopituitarism. Early recognition enabled Mr. J to receive hormonal replacement and aided in his postoperative recovery.

Even though surgical option remains the mainstay treatment option, only 50- 80% of patients have complete removal of EC. Therefore, the recurrence rate for intracranial epidermoid cysts was stated at 24%.[9]

CONCLUSION

Identifying the nature of sellar and parasellar lesions remains challenging because of the complexity of anatomical structure of the skull base.[10] The extensive variations in pathology that one may encounter, and the similar imaging appearance and clinical presentation of some entities continue to test the acumen of clinicians. Physical findings like worsening visual field without apparent reason and compressive symptoms like headache should prompt clinicians even at primary care level to investigate further. It is also interesting to note that despite the compressive symptoms, post-surgery ITT was fairly normal. Only when the EC recurred, and Mr. J went for a second surgery did he develop cranial DI and hypopituitarism. The site of the lesion at suprasellar may mimic craniopharyngioma which may cause difficulty in diagnosis. Moreover, craniopharyngiomas accounts for 6% of brain tumors in children while EC only constitutes 1 to 2% of brain tumors – highlighting diagnosis challenge. In summary, revisiting HPE sample when encountering diagnosis dilemma and prompt intervention will be able to prevent complications and provide comfort for the patients.

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DECLARATION

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