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Supplement Copy on

Case Reports

Contents

CASE REPORT

Complicated Kartagener Syndrome Presenting as Type II Respiratory Failure: A Case report

Poonam Gupta[1*], Ajeet Kumar Chaurasia[2], Surendra Kumar Gupta[3]

Received: 19 July 2024; *Accepted:* 23 May 2025

Abstract

We report a case of a 22-year-old male who was previously treated for asthma from childhood, and his repeated respiratory infections prompted the physician to start antitubercular therapy (ATT) thrice, suspecting pulmonary tuberculosis despite being sputum acid-fast bacillus (AFB) negative every time. Diagnosis of Kartagener syndrome (autosomal recessive inheritance having a triad of bronchiectasis, chronic sinusitis, situs inversus, and strongly associated with infertility) was made in this case at our tertiary care referral hospital, but it was already too late when he presented with life-threatening bilateral pneumonia, bilateral pleural effusion with type II respiratory failure, and associated cystitis warranting mechanical ventilation, and he succumbed because of extremely and irreversibly damaged lungs.

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Introduction

In India, which is a developing country with maximum population density and where infections are rampant, transmission is very extensive and uncontrolled because of close cohabitation, so most of the time frequent respiratory infections in children are taken very casually and dealt with in a very simple manner without finding a need to search for an attributing syndrome. Breathlessness, especially if episodic, is mistaken for asthma. We report a case of a 22-year-old male who was previously treated for asthma from childhood, and his repeated respiratory infection prompted the physician to start antitubercular therapy (ATT) thrice, suspecting tubercular lung despite sputum being acid-fast bacillus (AFB) negative every time. Repeated damage due to recurrent stress in incompetent lungs always contributes to the worsening and irreversible progression of the structural and functional capacity of the lung day by day. Diagnosis of Kartagener syndrome was made in this case at our tertiary care referral hospital, but it was already too late. Kartagener syndrome is an inherited disorder producing a defect in ciliary motility, having autosomal recessive inheritance leading to a triad of bronchiectasis, chronic sinusitis, situs inversus, and strongly associated with male as well as female infertility. The patient presented with bilateral pneumonia, bilateral pleural effusion, and type II respiratory failure and could not be salvaged. Diagnosing this disorder early and intervening early could have delayed the sequelae and complications of long-term infections and could have curtailed premature death and would have prolonged survival and enhanced well-being of the patient.[1] The extent to which early diagnosis and timely management have an impact on the natural course of Kartagener syndrome is yet to be studied, and there is hardly any literature or research on it. Medical literature is just limited to case studies, especially of those cases that are recognized while they become symptomatic and seek treatment. Case reports or any medical literature about those cases of Kartagener syndrome who are in the complicated life-threatening stages are hardly documented, and the total lack of it prompted and essentialized these types of reporting so that awareness and knowledge can be further enhanced and imparted to other treating physicians.

Case Description

A 22-year-old male presented to SRN Hospital in the last week of February 2024 with complaints of breathlessness for 1 month, which aggravated for 1 day, and fever along with cough and expectoration for 15 days.

Past history of frequent lung infections from childhood, for which he was repeatedly treated as asthma.

Physical examination revealed pectus excavatum in the front of the chest and scoliosis on the back. The cardiac apex was felt on the right 5th intercostal space at the midclavicular line. On respiratory system examination, besides pectus excavatum on inspection, poor air entry, rhonchi, and coarse crepitations were audible in all areas except at the bases of both lungs. There was no evidence of ear involvement even by otoscopy. On genitourinary examination, no epispadias was found.

As some congenital heart diseases also present with breathlessness and recurrent lung infections, these were included in the differential diagnosis besides young-age-onset asthma. Congenital heart diseases are mostly seen with a precordial bulge, and asthmatic patients have a hyperinflated elliptical chest with increased anteroposterior dimension of the chest, but here, pectus excavatum was observed. As the apex beat was clinically on the right side, chest X-ray, ECG, and 2D echo were done besides blood tests to further evaluate these differentials.

Investigation

Diagnosis of Kartagener syndrome was made on the basis of history; pectus excavatum (Fig. 4), apical impulse on the right side with electrocardiogram showing dextrocardia, RAD, and QRS progressively diminishing in leads V1–V6, and CXR PA view confirming dextrocardia and scoliosis. 2D echocardiography showed dextrocardia and no other defects (Table 1). Doppler study showed situs inversus of great vessels like the aorta and inferior vena cava. CT thorax suggested bronchiectasis, bilateral pneumonia, bilateral pleural effusion, and scoliosis, and CT paranasal sinuses (PNS) showed chronic sinusitis. Diagnostic criteria for Kartagener syndrome[1,2] are shown in Table 2.

Our patient was diagnosed with Kartagener syndrome in accordance with the abovementioned criteria. As the patient presented in severe respiratory distress, urgent ABG was done. ABG showed respiratory acidosis with hypercapnia and hypoxia, suggestive of type 2 respiratory failure. The patient was kept in the intensive care unit

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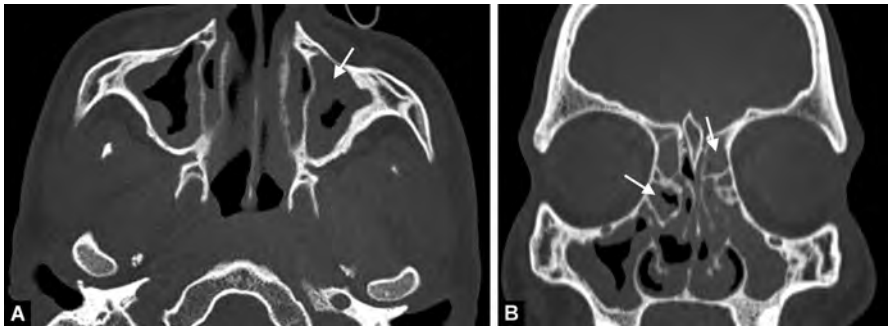
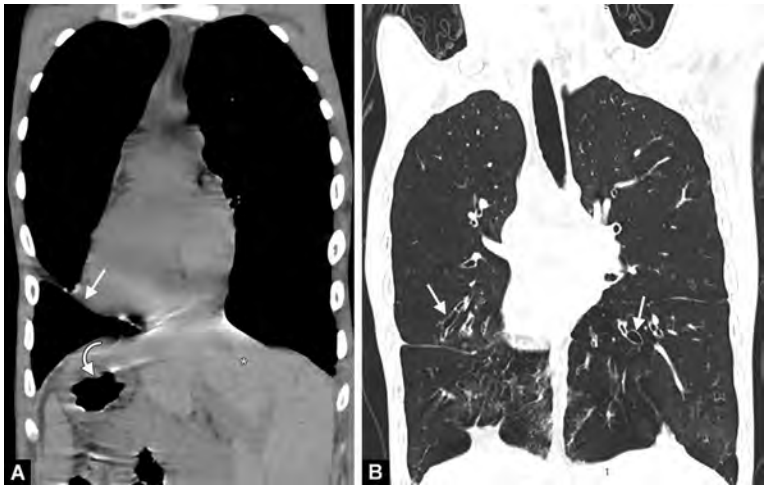
Table 1: Showing investigations of the case

Tests	*Patient's value*
ABG on admission day 1	pH = 7.210, pCO_2 = 91.4 mm Hg, HCO_3 = 35.7 mEq/L
ABG day 3	pH = 7.333, pCO_2 = 76.6 mm Hg, HCO_3 = 39.8 mEq/L
Endotracheal tube tip culture and sensitivity day 7	*Klebsiella* sp.
TLC day 1 Day 4	14,400/mL (normal = 4,000–10,000/mL) 10,800/mL
S. Albumin day 1 Day 4	2.9 mg/dL (normal = 3.5–5.5 mg/dL) 2.7 mg/dL
USG abdomen	Liver situated on the left Spleen and stomach situated on the right
CXR	Scoliosis Hyperinflated lungs Dextrocardia
CT paranasal sinuses	Thickened mucosa in all the sinuses—frontal, sphenoidal, ethmoidal, and maxillary—suggestive of chronic sinusitis (Figs 1A and B)
CT thorax	Bronchiectatic consolidation in bilateral lower lobes and pleural effusion, scoliosis (Figs 2 and 3)
ECG	QRS complexes becoming smaller in lateral V5 and V6 leads, showing dextrocardia



Figs 1A and B: Plain axial CT paranasal sinuses bone window (A) showing mild mucosal thickening in bilateral maxillary sinuses (black arrow) opacifying sinus cavities. Plain axial CT paranasal sinuses coronal MPR bone window (B) showing mucosal thickening and retained secretions in bilateral paranasal sinuses (small arrows)



Figs 2A and B: Plain CT scan chest mediastinal window coronal MPR (A) showing cardiac apex directed toward the right side (down white arrow), liver on the left side (white star), and stomach on the right side (curved arrow) suggestive of situs inversus. Plain CT scan, lung window, coronal MPR (B) showing bilateral hyperinflated lungs with cylindrical bronchiectatic changes in bilateral lower lobes (small black arrows)

on noninvasive BIPAP ventilator support along with oxygenation. Broad-spectrum antibiotic to combat infection, antipyretics, bronchodilators, and mucolytics were given. Deterioration in condition warranted invasive mechanical ventilator support, but he could not be revived even with the best possible management and succumbed.

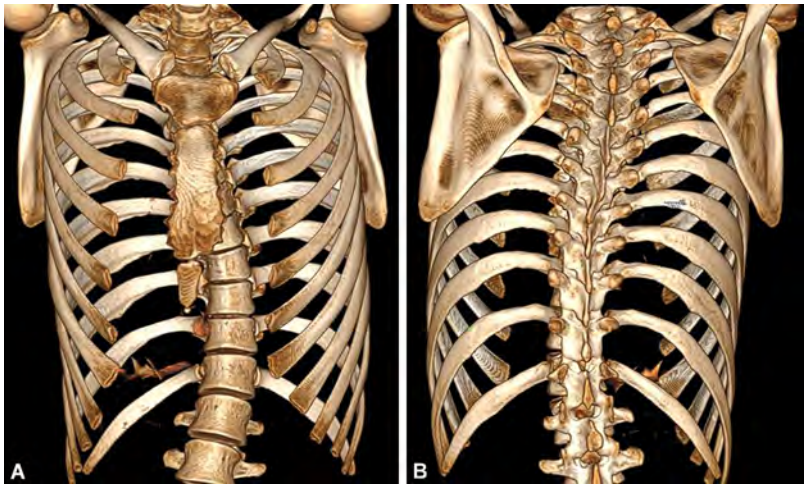
Discussion

Any patient having recurrent respiratory illnesses, especially from childhood, needs a thorough workup to look for any predisposing medical illness. Even suspected tuberculosis, if sputum AFB negative, warrants a thorough etiological evaluation. Asthma and bronchiectasis are both airway diseases with hyperinflated chest, rhonchi on auscultation, and spirometry suggestive of obstructive airway disease in common. Both have a bimodal onset, once in childhood and second in middle to elderly age. Bronchiectasis can be congenital or acquired; acquired usually occurs in later ages. Our patient had a history of repeated respiratory tract infection from early stages of life. CT scan paranasal sinuses was suggestive of chronic sinusitis, showing diffuse mucoperiosteal hypertrophy with rarefaction of the underlying bone involving frontal, ethmoid, maxillary, and sphenoidal sinuses; ECG, USG abdomen, and CT thorax confirmed situs inversus and dextrocardia.

Kartagener syndrome belongs to a category of primary ciliary dyskinesias (PCDs), which includes entities with defective ciliary movement. In 1904, Siewert[3] was the foremost to bring the concept of the association of bronchiectasis, situs inversus, and chronic sinusitis. Kartagener[4] was the earliest to discover it to be congenital in 1933, detailing and naming it. The calculated incidence is about 1 out of 30,000 live births.[2]

Primary ciliary dyskinesias are either congenital or acquired. Congenital ones are known as PCDs. Situs inversus is seen in approximately half the cases of PCDs. Those PCDs with situs inversus are termed Kartagener syndrome.[5] There is no genderwise predisposition.[6]

PCD is a phenotypically and genetically heterogeneous condition where abnormality in ultrastructure, such as dynein arms, or function of cilia is present in approximately 90% of patients, with 38%[7–9] of the PCD patients carrying mutations of the dynein genes DNAI[10] and DNAH5.[5] The age at presentation, extent of manifestations, and the time at which diagnosis gets confirmed vary, despite symptoms manifesting early in life.[11,12] Airway obstruction can be reversible to a variable extent in Kartagener syndrome.[13]



Figs 3A and B: (A) Kartagener syndrome 3D VRT scoliosis; (B) Scoliosis 3D VRT in Kartagener syndrome

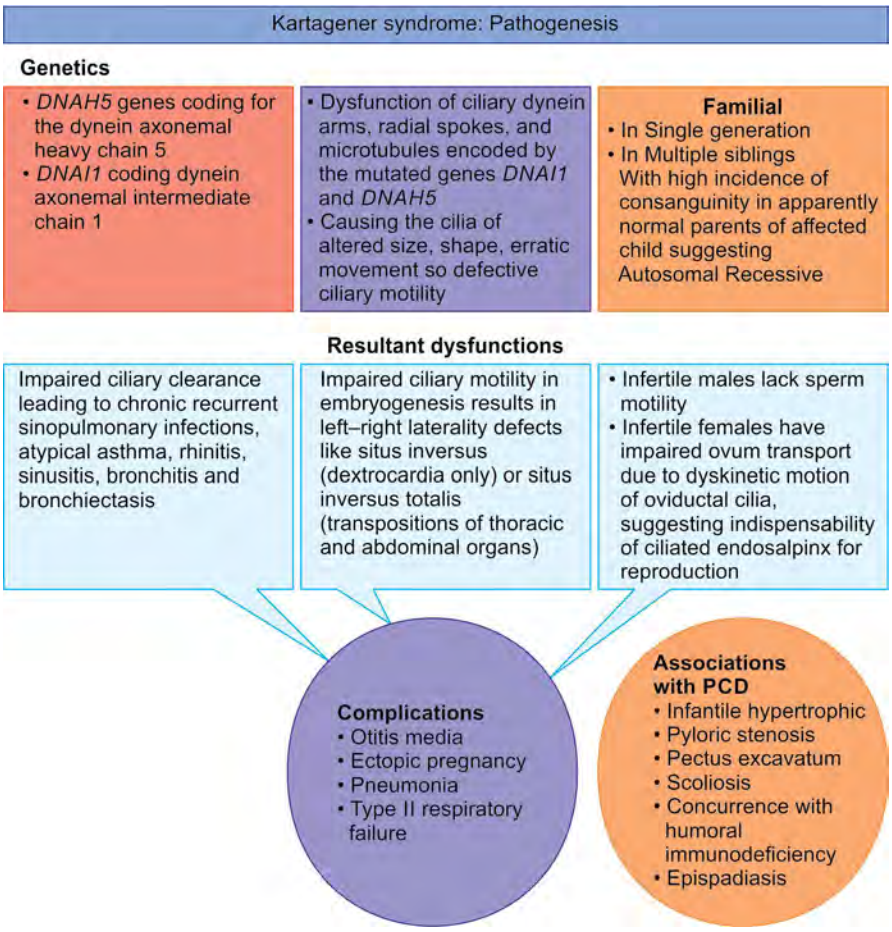


Fig. 5: Showing pathogenesis of Kartagener syndrome

The pace of deterioration varies, sometimes necessitating lung transplantation in extreme worsening.

In our patient, no history of consanguinity was present in the parents. Pathogenesis of Kartagener syndrome is shown in Figure 5 in the form of graphics.[6,9,14–22] Most infertile patients with KS have a normal spermatozoid count but with a structural defect and a complete lack of motility.[17] As our patient presented in critical condition, semen analysis could not be done.

In the present case, all confirmatory tests for ciliary dysfunction could not be performed because of nonavailability, so the diagnosis of KS in this case was based on clinical criteria and basic imaging studies. KS, being a genetic disorder, is incurable and has

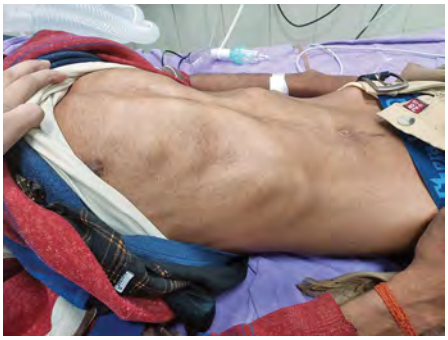


Fig. 4: Pectus excavatum in Kartagener syndrome

Table 2: Diagnostic criteria for Kartagener syndrome

Any symptoms from early life:	*Additional any or more:*
i. Chronic respiratory infection	i. Having situs inversus or dextrocardia in self or a sibling
ii. Chronic bronchitis	ii. Immotile sperms
iii. Chronic rhinitis	iii. Defective airway clearance
iv. Chronic sinusitis	iv. Ciliary structural defect on electron microscopy
	v. Bronchiectasis

no specific treatment. Treatment should be in accordance with the main manifestations and complications as shown in Table 3.[16,23–35]

Our patient was diagnosed late and had full-blown bronchiectasis with bilateral pneumonia and pleural effusion, having the worst prognosis, and thus succumbed despite all efforts. A high degree of suspicion among physicians could have been lifesaving. The assumption that early diagnosis maintains good lung function, good quality of life, and prolongs survival[36,37] has yet to be confirmed. Previous case reports have shown infertility in males and a few with medically assisted progeny using subzonal insemination (SUZI) and intracytoplasmic sperm injection (ICSI).[38] Women too have reduced fertility.[17] Diminished sperm motility causes infertility in men, while in women it is due to defective ovum transport because of improper motion of fallopian tubal cilia, attributing it as essential for human reproduction.[18]

In the absence of feasible and accessible diagnostic tests, diagnosis is often delayed, lowering the quality of life[16,23–26] and causing patients to land up in type II respiratory failure. See Table 3 for diagnostic tests used in Kartagener syndrome and its pointwise management.[16,23–35] Despite the latest diagnostic tests, a full standard test to confirm the diagnosis is lacking.

Discovery of novel mutant genes related to this disease supports the existence of some nonmanifesting ciliary mutations, indicating that genetic testing carries great potential

Table 3: Showing all diagnostic tests and management

Diagnostic tests			*Standard therapy*
Imaging	*Testing cilia function*	*Microscopy*	
• Dextrocardia: ECG, CXR, ECHO • Sinusitis: CT PNS • Situs inversus and bronchiectatic changes: CT thorax and abdomen	• Semen analysis—sperm immotility • The saccharin test—abnormal mucociliary clearance. Test measures the time taken for a pellet of saccharin placed on the inferior turbinate to be tasted (30 minutes is the cutoff point that discriminates normal individuals from patients with impaired nasal mucociliary clearance) • Measurement of the exhaled NO from each nostril—consistently only 10–20% of the average normal values; low in cystic fibrosis, very low in PCD. Also helps in assessing ciliary motility • Mucociliary transport measured *in situ* by administering an inhalation aerosol of colloid albumin tagged with 99mTc. This test uses aerosol particles tagged with 99mTc and external measurement of the radioactivity	• Electron microscopy visualizes the ciliary structure in nasal scrape, brush biopsy, or bronchial biopsy • High-speed video microscopy of ciliary beats • With immunofluorescence technique, parts of the ciliary structure are stained by specific antibodies and show complete absence of dynein arms on cross-section • Testing of mutated genes DNAI1 and DNAH5 in specialized labs	• Antibiotic coverage • Mucolytics • Nebulization • Chest physiotherapy and postural drainage • Long-term low-dose prophylactic antibiotic, especially azithromycin thrice a week in those with frequent exacerbation of bronchiectasis (≥3 times/year) • Influenza and pneumococcal vaccination are also indicated • Lung transplantation • Functional endoscopic sinus surgery

as a confirming diagnostic tool for these patients in the future.[39] A single case report of Kartagener syndrome in type II respiratory failure was reported in a toddler in medical literature and was weaned off invasive ventilator support and survived that episode,[1] but as the case was too young, the possibility of survival cannot be compared with our case as ours was an adult. Moreover, the child presented acutely in just 3 days of respiratory illness with normal lungs on imaging and total absence of bronchiectasis,[1] while our case presented with a history of 1-month duration with gross lung involvement with bilateral pneumonia and bilateral pleural effusion, making the prognosis worse. In our case, due to delayed diagnosis, our patient developed scoliosis, pneumonia, pleural effusion, and type II respiratory failure, culminating in his demise.

There is a total lack of medical literature regarding sequelae, complications, associated musculoskeletal features, and prognostic factors in Kartagener syndrome. Some cases of Kartagener syndrome have been reported with associated congenital heart disease like TOF, TGA, ASD, VSD,[40,41] Bochdalek hernia, and inguinal hernia[42] besides what is shown in Figure 5. This case had the worst prognosis and needs to be considered thoroughly to understand how the impact of defective ciliary clearance culminates in the death of the patient.

Clinical Significance

Delayed diagnosis of Kartagener syndrome does not give an opportunity to halt disease progression, and the patient succumbed because of early-onset type II respiratory failure, thus decreasing the survival of young adults. This patient had associated pectus excavatum and scoliosis. In patients presenting with frequent respiratory infections, Kartagener syndrome should always be considered, especially if there is evidence of situs inversus. It is very important to diagnose this disorder early in life to curtail sequelae and complications, prolong survival, and enhance the well-being of the patient.

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CASE REPORT

A Rare Occurrence of Microscopic Polyangiitis and Aortitis

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Abstract

We present a case of a 60-year-old male with a fever of unknown origin (FUO) who was ultimately diagnosed with perinuclear antineutrophil cytoplasmic antibodies (p-ANCA)–associated microscopic polyangiitis (MPA) and aortitis. This case underscores the diagnostic intricacies and therapeutic challenges of managing such rare and severe multisystem involvement. It also highlights the critical importance of clinician awareness for prompt recognition and effective management of similar presentations.

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Introduction

Petersdorf and Beeson initially defined fever of unknown origin (FUO) in 1961 as a body temperature exceeding 38.3°C (101°F) on three or more occasions, lasting for at least 3 weeks, without a diagnosis after 1 week of hospital admission.[1] Over time, this definition has been modified to exclude immunocompromised patients.[2] FUO causes are infections, malignancies, noninfectious inflammatory diseases (NIID), and miscellaneous causes. Infections are the leading cause in developing countries, while NIID predominates in developed countries. Microscopic polyangiitis (MPA) is a rare systemic vasculitis primarily affecting small vessels, characterized by the presence of antineutrophil cytoplasmic antibodies (ANCA), particularly perinuclear ANCA (p-ANCA).[3] The association of MPA with aortitis is even more uncommon and presents a diagnostic challenge due to its overlapping symptoms with other febrile conditions.[4] This case highlights the importance of considering systemic vasculitis in the differential diagnosis of FUO, particularly when standard investigations fail to reveal an etiology. Through a detailed clinical course, we explore the diagnostic process, therapeutic interventions, and the complexities of managing this rare presentation.

Case Description

A 60-year-old male comes to the outpatient department (OPD) with the chief complaint of persistent fever for the past 6 weeks, with temperatures reaching up to 103°F on multiple occasions. The patient's symptoms began insidiously, initially presenting as low-grade fevers accompanied by generalized fatigue. Over the following weeks, the fever became more pronounced, occurring daily, and was associated with unintentional weight loss of approximately 3 kg. There was no history of any recent travel, animal exposure, or contact with individuals with similar symptoms. There were no associated respiratory, gastrointestinal, or urinary symptoms, or history of joint pain, skin rashes, neurological deficits, or any respiratory or cardiovascular ailment. The patient has had a history of hypertension for the past 8 years and was treated for an episode of invasive pulmonary aspergillosis 2 years ago.

On admission, the patient appeared mildly ill but was alert and oriented. His vital signs showed a temperature of 101.5°F, a heart rate of 98 beats per minute, blood pressure of 135/85 mm Hg, respiratory rate of 18 breaths per minute, and oxygen saturation of 98% on room air. The physical examination was unremarkable, with no apparent source of infection or inflammation. There were no lymphadenopathies, and cardiovascular, respiratory, and neurological examinations were normal. No skin lesions, rashes, or temporal artery tenderness were noted. Initial investigations revealed normocytic normochromic anemia with a hemoglobin level of 6.8, a normal white blood cell count of 9.5×10^3/µL, and an elevated platelet count of 645×10^3/µL. Inflammatory markers were significantly elevated, with an erythrocyte sedimentation rate (ESR) of 120 mm/hour and a C-reactive protein (CRP) level of 168 mg/L. Liver function tests (LFT) and renal function tests (RFT) were within normal range. Urinalysis revealed microscopic hematuria [10–15 red blood cells (RBCs)/high-power field (HPF)] and 1+ proteinuria.

Blood, urine, and sputum cultures were negative for bacterial, fungal, and mycobacterial infections. Viral serologies for hepatitis A, B, C, and E, cytomegalovirus, Epstein–Barr virus, and human immunodeficiency virus (HIV) were also negative. The autoimmune panel revealed a positive p-ANCA and a positive anti-myeloperoxidase (MPO), suggesting a possible vasculitic process. The titer for anti-MPO was 26 IU/mL, which was determined using the fluorimetric enzyme-linked assay (FEIA). Other tests for antinuclear antibody (ANA), rheumatoid factor, anticyclic citrullinated peptide (CCP), antidouble-stranded deoxyribonucleic acid (dsDNA), and antiglomerular basement membrane (GBM) were negative. IgG4, C3, C4, and complement levels were within normal range. A subsequent 24-hour urinary protein revealed 504 mg, which is significant proteinuria. Chest X-ray and two-dimensional (2D) echo revealed no significant findings. Given the persistent fever, elevated inflammatory markers, positive p-ANCA, and microscopic hematuria with proteinuria, further investigations included renal Doppler ultrasound, which demonstrated increased bilateral cortical echogenicity, raising the possibility of underlying renal pathology. Positron emission tomography (PET) scan revealed metabolically active diffuse circumferential wall thickening involving the arch (Fig. 1) and lower abdominal aorta (Fig. 2), indicating ongoing inflammation, findings consistent

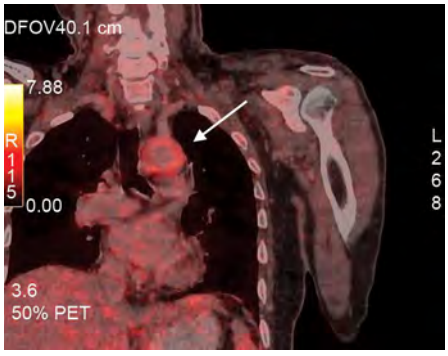

Fig. 1: Fluorine-18 fluorodeoxyglucose (18F-FDG) PET-CT in sagittal view showing avid tracer uptake in the arch of the aorta (white arrow)

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with large-vessel vasculitis, indicative of aortitis.

Temporal artery ultrasound was performed to rule out giant cell arteritis and was normal, with no evidence of temporal artery inflammation. A temporal artery biopsy was not performed due to its invasive nature and lack of any clinical features of giant cell arteritis. Positive p-ANCA, microscopic hematuria, and proteinuria with increased bilateral cortical echogenicity led us to perform a renal biopsy, which revealed pauci-immune crescentic glomerulonephritis (Figs 3 and 4), confirming the presence of small-vessel vasculitis.

The clinical presentation, positive p-ANCA serology, urinalysis, renal biopsy findings, and PET scan results led us to diagnose MPA with associated aortitis.

The patient was started on high-dose corticosteroids (prednisone 60 mg daily) to control the systemic inflammation. Additionally, cyclophosphamide was initiated as an immunosuppressive therapy to manage the vasculitis and prevent further disease progression.

The patient responded well to the treatment, significantly reducing fever and improving his overall condition within days. On a 10-day follow-up, the fever had completely resolved, his inflammatory markers had decreased, and there was no microscopic hematuria or proteinuria on urinalysis. We plan a follow-up PET scan 3 months later to investigate the aortic inflammation.

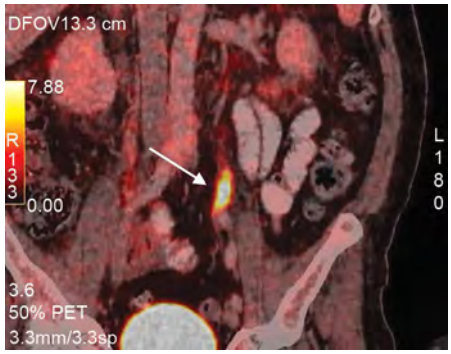

Fig. 2: 18F-FDG PET-CT in sagittal view showing avid tracer uptake in the lower abdominal aorta (white arrow)

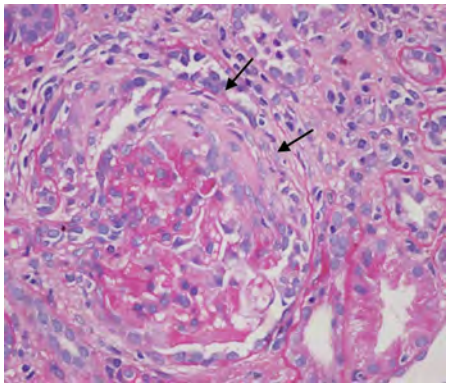

Fig. 3: Photomicrograph showing a glomerulus with cellular crescents—periodic acid-Schiff 400× (black arrows)

Discussion

The FUO is defined as a body temperature higher than 38.3°C (100.9°F) that lasts >3 weeks and has no apparent source despite an appropriate investigation being carried out.[1] It is further broken down as a differential into four major categories: infectious, malignancies, autoimmune conditions, and miscellaneous. Infections remain the most common cause of FUO in study reports. FUO remains a diagnostic challenge that requires extensive work-up; even after that, many cases remain undiagnosed.

We present a case where our patient came to the OPD with 6 weeks of fever. The initial investigations in our case, including cultures and imaging, were inconclusive, with a single clue of elevated CRP and ESR, which led us to probe further, and p-ANCA and MPO antigen positivity took us closer to the diagnosis. In a study[5] of 857 published

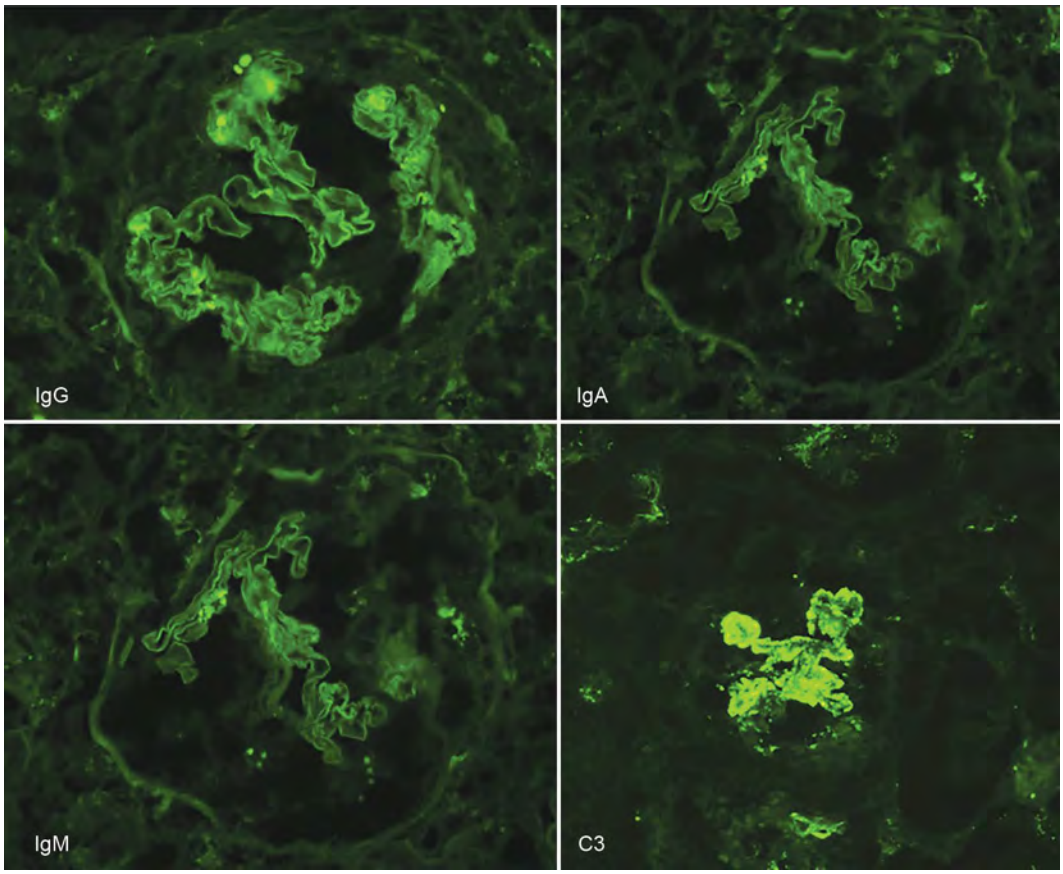

Fig. 4: Immunofluorescence shows absence of immunoglobulin deposits, favoring pauci-immune glomerulonephritis

adult FUO cases, collagen vascular diseases constituted 14.7% of the cases, and 25% of collagen vascular diseases were diagnosed as vasculitis. Vasculitis is a group of disorders characterized by inflammation of blood vessels that may occur as a primary process or secondary to another underlying disease. The Chapel Hill classification[6] of vasculitis is given in Table 1.

Our patient had a rare manifestation of a small- and large-vessel disease. The PET-computed tomography (CT) revealed inflammation of the arch and lower abdominal aorta, whereas ANCA positivity and renal biopsy findings cemented the diagnosis of MPA. ANCA-associated vasculitides (AAV) include granulomatosis with polyangiitis (GPA), MPA, and eosinophilic granulomatosis with polyangiitis (EGPA).

Microscopic polyangiitis commonly affects the kidneys, and this was evident in our patient, who presented with microscopic hematuria, proteinuria, and increased cortical echogenicity on renal Doppler ultrasound. The renal biopsy confirmed pauci-immune crescentic glomerulonephritis with fibrinoid necrosis, which is pathognomonic for MPA. This finding was critical in forming the diagnosis and guiding the subsequent therapeutic approach.

In the renal biopsy findings, 100% of patients with MPA have focal segmental necrotizing glomerulonephritis, whereas 90% have glomerular crescents.[7] About 20% of cases have frank vasculitis and fibrinoid necrosis, a less common finding. Interstitial nephritis and tubular atrophy affect about half of MPA patients.[7] The diagnosis of MPA was clinched on the criteria defined by the latest guidelines of the 2022 ACR/EULAR classification of AAV, which we have also elucidated in Table 2.[8–10] Our case scored 9 points with positive p-ANCA or MPO (+6) and pauci-immune glomerulonephritis on biopsy (+3), meeting the criteria for MPA.

The MPA has an autoimmune pathophysiology with an idiopathic origin, primarily affecting the small-caliber blood vessels.[3]

Its common presentation is pulmonary capillaritis and glomerulonephritis, involving the skin and gastrointestinal tract. It is one of the common causes of pulmonary-renal syndrome.[3] This group of disorders also includes Goodpasture syndrome, which is

Table 1: Chapel Hill classification

Large vessel vasculitis	Giant cell arteritis Takayasu arteritis
Medium vessel vasculitis	Polyarteritis nodosa Kawasaki disease
Small vessel vasculitis	1. ANCA–associated vasculitis: • MPA • GPA (Wegener's) • EGPA (Churg–Strauss) 2. Immune complex SVV • Anti-GBM disease • Cryoglobulinemic vasculitis (CV) • IgA vasculitis (IgAV) (Henoch–Schönlein) • Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis) 3. Variable vessel vasculitis (VVV) • Behçet disease (BD) • Cogan syndrome (CS) 4. Single-organ vasculitis (SOV) • Cutaneous leukocytoclastic angiitis • Cutaneous arteritis • Primary central nervous system vasculitis isolated aortitis • Others 5. Vasculitis-associated with systemic disease • Lupus vasculitis • Rheumatoid vasculitis • Sarcoid vasculitis • Others 6. Vasculitis-associated with probable etiology • Hepatitis C virus-associated CV • Hepatitis B virus-associated vasculitis • Syphilis-associated aortitis • Drug-associated immune complex vasculitis • Drug-associated ANCA-associated vasculitis • Cancer-associated vasculitis • Others

Table 2: The 2022 ACR/EULAR classification for AAV criteria

	GPA	*MPA*	*EGPA*
Clinical	Nasal (+3) Crusts, discharge, congestion, ulcers, perforation Cartilage (+2) Ear, nose, stridor, saddle nose, endobronchial Hearing loss (+1)	Nasal (–3) Crusts, discharge, congestion, ulcers, perforation	Asthma (+3) Nasal polyps (+3) Mononeuritis multiplex (+1)
Lab, imaging, serology	Positive cytoplasmic antineutrophil cytoplasmic antibody (cANCA) or PR3 (+5) Sinus imaging—effusion, consolidation (+1) Chest imaging—nodules, mass, cavitation (+2) Granuloma on biopsy (+2) Pauci-immune GN on biopsy (+1) Positive pANCA or MPO (–1) Blood eosinophils $\geq 1 \times 10^9$/L (–4)	Positive p-ANCA or MPO (+6) Chest imaging—fibrosis/ILD present (+3) Pauci-immune GN on biopsy (+3) Positive cANCA or PR3 (–1) Blood eosinophils $\geq 1 \times 10^9$/L (–4)	Blood eosinophils $\geq 1 \times 10^9$/L (+5) Extravascular eosinophil-rich inflammation on biopsy (+2) Positive cANCA or PR3 (–3) Hematuria (–1)
Scoring	≥5 = GPA	≥5 = MPA	≥6 = EGPA

linked to anti-GBM antibodies, systemic lupus erythematosus (SLE), and GPA.[3]

A particularly unusual aspect of this case was the involvement of the aorta, as demonstrated by active ongoing inflammation in the ascending arch and abdominal aorta on a PET scan. Aortitis is a rare feature of MPA, making this an atypical and noteworthy presentation. Aortitis is classified into categories of infectious and rheumatologic diseases, along with a subset of isolated aortitis.[11]

There are multiple factors that determine the way ANCA affects the vessels, which primarily include infections, drugs like propylthiouracil and hydralazine, and various environmental factors along with genetic elements.[12,13]

In one of the mechanisms proposed, it is stated that ANCA causes vasa vasorum vasculitis in the adventitia, which further spreads to the media and intima, ultimately leading to aortitis.[14]

Aortic inflammation is also proposed to be caused by retroperitoneal arteries involvement (periaortitis).[15]

Aortic involvement is reported in both GPA and MPA but not in EGPA.[14] Misdiagnosis becomes common in such cases due to a presentation with constitutional symptoms, potentially leading to fatal outcomes in ANCA-related aortitis.[14] In a case presented by Chirinos et al.,[14] a 53-year-old woman came to the hospital with the chief complaints of fever, weight loss, night sweats, and pulmonary infiltrates. She was diagnosed with community-acquired pneumonia and treated for the same. There was a surprising twist in the case when she was later diagnosed with MPA and had a fatal aortic dissection.[14]

The ANCA targets specific antigens in small-vessel vasculitis, with antiproteinase 3 (PR3) linked to GPA and anti-MPO to MPA.[16] The pathogenic process may involve epitope spreading or complementary protein interaction, leading to T-cell-driven inflammation. Neutrophils, monocytes, and B-cells also play crucial roles.[17] While ANCA-associated large-vessel vasculitis mechanisms remain unclear, evidence suggests involvement through intimal inflammation without affecting deeper vessel layers, warranting further research to elucidate the pathophysiology.[18]

Treating aortitis-associated MPA primarily involves glucocorticoids and a cytotoxic agent such as cyclophosphamide.[3,10,14] We started our patient on high-dose prednisolone at 60 mg/day and cyclophosphamide at 2 mg/kg/day. At a 2- and 8-week follow-up, he remained afebrile, and his RFT and urine microscopy were within normal range.

Along with showcasing the rare association of aortitis with MPA, we highlight the importance of early diagnosis and initiation of treatment in such cases. Renal involvement in MPA is a known cause of morbidity. It can lead to progressive renal failure if not promptly treated.[3]

Patient education and compliance also play a pivotal role in managing such cases, as they require long-term monitoring and follow-up.

Conclusion

This case highlights the diagnostic complexity and therapeutic challenges of managing MPA with aortitis, a rare and atypical manifestation. The prompt identification of p-ANCA positivity and renal biopsy findings was critical in confirming the diagnosis and guiding effective treatment. Early intervention with high-dose corticosteroids and cyclophosphamide led to significant clinical improvement, emphasizing the importance of clinician awareness in recognizing such presentations. The involvement of the aorta in MPA, as demonstrated by PET-CT, underscores the need for further research into the pathophysiology and optimal management of ANCA-associated large-vessel vasculitis.

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CASE REPORT

Myasthenic Crisis Unmasking Myocardial Infarction with Nonobstructive Coronary Arteries in a Patient with Undiagnosed Myasthenia Gravis

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Abstract

We present a case of a patient with undiagnosed myasthenia gravis presenting in myasthenic crisis. In this case, the patient presented primarily with myocardial infarction with nonobstructive coronary arteries and respiratory failure and was later diagnosed to be in myasthenic crisis. The myasthenic crisis was treated with intravenous immunoglobulin (IVIg) and corticosteroids. Given the inadequate response to IVIg and glucocorticoids, the patient was subsequently administered an anti-CD20 monoclonal antibody in the form of rituximab. The patient responded well to rituximab, and her cardiac function subsequently improved.

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Introduction

Undiagnosed myasthenia gravis (MG) very rarely presents with myasthenic crisis as a presenting feature. There have been few case reports in which the patient presented with refractory respiratory failure and was later diagnosed with MG.[1,2] Cardiac manifestations of MG include myocarditis, heart failure, cardiomyopathy, arrhythmias, and pericarditis. However, MG presenting in myasthenic crisis with myocardial infarction with nonobstructive coronary arteries (MINOCA) is a rare and noteworthy occurrence.

Case Description

A 71-year-old female with diet-controlled dyslipidemia and hypothyroidism on levothyroxine initially presented in the outpatient department with complaints of generalized weakness and fatigue for 2 days, where she was given symptomatic treatment and advised follow-up with investigations.

Two days later, she presented in our emergency department with complaints of progressive difficulty in swallowing (solids more than liquids), breathlessness beginning 1 day before, and inability to walk along with altered neck holding since the morning of the day of presentation. On assessment in the emergency department, she had stable vital signs. Neurological examination revealed bilateral ptosis along with proximal upper and lower limb and neck muscle weakness (Medical Research Council grade 3/5). There was no neck stiffness or rigidity on examination. The rest of the systemic examination was unremarkable.

The electrocardiogram (ECG) (Fig. 1) revealed nonspecific ST-T changes in the V4 and V5 leads, and troponin I was elevated (2754 ng/L). Two-dimensional echocardiography (2D ECHO) revealed a left ventricular ejection fraction (LVEF) of 35% with mid-distal inferoposterolateral wall hypokinesia. The patient was shifted for coronary angiography (CAG), which was indicative of nonobstructive coronary artery disease (Fig. 2).

The patient became drowsy and disoriented after CAG. Arterial blood gas (ABG) analysis revealed hypoxemia with hypercapnia (PCO_2 of 99 mm Hg); hence, the patient was intubated and put on a mechanical ventilator. The patient became conscious and alert on ventilator support but continued to have neck and proximal muscle weakness. Magnetic resonance imaging (MRI) of the brain was normal. The creatine kinase level (586 U/L) was not substantially high. The electromyography and decremental study showed no abnormality. The antiacetylcholine receptor (anti-AChR) antibody titer was >80 nmol/L (strongly positive), which confirmed the diagnosis of generalized myasthenia gravis (GMG). Antimuscle-specific kinase (anti-MuSK) antibodies were negative.

The patient was started on pyridostigmine and soon upscaled to a dosage of 180 mg/day. Only marginal improvement was observed with pyridostigmine; hence, glucocorticoids were added from the armamentarium (tablet prednisolone 50 mg OD), and intravenous immunoglobulin (IVIg) was administered in view of the crisis (2 mg/kg dose OD over 5 days). The patient was weaned off the ventilator and placed on noninvasive pressure support ventilation (NIPSV). She had a second flare-up of GMG triggered by ventilator-associated pneumonia (VAP) and was reintubated. VAP was treated with broad-spectrum antibiotics.

The patient experienced marginal improvement in neck muscle weakness and proximal muscles after 12 days of treatment with glucocorticoid. It was later decided to start rituximab (375 mg/m^2 once a week for 4 weeks) in view of the unsatisfactory response to ongoing therapy. She was weaned off the ventilator, extubated, and shifted to NIPSV support. Power in the neck muscles improved, and dysphagia decreased with the following doses of rituximab. She was weaned off NIPSV support.

The patient continued to follow up for maintenance doses of rituximab (6 monthly). On follow-up, the patient showed no muscle weakness or dysphagia. Cardiac ultrasound after 6 months revealed a normalized ejection fraction (60%) with no regional wall motion abnormalities.

Discussion

Approximately one-fifth of patients experience crisis episodes in the first year of their disease, and myasthenic crisis typically occurs within the first 2 years after the disease process begins.[3] Patients with generalized myasthenia most frequently land in myasthenic crisis. In 30–40% of cases, infections were found to be the most common trigger, as witnessed in the second flare up in this case as well. A number of medications that impact the neuromuscular junction are also linked to myasthenic

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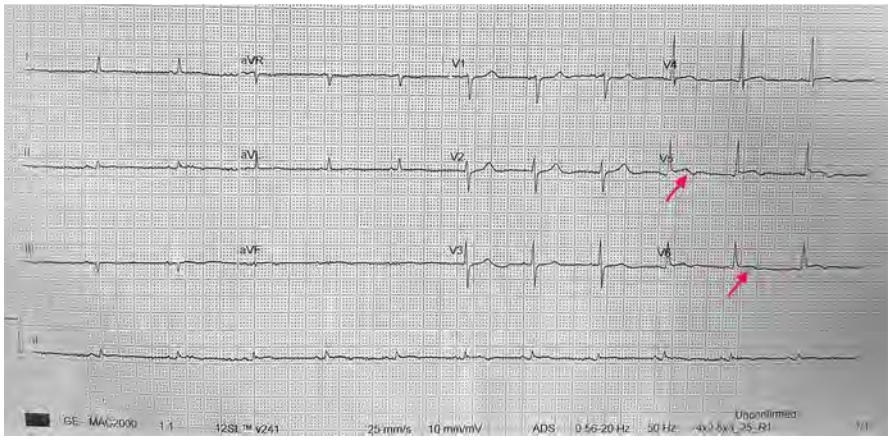

Fig. 1: Electrocardiogram showing ST-T changes in the V4 and V5 leads (red arrows)

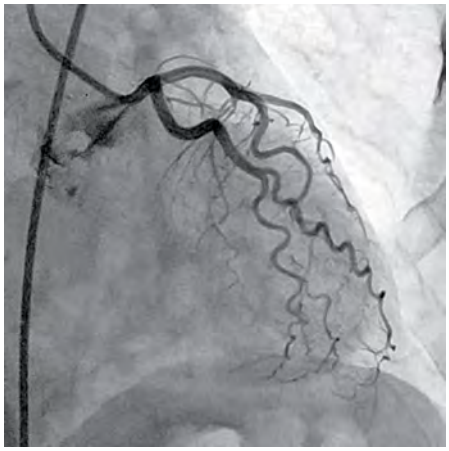

Fig. 2: Coronary angiography showing no obstructive lesions

crisis.[4] However, in 30–40% of patients with myasthenic crisis, no risk factors are found.

The differential diagnosis in this case included Miller Fisher syndrome due to rapid onset but was ruled out because of normal deep tendon reflexes. Another differential diagnosis was inflammatory myopathies, which were ruled out with near normal creatine kinase.

Cardiac manifestations of MG include myocarditis, heart failure, cardiomyopathy, arrhythmias, and pericarditis. Patients with MG are more likely to have cardiac manifestations associated with a thymoma (10–15%). Anti-striational antibodies (anti-titin antibodies, anti-ryanodine receptor antibodies, and anti-Kv 1.4 antibodies) are commonly reported in MG patients with cardiac involvement.[5] We did not measure anti-striational antibodies, although the presence of these antibodies has not been associated with an isolated myocardial infarction so far. MG has also been linked to Takotsubo cardiomyopathy and giant cell myocarditis (GCM). MG can trigger significant stress, especially during crisis. Takotsubo cardiomyopathy is known to be triggered by physical or emotional stress that results in a spike in catecholamine levels.[6]

Coronary artery vasospasm is a potential cause of MINOCA, characterized as a substantial (i.e., >90%) constriction of an epicardial coronary artery with reduced myocardial blood flow, which can occur spontaneously due to aberrant coronary vasomotor tone or in reaction to medications or toxins.[7] In view of the absence of apical ballooning on cardiac ultrasonography, we ruled out Takotsubo cardiomyopathy. However, we did not perform ventriculography for further confirmation.

In contrast to normal coronary arteries, which exhibit vasodilation by acetylcholine, the response of altered coronary arteries to acetylcholine is extremely sensitive, as they constrict abnormally when the endothelium is injured. Case reports of MINOCA in patients with MG have been reported in association with anticholinergic treatment. Cases of pyridostigmine-induced coronary vasospasm related to hypercholinergic crisis have been reported.[8] Both ST elevation and non-ST elevation myocardial infarction have been linked to IVIg-induced hypercoagulability.[9,10] In one case, myasthenic crisis was discovered after an instance of heart failure with trouble weaning the patient off the ventilator despite intensive therapy.[11]

We treated MINOCA with standard regimen of dual antiplatelet agents coupled with statins. Calcium channel blockers are considered the first line of treatment in cases with MINOCA along with angiotensin-converting enzyme inhibitors and statins.[7]

Conclusion

We conclude that MINOCA as a presenting event in a previously undiagnosed patient with MG in crisis is a rare and unusual occurrence. This case highlights the importance of considering MG in the differential diagnosis of patients presenting with muscular weakness, dysphagia, and increased cardiac enzymes or ECG changes suggestive of myocardial ischemia. Misdiagnosis of myocardial ischemia can lead to inappropriate management and delays in the correct treatment of MG. Therefore, clinicians should maintain a high index of suspicion for MG in such scenarios to ensure accurate and timely diagnosis.

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CASE REPORT

Autoimmune Hepatitis and Pregnancy: A Case Report

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Abstract

Autoimmune hepatitis (AIH) is a long-lasting liver ailment. It causes hepatocellular necrosis and inflammation, leading to fibrosis. It can develop into cirrhosis and liver failure. The disease predominantly affects young to middle-aged women more than men. AIH flares up during gestation and is linked with a high rate of embryonic and maternal problems. With maternal and antenatal care becoming advanced, this disorder should be identified and managed for successful maternal and embryonic outcomes. We present a case report of a primigravida diagnosed with AIH at 14 weeks antenatally. Our main aim in reporting this case is to create general awareness for healthcare professionals and thereby for patients and caregivers about this condition in pregnancy.

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Introduction

Autoimmune hepatitis (AIH) is a long-lasting liver ailment. It causes hepatocellular necrosis and inflammation, leading to fibrosis. It can develop into cirrhosis and liver failure. This type of hepatitis, if untreated, has a mortality of 40.0% at 6 months.[1] The underlying pathology is a slow hepatocellular inflammation. AIH presents with progressive liver injury secondary to cell-mediated immunologic onslaught on liver cells. The disease predominantly affects young to middle-aged women more than men. AIH flares up during gestation, and it can cause a high rate of embryonic and maternal problems. With maternal and antenatal care becoming advanced, this ailment should be identified and managed for successful maternal and embryonic outcomes. We present a case report of a primigravida diagnosed with AIH at 14 weeks antenatally.

Case Description

A primigravida aged 31 years admitted at 14 weeks for cervical cerclage had altered liver function tests (LFTs) that are depicted in Table 1. There was no history of food consumption outside, fever, malaise, joint pains, red eyes, rash, hematemesis, or melena. She had an *in vitro* fertilization (IVF) conception. Her ongoing medications were tab. dydrogesterone 10 mg TDS, tab. estradiol 2 mg TDS, inj. progesterone 100 mg OD, tab. thyroxine 12.5 µg OD, low-molecular-weight heparin (LMWH) 0.6 OD subcutaneously. She had undergone hysteroscopy before IVF.

Viral hepatitis markers were negative, and her antinuclear antibodies (ANA) were 416.09 by enzyme immune assay method. An ultrasonography of the abdomen revealed no hepatosplenomegaly or free fluid in the abdomen. An expert opinion from a hepatologist was sought. The differential diagnosis was an AIH flare vs a drug-induced liver injury due to hormonal treatment.

Further tests were ordered, and a decision of fibroscan over liver biopsy was made because of pregnancy and IVF conception and considering the risk to the fetus and the mother.[2] Her ANA by autoimmune immunofluorescence assay was positive 1:1000 speckled shape. An antismooth muscle antibody was feebly positive in 1:80 titer. Her total immunoglobulin was 17.9. Antisoluble liver antigen, liver kidney antibodies, p-antineutrophil cytoplasmic antibodies (p-ANCA), c-ANCA, and antimitochondrial antibody test were negative.

Fibroscan was done, and it showed a stiffness of 7.9. Her simplified AIH score was >7, which implied definitive AIH.[3] The patient was started on tab. prednisolone 60 mg and tab. azathioprine 75 mg. The patient was also given weekly cap. vitamin D 60 K and continued iron and calcium. The estrogen and progesterone were tapered and omitted. LMWH was continued. The patient and her relatives were counseled about the need for weekly monitoring of hemograms, LFTs, and bimonthly monitoring of blood pressure and sugars along with fetal monitoring as per the obstetrician protocol. The patient at 18 weeks had no symptoms of liver disease. Her LFTs were in the normal range (Table 1). Her anomaly scan for fetal development was normal. The patient was explained regarding complications, outcomes, and the need to monitor LFTs postpartum.

Discussion

It was reported that the embryonic outcome in children born to pregnant women having AIH is inconstant. The embryonic and perinatal deaths reported were 19 and 4%, respectively. The majority of embryonic losses were seen before the twentieth week of gestation.[4] The most common adverse result in females with AIH is premature births ranging from 6.0 to 17.0%. The proportion of adverse gestation results was 26%,[3] and the proportion of embryonic loss was between 14.3 and 24%.[5,6]

The children born to females with AIH have no higher rate of inborn deformities. But pyloric stenosis, fetal heart block, Edward's syndrome, the Smith–Lemli–Opitz syndrome, spastic tetraparesis, and Perthes' disease of the hip have been described.[5–8] AIH with compensated liver cirrhosis can be controlled during gestation in women who follow an immunosuppressive treatment, with successful perinatal results.[9]

Most of the pregnant women with AIH need pharmacological treatment for both stable illness and flare-ups. The chances of inborn deformities in children are 3.4 times higher whose mothers were given azathioprine for inflammatory bowel disease.[10] But babies born to pregnant women who were given azathioprine for lupus did not have congenital malformations.[11] However, current data recommend that the continuance of low-dose treatment of azathioprine may be acceptable in well-controlled pregnant women.[3]

It is suggested that azathioprine and its metabolites, as 6-thioguanine nucleotides, cross the placenta but 6-methyl mercaptopurine does not. The fetus is exposed to a lower concentration of thiopurine metabolites, such as 6-thioguanine nucleotides, during pregnancy than the mother. Nevertheless, in women who have been earlier given azathioprine with no stated adverse effects, it is possibly safe.[6,12]

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Table 1: Liver function tests at admission and 1-month follow-up

Test	*Finding*		*Reference range*
	At admission	*At 1-month follow-up*	
Total bilirubin (mg/dL)	5.3	1.23	0–1
Direct bilirubin (mg/dL)	4.04	0.4	0–0.3
Alanine aminotransferase (U/L)	492	32	15–37
Aspartate aminotransferase (U/L)	148	20	14–59
Serum alkaline phosphatase (U/L)	163	103	46–116
Serum gamma-glutamyl transferase (U/L)	111	109	5–85
Serum albumin (gm/dL)	3.1	4.0	3.4–5

Lastly, since flare-ups often happen in women after childbirth, it is essential to up-titrate immunosuppressive treatment immediately after childbirth. Even if only 1.2% of the absorbed amount of azathioprine appears to be excreted in breast milk, nursing during treatment with azathioprine is not suggested. However, in a recent report of six women with renal transplants who were taking azathioprine during nursing, no adverse effects were described in the babies. Hence, the azathioprine was reclassified as "possibly harmless" for nursing newborns.[13]

Conclusion

Our main aim in reporting this case is to create general awareness for healthcare professionals and thereby for patients and caregivers about this condition in pregnancy. It may be diagnosed with a high index of suspicion and can be managed with a team of obstetricians, a physician, and a hepatologist. With increasing ages of conception, preexisting medical conditions, and assisted reproductive technology, an obstetric physician may emerge as a specialty by itself.

Conflict of Interest

The authors declare that they have no conflict of interest. The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

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CASE REPORT

Dabigatran-induced Gastrointestinal Bleed Treated by 4-factor Prothrombin Complex Concentrate in a Tertiary Care Hospital in Sikkim

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Abstract

An immediate need exists for a safe, quick, and effective reversal agent in patients who present with anticoagulant-induced major bleed. Dabigatran, a newer oral anticoagulant and a direct thrombin inhibitor (DTI), can also induce bleeding risk. Idarucizumab is a specific dabigatran reversal drug that the United States Food and Drug Administration (US FDA) has approved in the event of a significant bleeding caused by this drug. In this particular drug-related bleeding, it can be challenging to precisely dose alternative reversal agents like prothrombin complex concentrates (PCCs) and activated PCCs (aPCCs) depending on coagulation characteristics. Additionally, they may result in thromboembolic problems. Despite these drawbacks, the inability to get idarucizumab may necessitate the use of these medications in cases of life-threatening bleeding. We describe the case of a 65-year-old male who reported to the hospital with coagulopathy, anemia, and fresh bleeding per rectum (Hb: 5.8 gm/dL, PT 20.02 seconds, INR: 1.55). He was on dabigatran for the past 1 month. Even after stopping dabigatran, injection of vitamin K, 4 units of blood transfusion, and 8 units of fresh frozen plasma (FFP), he was still bleeding, with fall in hemoglobin level. Following the administration of PCC, he significantly improved, and no additional transfusion products were needed. He could be sent home after 4 days. After 1 month, he returned for follow-up with no further complications.

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Background

Dabigatran etexilate is a direct thrombin III inhibitor (DTI). It is approved for the prevention of stroke in patients with nonvalvular atrial fibrillation. It is also recommended and approved for the prevention and treatment of recurrent venous thromboembolic events by the United States Food and Drug Administration (US FDA).[1] It raises the risk of gastrointestinal bleeding even though it has demonstrated superiority over warfarin in terms of stroke prevention, with a reduced rate of potentially fatal bleeding events.[2] A particular dabigatran reversal medicine, idarucizumab, causes an immediate reversal of coagulopathy. Hence, it is found to be beneficial in major bleeding caused by this drug.[3] The use of a 4-factor prothrombin complex concentrate (4F-PCC) in dabigatran-induced hemorrhage has shown some potential in a recent case series.[4] All of the coagulation factors dependent on vitamin K are present in PCCs. Therefore, in the event of overanticoagulation brought on by vitamin K antagonists, they are helpful for the quick reversal of coagulopathy and the restoration of normal hemostasis.[5]

We describe a case where a patient reported to the emergency department of Central Referral Hospital, Sikkim, with severe dabigatran-induced multisite (gastrointestinal and pulmonary) hemorrhage. He was treated effectively with 4F-PCC.

Case Description

A 65-year-old male with a history of hypertension, T2DM, ILD, and hypothyroidism presented to the emergency department with complaints of large fresh bleeding while passing stools, with associated generalized weakness and dizziness for 2 days. His vitals on arrival revealed a pulse rate of 102/minute, BP of 120/60 mm Hg, respiratory rate of 22/minute, and SpO_2 of 99%. He was afebrile. Pallor and basal crepitation were present on examination. He was on tablets of mycophenolate mofetil 500 mg twice a day, thyroxine 25 µg, amlodipine, iron tablets, linagliptin 5 mg, tamsulosin 0.4 mg, and dabigatran 110 mg BID, along with inhaled medicines. He was taking dabigatran for the last 30 days, given for high D-dimer level (1188.5) in his previous admission. History revealed that he was compliant with his medications and had consumed dabigatran 6 h before arrival at the hospital.

The patient was treated in the medical ICU, and dabigatran was stopped immediately. He was transfused 2 units of packed red blood cells (PRBCs) and 4 units of fresh frozen plasma (FFP) and received a proton pump inhibitor and injection vitamin K in view of coagulopathy on the first 2 days of his admission. His PT and INR were 20.2 seconds and 1.59, respectively, and his Hb was 5.8 gm/dL at admission. The history and investigations did not reveal any other reason for coagulopathy. He received 2 units of PRBCs and 4 units of FFP again on day 3. Despite that, the patient's Hb continued to fall (4.6 gm/dL), along with a fall in O_2 saturation. His tachycardia and tachypnea persisted. He underwent an upper GI endoscopy, in which blood and blood clots were seen in the stomach, whereas colonoscopy did not reveal any abnormality. He also had an episode of hemoptysis.

On day 4, around 72 hours after admission, he received 1,500 units of PCC based on his body weight of 60 kg (25 units/kg of PCC). The patient showed signs of improvement the following day. His tachycardia and tachypnea settled, and no more O_2 was required. His repeat coagulation profile also normalized. The INR was 1.1, and a rise in Hb from 5.8–10.5 gm/dL was noted. A repeat upper GI endoscopy did not show any active bleeding, and no further blood transfusions were required. A repeat colonoscopy was not performed, as the initial one was normal. CT angiography was planned but could not be done due to unavailability. The patient was continued on vitamin K for 3 more days and was discharged 4 days later with a normalized PT, INR, and stabilized anemia.

Discussion

Dabigatran functions as a direct thrombin inhibitor (DTI), which stops fibrinogen from becoming fibrin and stops thrombin from

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activating factors V, VIII, and XI. This action makes dabigatran a powerful anticoagulant. In individuals with normal renal function, its half-life is around 13.8 hours, but in creatinine clearance <30 mL/minute, it is prolonged.[6] It is mainly eliminated by the kidneys and reaches its highest concentration in approximately 2 hours.[6,7] As of now, there are no reliable tests available to verify dabigatran-induced coagulopathy in a medical environment. The most reliable assays for tracking this medication's anticoagulant action are thrombin clotting time (TT) and ecarin clotting time (ECT), yet they are not commonly accessible. While the majority of research did not find a linear association between high aPTT >90 seconds and INR >2 and overdose or dabigatran accumulation, several studies did.[8] Compared with warfarin, there is a decreased risk of cerebral hemorrhage and other major bleeding; however, there is an increased risk of gastrointestinal hemorrhage.[2,9]

The majority of bleeding events can be controlled with supportive care and brief pharmacological withdrawal. Nonetheless, individuals experiencing life-threatening bleeding requiring urgent or emergency surgery or other invasive procedures, or conditions necessitating hemostasis, may require other approaches.[10] Idarucizumab, a particular dabigatran reversal medication, has been approved by the US FDA.[11–13] It has not been licensed in many nations yet, and in the interim, several treatment approaches have been implemented to quickly counter the coagulopathy caused by dabigatran. These alternatives include recombinant activated factor VII (rFVIIa), PCCs, and aPCCs.[14–16] Since 4F-PCC was the sole reversal drug available, it was given to our patient. He tolerated this treatment without any complication. Numerous published case studies demonstrate the effectiveness of PCCs and aPCCs in the treatment of dabigatran-related coagulopathy.[17]

In a case study involving 4 individuals, cessation of this specific drug-induced bleeding was also noted following the delivery of a PCC. Out of those 4 patients, 3 had GI bleeding, subdural hemorrhage, and intracerebral hemorrhage, whereas 1 patient required surgery for pacemaker implantation.[18] Several other case reports have also documented favorable results in individuals treated with PCC or aPCC in dabigatran-induced bleed.[19] Gastrointestinal hemorrhage affects a large number of these patients.[20–22] However, because several of those patients also received rFVIIa concurrently, it was challenging to determine the precise effect of PCC or aPCC on dabigatran-induced coagulopathy. Conversely, a study revealed that PCC use was unsuccessful. Even after concurrent rFVIIa therapy, no improvement in coagulation profile or decrease in bleeding was seen in that study.[23]

Inconsistent outcomes were revealed with PCC use in animal models treated with dabigatran. Animals treated with PCC showed improvements in bleeding time in 1 trial, but the coagulation tests were unaffected.[24,25] Similarly, thrombin production characteristics improved in the presence of therapeutic dosages of dabigatran following PCC administration.[26] However, in a mouse model, there was no discernible reduction in blood loss.[27] A crossover study was conducted to evaluate the impact of 4F-PCC on bleeding associated with dabigatran and rivaroxaban. This study was randomized, double-blind, and placebo-controlled. The 4F-PCC treatment did not affect patients receiving dabigatran on a number of coagulation tests, such as PTT, endogenous thrombin potential, lag time, TT, and ECT, even though it might prevent rivaroxaban-induced bleeding.[28] A few experts have reviewed the literature and determined that aPCC and nonactivated 4F-PCC should be used as the first option for dabigatran reversal.[29]

Our patient presented with upper GI bleed, and no underlying cause was found on colonoscopy or repeat upper GI endoscopy. Rectal bleeding is the most common bleeding complication of dabigatran treatment, and a higher risk of bleeding is associated with an underlying history of rectal, colonic, or diverticular bleeding.[30] In severe GI bleed, idarucizumab can rapidly reverse the effect of dabigatran. However, this cannot be recommended routinely for all patients in view of the high cost and limited availability.[31]

Although the relevance of PCC in this bleed reversal is debatable, some experts believe it might be useful in certain situations.[10] Despite inconsistent statistics and case reports, our experience demonstrates that 4F-PCC can successfully treat bleeding associated with dabigatran. The patient's Hb stabilized, his coagulation profile returned to normal, and his clinical outcome was favorable. He could be sent home without further morbidity from his illness.

Conclusion

Although more thorough research is required to identify the optimal strategy for managing dabigatran-induced bleeding, the use of 4-factor PCC ought to be considered, particularly in cases when dabigatran's major hemorrhagic side effects must be addressed.

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CASE REPORT

A Case of Drowning with Acute Kidney Injury and Raised Intracranial Tension

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Abstract

Background: Drowning is the third leading cause of unintentional injury and death worldwide, accounting for 7% of all injury-related deaths. People who are at higher risk include those who have free accessibility to water and younger children lacking supervision. The common complications of drowning are mainly due to hypoxia. It mainly affects the respiratory, cardiac, and central nervous system. Rarely, drowning may cause acute kidney injury (AKI) secondary to rhabdomyolysis. Here, we present a case of near drowning with AKI, rhabdomyolysis, and elevated intracranial tension (ICT) with a false localizing sign (abducent nerve palsy).

Case description: A 21-year-old female patient was brought with a history of alleged drowning for about 3–5 minutes. The patient presented with loss of consciousness; she was gasping and had diffuse subcutaneous emphysema. On examination, the patient had bilateral coarse crepitations. She was started on mechanical ventilation. After 2 days, the patient developed elevated renal parameters and had an episode of ventricular tachycardia. After 10 days, the patient developed diplopia and blurring of vision. Ophthalmological examination revealed bilateral abducent nerve palsy with established papilledema and hemorrhagic retinopathy. The patient was treated with IV antibiotics, IV fluids, DC shock, inotropes, hemodialysis, and acetazolamide. After 15 days, the patient recovered from bilateral lateral rectus palsy and had no blurring of vision.

Conclusion: Drowning is a leading cause of accidental death. This patient had diffuse subcutaneous emphysema, rhabdomyolysis with AKI, ventricular tachycardia, and raised ICT. In drowning, raised ICT often has a poor outcome. However, with constant monitoring and timely intervention this patient survived.

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Introduction

In drowning, victims suffer from respiratory distress due to submersion/immersion in liquid. The common complications of drowning are hypoxic encephalopathy, acute respiratory distress syndrome (ARDS), noncardiogenic pulmonary edema, dysrhythmia, respiratory and metabolic acidosis, and hemodilution.[1,2] A rare complication includes acute kidney injury (AKI) following rhabdomyolysis.[3,4] Hypoxia causes cerebral edema, which in turn causes elevated intracranial tension (ICT).[2,5] Hypoxia also causes cardiac arrhythmia, leading to sudden cardiac arrest. Hypothermia resulting from near drowning causes peripheral vasoconstriction, which in turn leads to myocyte damage resulting in rhabdomyolysis.[4] We present a case of near drowning of a 21-year-old female patient who was submerged in dam water (fresh water) for about 3–5 minutes following which she developed cardiac arrhythmia, rhabdomyolysis with AKI, and raised ICT.

Case Description

A 21-year-old female patient was brought with a history of alleged drowning for about 3–5 minutes in water flowing from a dam. The patient was brought to our emergency department within 1 hour in an unconscious and gasping state. On examination, the patient was unconscious and gasping, with bilateral coarse crepitations present in both lung fields, a blood pressure of 90/60 mm Hg, pulse rate (PR) 109/minute, and respiratory rate (RR) 30/minute. Saturation was not recordable. The patient was intubated and connected to mechanical ventilation.

The patient had diffuse subcutaneous emphysema all over the body, including the face, both upper and lower limbs, chest, and abdomen (Fig. 1).

She was treated with intravenous fluids, antibiotics, and mechanical ventilation [low tidal volume, high positive end-expiratory pressure (PEEP)]. Initial investigations showed normal complete blood count (CBC), renal function test (RFT), liver function test (LFT), and metabolic acidosis on arterial blood gas (ABG) test.

Computed tomography (CT) of the chest showed diffuse ground-glass opacities with no evidence of pneumothorax or pneumomediastinum (Fig. 2), and CT of the brain showed effacement of sulci and gyri (Fig. 3).

After 2 days, the patient had elevated renal parameters with elevated total creatine phosphokinase (CPK) and MB and was started on peritoneal dialysis. On that day, the patient developed ventricular tachycardia and was treated with DC shock and reverted to normal sinus rhythm; the patient did not have further episodes of ventricular tachycardia. Since the patient had further worsening of renal parameters, she was started on hemodialysis.

Serial monitoring was done by taking chest X-ray to look for the source of diffuse subcutaneous emphysema. It showed no evidence of pneumothorax or pneumomediastinum. Diffuse subcutaneous emphysema resolved spontaneously after 4 days. Due to a fall

Fig. 1: Diffuse subcutaneous emphysema

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Fig. 2: Diffuse ground-glass opacities

in hemoglobin, the patient was transfused with two units of packed red blood cells. Gradually, the patient was weaned off mechanical ventilation on day 9. On day 10, the patient complained of blurring of vision and diplopia. Ophthalmological examination revealed bilateral abducent nerve palsy with established papilledema with hemorrhagic retinopathy (Fig. 4).

The patient was treated with tablet acetazolamide 250 mg BD for 2 weeks, following which the patient recovered from bilateral lateral rectus palsy and there was improvement in vision.

Discussion

Drowning is a type of suffocation caused by submersion in water. About 90% of drowning cases are due to freshwater drowning and about 10% are due to saltwater drowning. Drowning accounts for 7% of all injury-related deaths.

Due to drowning, vital tissues of a person may become hypoxic and acidotic, and this leads to cardiac arrhythmias such as tachycardia, bradycardia, and asystole. The aspirated fluid can cause surfactant washout, damage to the alveolar capillary membrane, reduced lung compliance, and ventilation–perfusion mismatch. This leads to noncardiogenic pulmonary edema, and it presents as ARDS.[1,2]

Central nervous system (CNS) hypoperfusion induces the release of excitotoxic neurotransmitters, free radicals, and lipid peroxidation; this leads to cerebral edema and raised ICT.[2,5] The clinical manifestations of raised intracranial pressure (ICP) include headache, 6th cranial nerve palsy, papilledema, Cushing's triad (bradycardia, hypertension, respiratory depression), and Kernohan's notch phenomenon (contralateral pupil dilatation with ipsilateral weakness due to compression of the tectum). Approximately

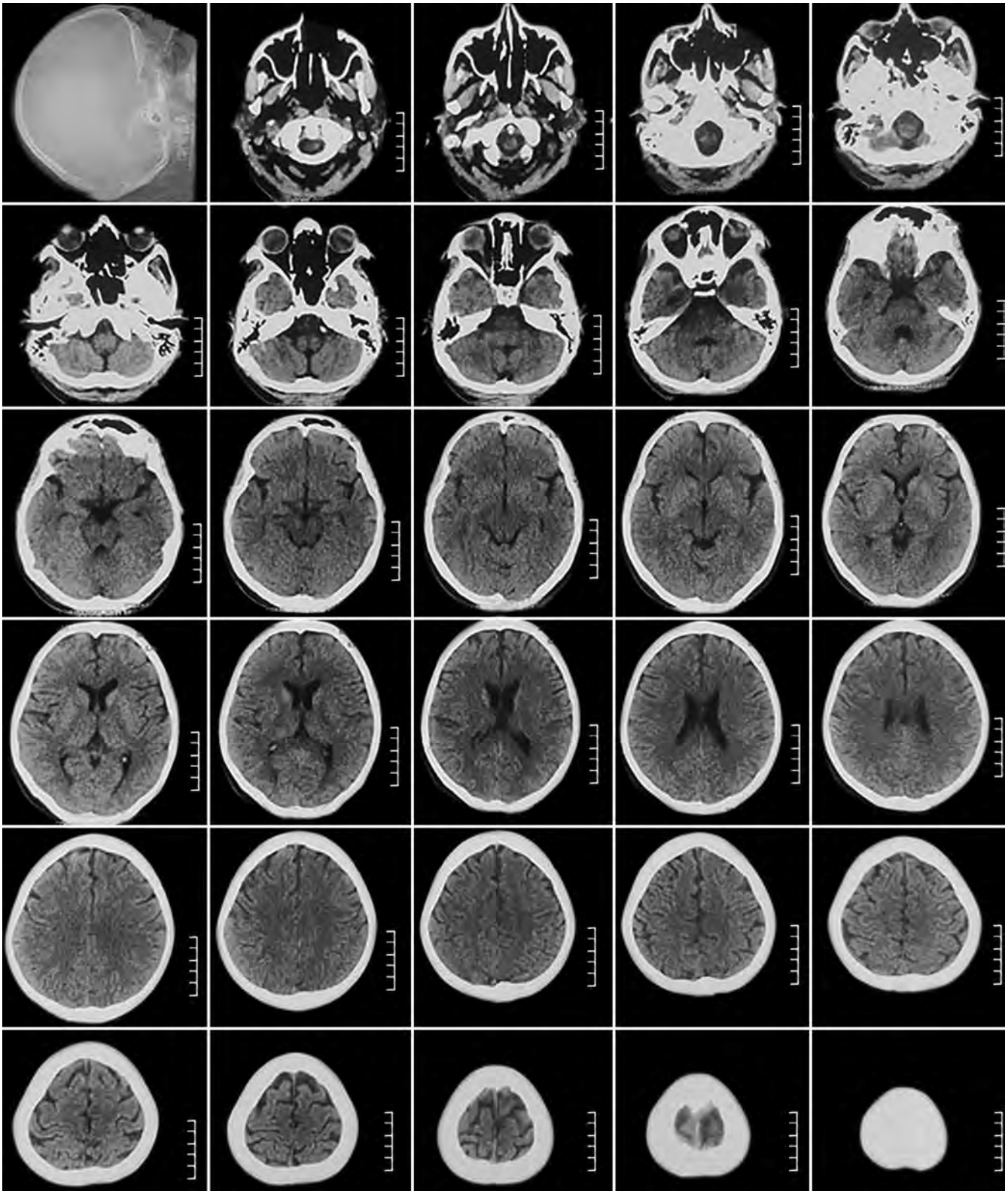

Fig. 3: Effacement of sulci and gyri

12% of adults with raised ICT manifest with 6th cranial nerve palsy. Raised ICT in drowning victims has a poor outcome.

Rhabdomyolysis in drowning is due to peripheral vasoconstriction caused by hypothermia. This leads to injury to myocytes and release of myoglobin.[4] The most frequent clinical conditions linked with rhabdomyolysis in adults are trauma, infections, drugs, and surgery. Only a few cases of rhabdomyolysis complicated by near drowning exist in the literature.

Acute kidney injury in drowning may develop because of hypoxic renal injury, reduced renal blood flow, and systemic

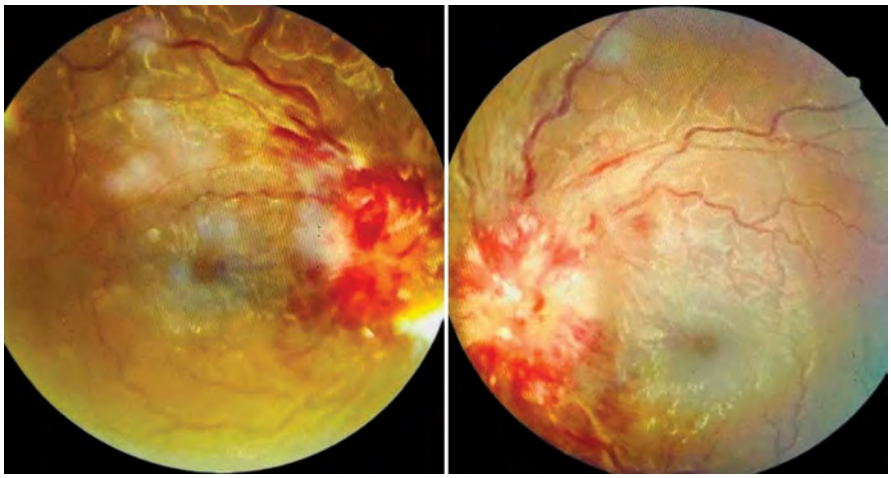

Fig. 4: Papilledema with hemorrhagic retinopathy

inflammatory response. AKI is mild and is probably caused by acute tubular necrosis.[3]

There is no literature evidence for diffuse subcutaneous emphysema in drowning victims.

Conclusion

Drowning is one of the leading causes of accidental death, most commonly in young children. The major complications include respiratory (ARDS), cardiac (arrhythmias), and CNS (cerebral edema, hypoxic-ischemic encephalopathy, seizures, coma). Rare complications include rhabdomyolysis and AKI. Patients who are alert or mildly confused at the time of presentation have a good prognosis, and those who are comatose have a poor outcome. Victims who are resuscitated with cardiopulmonary resuscitation (CPR) may develop severe brain injury and hypoxic-ischemic encephalopathy and require long-term rehabilitation. Drowning does not usually cause subcutaneous emphysema, but this patient had diffuse subcutaneous emphysema all over the body which resolved spontaneously after 4 days; the cause of this remains unknown.

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CASE REPORT

A Rare Case of Secondary/Acquired Hemophagocytic Lymphohistiocytosis due to Epstein–Barr Virus Presenting with Neuropsychiatric Features

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Abstract

We present a case of a 30-year-old female patient who presented with fever for 1 month. All the causes of pyrexia and all other possible causes were ruled out before diagnosing hemophagocytic lymphohistiocytosis (HLH). Although it is common in children, a 2% prevalence rate is suggested in adults according to the literature. HLH was confirmed after bone marrow aspiration showing hemophagocytes.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe, hyperinflammatory condition that leads to multiorgan failure and death. The systemic inflammation characteristic of HLH arises from the inappropriate and dysregulated activation of natural killer (NK) cells, CD8+ cytotoxic T cells, and macrophages.

The ineffective interaction between NK cells, CD8+ cytotoxic T cells, and their targets leads to a vicious cycle of inflammation. More cytotoxic cells are recruited but remain unable to eliminate the pathological antigen, resulting in a massive increase in circulating cytokines. This hypercytokinemia leads to widespread activation of macrophages, hemophagocytosis, and excessive, organ-damaging inflammation.[1]

The disease can be classified into two main types—primary/familial and secondary HLH.

Primary HLH, also called familial HLH, typically manifests in early childhood and results from genetic mutations. These mutations disrupt the normal interaction between NK cells, CD8+ cytotoxic T cells, and antigen-presenting cells, leading to excessive production of proinflammatory cytokines. The resulting cytokine storm drives widespread macrophage activation, ultimately causing tissue damage.[2]

Secondary HLH is more commonly observed in adults, with an average onset around 50 years of age. Unlike primary HLH, it is not linked to genetic mutations but is instead triggered by acute illnesses. Common causes include infections, malignancies, and autoimmune diseases. When HLH develops in association with an autoimmune condition, it is referred to as macrophage activation syndrome (MAS).[1]

Case Description

A 30-year-old Hindu female patient, who is a housewife belonging to a lower-middle-class family residing in Rajkot, with no comorbidities, presented with sudden onset of fever since 1 month, followed by vomiting since 10 days, weakness with staring look, slowed movements since 2 days, and altered sensorium since 1 day. She has a history of fever for 1 month, high-grade, with two spikes per day and at least one spike in the morning, resolved by medication, followed by vomiting since 10 days—nonprojectile in nature, greenish in color. Associated symptoms include weight loss of 3 kg in 1 month, giddiness, and generalized weakness since 2 days. There was no association with bleeding from any site, loose stools, abdominal pain, headache, loss of vision, body pains, tingling and numbness of limbs, seizure-like activity, loss of consciousness, or focal neurological deficits. There were no similar complaints in the past. The patient has had a disturbed sleep pattern since 10 days, with normal bowel and bladder habits and was on a vegetarian diet before the symptoms. She has no addiction history and no significant family history.

The patient had a 10-year-old male child, vaginally delivered with no complications after an uneventful gestation period. The patient's last menstrual period was 3 days ago, with last intercourse 2 years back. On examination, the patient was conscious but not fully oriented. She was well-built and well-nourished for her age. The patient was vitally stable. There were no abnormal findings on general examination. Pupils were bilaterally equal and reactive to light, with direct and consensual light reflex present. Fundus examination revealed no changes of papilledema. The patient had equal movements of all four limbs with normal tone. There was no evidence of nystagmus or ataxia. Abnormal involuntary movements were absent. All reflexes were present, and bilateral plantar reflexes were flexor. All peripheral and cortical sensations were intact. No neck rigidity was observed. Her cardiovascular, respiratory, and gastrointestinal system examinations were unremarkable.

Differential Diagnosis

- Koch's etiology.
- Meningitis.
- Viral encephalitis.
- Metabolic encephalopathy.
- Sepsis.
- Multisystem inflammatory syndrome.
- Autoimmune encephalitis.
- Systemic lupus erythematosus (SLE).

Investigations

Her routine investigations include:

- Hemoglobin (Hb): 9.1/9.0/7.3/6.9/7.5.
- White blood cell (WBC): 2,600/2,700/2,400/3,400/5,200.
- Platelet: 50,000/64,000/44,000/58,000/2,47,000.
- Sodium: 129/133/134.
- Potassium: 3.4/3.15/3.5.
- Creatinine: 0.7.
- Total bilirubin: 1.91/1.04.

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- Direct bilirubin: 0.64/0.38.
- Indirect bilirubin: 1.27/0.66.
- Serum alanine aminotransferase (S. ALT): 35.
- Total protein: 4.7.
- Serum albumin: 1.85.
- Serum ferritin: >2000 (13–150).
- Serum iron: 88 (50–170).
- Total iron-binding capacity (TIBC): 148 (250–450).
- Percent saturation: 59 (13–45).
- Serum vitamin B12: <55.
- Serum fibrinogen: 109 (high).
- Serum antinuclear antibody (S. ANA): Negative.
- Erythrocyte sedimentation rate (ESR): 19.
- Chest X-ray: No abnormality.
- Mantoux's test: Negative.
- Blood culture and urine culture: Negative.
- Malarial parasite not detected.
- Dengue IgM, NS1: Negative.
- Serum widal: Negative.
- Cerebrospinal fluid (CSF) picture: Proteins—30, sugar—53, total count—3, adenosine deaminase (ADA)—negative.
- Expert smear suggestive of pancytopenia due to hypersplenism [predominantly hypochromic, microcytic red blood cells (RBCs) with few macrocytic RBCs].
- Hypertriglyceridemia (S. triglycerides): 386.
- Hypofibrinogenemia: 109.
- Hypocalcemia and high lactate dehydrogenase. Sonography suggests borderline hepatosplenomegaly with a few enlarged right inguinal fossa, mesenteric, bilateral inguinal, and cervical lymph nodes.
- CD25: Negative.
- Epstein–Barr virus viral capsid antigen immunoglobulin G (EBV VCA IgG): High positive.
- EBV VCA IgM: Negative.
- Bone marrow aspiration revealed hematolymphophagocytosis with hypercellular marrow and erythroid hyperplasia (as shown in Fig. 1).

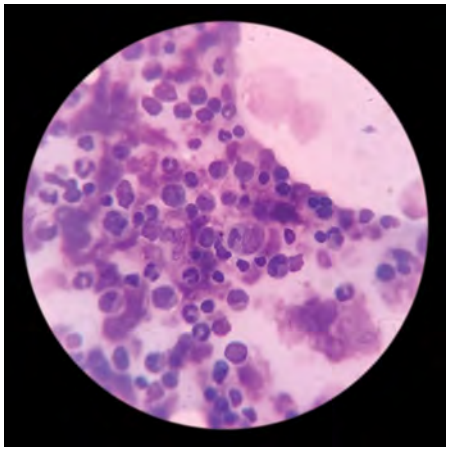

Fig. 1: Histopathological image of hemophagocytes on bone marrow aspirate

Other investigations, including thyroid function test (TFT) and coagulation profile, were not significant.

Treatment

The patient was started on antibiotics and steroids—injectable dexona 10 mg/kg/day (according to HLH-2004 criteria) for 7 days, after which the patient recovered and is now on a tapering dose. Antivirals (tablet acyclovir) were started against Epstein–Barr virus, with tapering.

Discussion

Patient presented in altered sensorium with absent neck rigidity and Kernig's sign and a normal CSF picture, ruling out meningitis and encephalitis. Normal magnetic resonance imaging (MRI) ruled out vascular causes. She had a history of chronic fever with lymphadenopathy, indicating an infective or inflammatory condition.

The HLH-2004 diagnostic criteria are widely used and include the following—HLH-2004 Diagnostic Criteria.[3]

The diagnosis of HLH requires meeting at least five of the following eight criteria:

- Fever: A persistent body temperature of ≥38.5°C.
- Splenomegaly: Enlargement of the spleen.
- Cytopenias: A reduction in blood cell counts affecting at least two of the following: (1) Hb <90 gm/L (or <100 gm/L in infants under 4 weeks old), (2) platelets $<100 \times 10^9$/L, or (3) neutrophils $<1.0 \times 10^9$/L.
- Metabolic abnormalities: Presence of either or both of the following: (1) elevated fasting triglycerides ≥3.0 mmol/L (or ≥265 mg/dL) and (2) low fibrinogen levels ≤1.5 gm/L.
- Hemophagocytosis: Evidence of engulfed blood cells within the bone marrow, spleen, or lymph nodes, without signs of malignancy.
- Reduced or absent NK cell function: Impaired or undetectable NK cell activity.[4]
- Hyperferritinemia: Serum ferritin levels ≥500 µg/L.
- Elevated soluble CD25 (sCD25) [soluble interleukin-2 (sIL-2) receptor]: Increased levels of soluble CD25 (sIL-2R), indicative of excessive T-cell activation.

While an elevated sIL-2 receptor (CD25) is an important marker and often elevated in HLH due to excessive immune activation, it is just one of several criteria. If sCD25 is not elevated but other criteria are met, HLH can still be diagnosed. The presence of other criteria, such as fever, cytopenias, splenomegaly, hypertriglyceridemia, hemophagocytosis, hyperferritinemia, and decreased NK cell activity, can lead to a diagnosis in the absence of elevated sCD25.

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CASE REPORT

Atypical Presentation of Multiple Myeloma as Acute Renal Failure of Unknown Etiology: Two Case Reports

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Abstract

Multiple myeloma (MM) is a clonal plasma cell proliferative disorder that accounts for 1% of all cancers (Rajkumar). It is a disease of older adults, presenting with anemia, bone pain, and end-organ damage in the form of CRAB features. With increasing awareness regarding this entity and the availability of more-sensitive diagnostic modalities, involvement of younger age-groups with atypical presentations is becoming more common. Newer case series report that nearly 50% of MM cases present initially with renal failure of unknown etiology (Shankar et al.), highlighting the unique role of the nephrologist in the diagnosis of this condition. In these two case reports, we wish to highlight two cases presenting with acute renal failure of unknown etiology, who were subsequently diagnosed to have occult MM with light chain deposition disease (LCDD).

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Case Report 1

A 65-year-old male, known case of systemic hypertension on antihypertensive medication for 4 years, was referred to us in March 2023 with the chief complaints of generalized weakness with loss of appetite for 3 months and loose stools (3–4 episodes/day) for the last 5 days. Drug history was significant for indigenous medicine use for a period of 3 months. On admission, he was hemodynamically stable, and general and systemic examination were unremarkable, except for pallor seen over the palpebral conjunctiva of the right eye. Laboratory investigations were significant for anemia (Hb 6.6 gm/dL), raised serum creatinine (8.89 mg/dL), and blood urea levels (206 mg/dL), along with hyperkalemia and hyperuricemia (Table 1). Ultrasonography (USG) of the abdomen showed normal-sized kidneys, with no evidence of obstruction (Table 1). Differential diagnoses considered at that time were acute kidney injury (AKI) related to dehydration or indigenous medication use. The patient was managed medically with intravenous saline therapy, correction of metabolic acidosis and hyperkalemia, blood transfusions for anemia, and uric acid-lowering therapy was started. As no cause for renal failure could be ascertained, a kidney biopsy was performed.

Case Report 2

A 49-year-old female, housewife by occupation, with no comorbidities, presented to this institute on February 18, 2023 with the chief complaints of loss of appetite and burning sensation in the chest, associated with bloating, for 3 months. Outside investigations revealed deranged renal parameters (serum creatinine 6.1 mg/dL, serum urea 106.7 mg/dL), for which she was admitted to the nephrology department. General examination did not show any significant abnormalities. Urinalysis revealed trace proteinuria with 2–3 red blood cells (RBCs) per high-power field and 4–5 pus cells per high-power field; however, urine cultures were sterile. Her reports showed the presence of anemia (Hb 7.7 gm/dL), leukocytosis [white blood cell (WBC) count 14,000 cells/mm^3], and deranged renal parameters (serum creatinine 6.0 mg/dL, blood urea 142 mg/dL). Liver function tests were within normal range, with serum albumin of 4.85 gm/dL and globulin of 2.0 gm/dL (Table 1). Serum antinuclear antibody (ANA), perinuclear antineutrophil cytoplasmic antibody (p-ANCA), and cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) were found to be negative. USG abdomen showed bilateral medical renal parenchymal disease with normal renal sizes, with no evidence of obstruction (Table 1). As no obvious cause could be found for the renal failure, renal biopsy was done, and the patient was discharged on oral medication.

Renal biopsy of the first case showed 13 glomeruli, of which five (38.4%) were globally sclerosed. Tubular atrophy and interstitial fibrosis involved 45–50% of the sampled cortex (Fig. 1A). Tubules showed atypical casts with evidence of severe acute tubular injury, and immunofluorescence (IF) showed diffuse linear staining for kappa light chain along the tubular basement membranes and in the atypical intratubular casts. In the second case, six glomeruli were visualized on light microscopy, with no pathological features; however, tubules again showed features of acute tubular injury with intratubular casts (Fig. 1B), and IF revealed linear staining for kappa light chain along the basement membranes and in the casts. Both biopsy reports were suggestive of monoclonal gammopathy with cast nephropathy and light chain deposition disease (LCDD). Oncologist opinion was taken, and both of the cases were reevaluated for myeloma (Table 2).

The constellation of all these investigations was consistent with a diagnosis of kappa light chain multiple myeloma (MM) with LCDD and cast nephropathy. Case 1 was started on steroids and bortezomib. His symptoms improved considerably after starting treatment for MM. His serum creatinine on last follow-up was 5.1 mg/dL (April 14, 2023). Case 2 was also started on a chemotherapy regimen of inj. bortezomib, high-dose dexamethasone, and oral cyclophosphamide. At present, she is clinically stable on medical management, and serum creatinine was 5.4 mg/dL on last follow-up (March 25, 2023).

Discussion

Light chain deposition disease is a rare hematological disorder characterized by the deposition of nonamyloid monoclonal light chains in several organs.[1] Due to its rarity, there is a paucity of randomized controlled trials (RCTs) to explore treatment strategies and no universally accepted standard-of-care treatment options. As LCDD is related to the overproduction of light chains by an abnormal clone of B cells, it is usually described during the course of plasma cell dyscrasias, including MM (11–65%).[1] However, it may occur in the absence of a demonstrable clonal plasma cell proliferation within the bone marrow (now known as monoclonal gammopathy of uncertain significance).

Clinically, the median age at diagnosis is around 58 years, with a slightly higher

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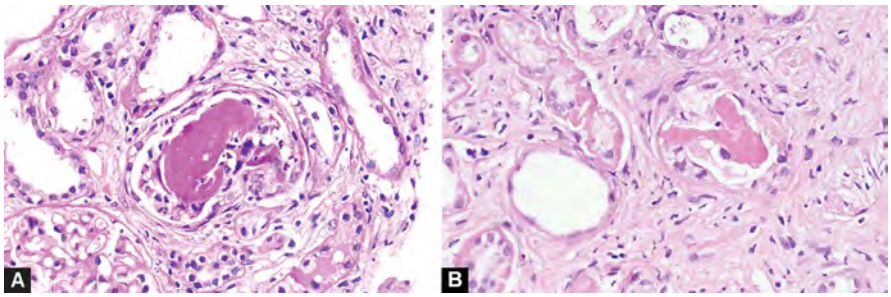
Table 1: Baseline characteristics of patients (at the time of admission)

Baseline characteristics	*Case 1*	*Case 2*
Hemoglobin (in gm/dL)	6.6	7.7
WBC count (cells/mm^3)	9,021	14,000
Platelet count (cells/µL)	1.36 lakh cells/mm^3	2.69 lakh cells/mm^3
Serum creatinine (in mg/dL)	8.89	6.0
Blood urea (in mg/dL)	206	142
Serum sodium (in mEq/L)	137	130
Serum potassium (in mEq/L)	7.1	4.99
Serum calcium (in mg/dL)	8.9	9.0
Serum uric acid (in mg/dL)	11.1	N/A
Urinalysis	1+ protein, nil RBCs, nil pus cells/hpf	Trace protein, 2–3 RBCs/hpf and 4–5 pus cells/hpf
Serum albumin (gm/dL)	3.84	4.85
Albumin-globulin ratio	1.3	2.4

Table 2: Further evaluation to confirm the diagnosis (of MM)

Laboratory investigations	*Case 1*	*Case 2*
Serum protein electrophoresis	M band—0.2 gm/dL seen in gamma region	Faint band seen in gamma region
Serum free light chain assay	Free kappa light chain (serum)—4304 mg/L Free lambda light chain (serum)—27.6 mg/L Ratio—155	Free kappa light chain (serum)—10766 mg/L Free lambda light chain (serum)—16.6 mg/L Ratio—645
Skeletal survey	No lytic lesions visualized	Skull X-ray—s/o?lytic lesions
Urinary beta-2 microglobulin levels	N/A	>40480.0 mg/mL
Serum ionized calcium	N/A	1.19 (N)
Bone marrow aspiration	Hypercellular marrow with increased plasma cell population (>35%)	Cellular bone marrow with increased plasma cell population (>22%)
Follow-up serum creatinine (1 month after starting chemotherapy)	5.1 mg/dL	5.4 mg/dL



Figs 1A and B: (A) Hematoxylin and eosin stain shows atypical intratubular cast formation with mild tubulointerstitial chronicity (case report 1); and (B) Hematoxylin and eosin stain shows intratubular cast formation with acute tubular injury (case report 2)

preponderance in men.[2] LCDD most commonly involves the kidney (96%), with less frequent involvement of other organs, such as the heart (21%), liver (19%), and peripheral nerves (8%).[3] Renal involvement can present as acute or rapidly progressive renal failure (in 30–40% cases) or in the form of chronic impairment of renal function, with or without reduced kidney sizes.[4] Presentation also varies with the site of deposition; predominantly glomerular deposition leads to nephrotic-range proteinuria, while predominantly tubular deposition causes renal insufficiency with low-grade proteinuria. Around one-third of patients with LCDD also develop extrarenal symptoms, which include congestive heart failure (cardiac LCDD), dyspnea and hemoptysis (pulmonary LCDD), and liver dysfunction (hepatic LCDD).[2]

In both of our cases, renal biopsy revealed evidence of atypical tubular casts, and IF revealed deposition of kappa chain-restricted deposits along tubular basement membranes and within the casts, suggestive of cast nephropathy with LCDD; further investigation unveiled the underlying paraproteinemia on bone marrow biopsy.

In the first case report, although the demographic profile of the patient (male, elderly age-group) supported the eventual diagnosis of nephropathy secondary to plasma cell dyscrasia, there was no history of significant bony pain that is usually associated with myeloma. Lab reports did not show hypercalcemia or albumin/globulin reversal, and there were no lytic lesions on skeletal survey. As the patient gave a history of constitutional symptoms for a duration of 3 months, the possibility of occult chronic kidney disease (CKD) was also considered. Hence, the diagnosis of MM with LCDD was established conclusively only on the basis of renal biopsy findings. No extrarenal features of LCDD could be detected.

In the second case study, neither the demographic profile (female, middle aged) nor the presenting complaints (loss of appetite with epigastric discomfort and bloating) were typical for MM. No hypercalcemia or albumin/globulin ratio reversal was seen. MM was diagnosed only on the basis of renal biopsy done for the evaluation of renal failure, and chemotherapy was started after a confirmatory bone marrow biopsy revealed an increased plasma cell population (>20%). Both patients showed significant improvement in renal function postchemotherapy and could be managed conservatively without hemodialysis.

Multiple myeloma is a clonal plasma cell proliferation that accounts for 10% of all hematological malignancies.[5] With increasing

awareness of the disease and the availability of sensitive screening tests, it is increasingly being diagnosed in younger populations with atypical presentations. Newer case series report that nearly 50% of MM cases present with renal failure of unknown etiology,[6] hence underscoring the need for a high index of suspicion along with both screening and invasive (renal biopsy) diagnostic modalities to prevent irreversible organ damage.

Hence, these cases illustrate that (1) signs and symptoms associated with MM (back pain, bone pain) may be absent in a subset of patients, (2) features such as hypercalcemia may be absent and albumin/globulin ratio may be normal; hence, overreliance on these markers may lead to a missed diagnosis, (3) a high index of suspicion and low threshold for both noninvasive (testing for paraprotein, radiological screening) and invasive (organ biopsy) diagnostic modalities may guide us to the correct diagnosis, and (4) timely detection of MM will lead to early institution of chemotherapy and save patients from morbidity associated with end-stage renal disease and maintenance hemodialysis.

Take Home Message

- Signs and symptoms associated with MM (back pain, bone pain) may be absent in a subset of patients.
- Features such as hypercalcemia may be absent and albumin/globulin ratio may be normal; hence, overreliance on these markers may lead to a missed diagnosis.
- A high index of suspicion and low threshold for both noninvasive (testing for paraprotein, radiological screening) and invasive (organ biopsy) diagnostic modalities may guide us to the correct diagnosis.
- Timely detection of MM will lead to early institution of chemotherapy and save patients from morbidity associated with end-stage renal disease and maintenance hemodialysis.

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CASE REPORT

Two Syndrome Progressing to Nine Syndrome

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Abstract

Internuclear ophthalmoplegia with ipsilateral horizontal gaze palsy is called one and a half syndrome. There are a number of numerical one and a half spectrum disorders. One such syndrome is nine syndrome, which is characterized by one and a half syndrome, ipsilateral lower motor neuron type facial palsy, and contralateral hemiparesis or hemihypesthesia or hemiataxia. Here we describe a case of nine syndrome with left one and a half syndrome, left lower motor neuron type facial palsy, and right hemiataxia.

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Introduction

Internuclear ophthalmoplegia (INO) is characterized by ipsilateral adduction deficit or slowing and nystagmus in the abducting eye and is due to a lesion in medial longitudinal fasciculus (MLF), which extends from midbrain to medulla. Involvement of nearby structures such as pontine paramedian reticular formation or abducens nucleus results in one and a half syndrome (OHS). Extension to neighboring structures such as facial nerve fasciculus or facial nucleus causes ipsilateral lower motor neuron (LMN) type facial palsy, and when it is associated with OHS, it results in eight and a half syndrome (EHS). Association of hemiparesis, hemihypesthesia, or hemiataxia with EHS is called nine syndrome, which is a very rare neurological syndrome.

Case Description

A 66-year-old man with diabetes mellitus presented with a 2-day history of swaying to right and right-hand paresthesia. There was no history of weakness, dysarthria, or diplopia. He had sustained an injury to left cornea in childhood and had no vision in left eye. On examination, he had left gaze palsy, left INO, and gait ataxia with swaying to right (Figs 1 and 2). Vestibulo-ocular reflex was absent to right. Motor system was normal. Plantars were flexor. Sensory system was normal. Next day, he developed facial deviation to right, and examination showed left LMN facial palsy (Fig. 3). Magnetic resonance imaging (MRI) of the brain showed an acute infarct in left lower dorsal pons (Fig. 4).

Discussion

One and a half syndrome, initially defined by Fisher CM, is a classical neuro-ophthalmological syndrome characterized by ipsilateral INO and gaze palsy to same side as the lesion.[1] One and a half spectrum disorders are a group of numerical syndromes related to OHS. There are a number of such syndromes like nine syndrome.[2] Combination of OHS with LMN type facial palsy (ipsilateral) is called EHS. Localization for EHS is lower dorsal paramedian pontine tegmentum. Structures involved are ipsilateral MLF, ipsilateral abducens nucleus/pontine paramedian reticular formation (PPRF), and seventh nerve fasciculus. EHS with contralateral hemiparesis or hemianesthesia or hemiataxia is called nine syndrome.[3,4] There is additional involvement of pyramidal tract, or medial lemniscus, or cerebellar peduncle. The subject in this report presented with left OHS and right hemiataxia (two syndrome), and next day he developed left LMN facial palsy (7th nerve), qualifying for nine syndrome. Rosini et al.[5] reported nine syndrome as a rare entity characterized by EHS with contralateral hemiparesis and hemihypesthesia, and there are only scanty reports of this entity in the literature.[6] Mahale et al.[3] described nine syndrome in two of their patients with EHS and hemiataxia. They did not have hemiparesis. In one patient hemiataxia was due to a lesion of inferior cerebellar peduncle and due to red nucleus involvement in another patient. Common causes of INO are

Fig. 2: Gaze palsy to left

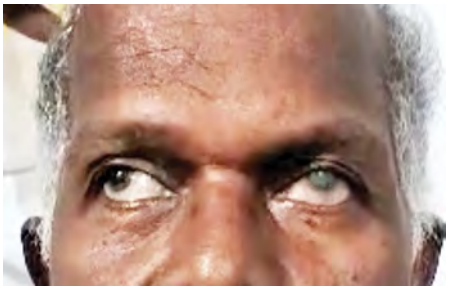

Fig. 1: Impaired adduction in left eye (left INO)

Fig. 3: Left LMN facial palsy

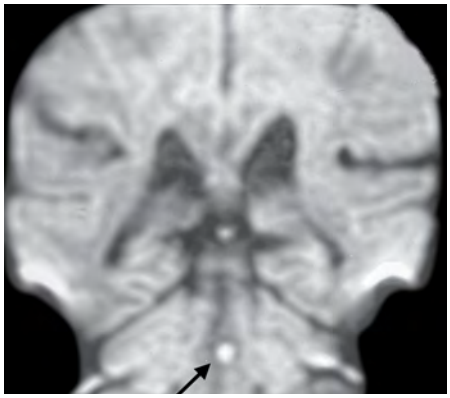

Fig. 4: Magnetic resonance imaging of the brain, coronal diffusion-weighted imaging (DWI), showing acute left paramedian pontine infarct

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stroke, multiple sclerosis, trauma, infection, and tumors. Dorsal pons is supplied by perforating branches of the basilar artery, and blockage of these branches causes paramedian pontine syndromes.

Conclusion

Internuclear ophthalmoplegia, OHS, and EHS are rare presentations of brainstem stroke in the elderly. Here we describe a case of OHS with contralateral ataxia (two syndrome) due to stroke who subsequently developed ipsilateral LMN facial palsy resulting in nine syndrome.

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CASE REPORT

Infective Myositis with Guillain–Barré Syndrome in *Enterococcus* Infection

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Abstract

Acute myositis and Guillain–Barré syndrome (GBS) occurring together in a single patient is a rare clinical phenomenon that poses both diagnostic and therapeutic challenges. This article discusses the pathophysiology and clinical presentation of these two neuromuscular disorders. The simultaneous occurrence of infectious myositis and GBS is uncommon, and the identification of *Enterococcus* as the causative agent is even rarer. In this report, we describe a case involving a middle-aged female who presents with both acute infectious myositis and GBS.

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Introduction

Infective myositis is a group of inflammatory myopathies resulting from a wide range of infectious organisms, including bacteria, fungi, viruses, and parasites. Clinically, infective myositis may present with an acute, subacute, or chronic course characterized by pain, swelling, and/or weakness. Viral infections have been identified as the etiological agent in some idiopathic cases of polymyositis. The standard of care depends on establishing the diagnosis based on clinical evaluation, serological or culture testing, and muscle biopsy from the affected muscle groups. According to Narayanappa and Nandeesh[1] molecular genetic testing is available for some infectious agents but is not routinely used as a diagnostic tool.

Myositis following a bacterial infection typically presents as a focal muscle infection, whereas viral and parasitic infections tend to cause more diffuse involvement of muscle groups, potentially leading to generalized myalgia or multifocal myositis.

Guillain–Barré syndrome (GBS)[2] is a rare neurological disorder in which a person's immune system mistakenly attacks the peripheral nervous system. GBS begins suddenly and can progress over a few hours, days, or weeks to a state of complete muscle paralysis. Some cases of GBS are mild, marked only by brief weakness without serious organ involvement. However, in severe cases, respiratory paralysis and/or significant autonomic dysfunction may occur, which can be life-threatening. Most patients recover with appropriate treatment, even in severe cases, though some may experience residual weakness despite full recovery.

Case reports describing the concurrent occurrence of infective myositis and GBS have been documented with cytomegalovirus, as stated by Sakthivadivel et al.[3] However, cases where *Enterococcus* is the causative infectious agent are rare. Here, we report an intriguing case of the simultaneous presence of acute infective myositis and GBS in a middle-aged female.

Case Description

A 45-year-old female patient presented with purplish lesions over all four limbs for 2 weeks, followed by four-limb weakness for 1 week. Both symptoms were insidious in onset, gradually progressive, and associated with high-grade fever and intense muscle pain (Figs 1 and 2).

On examination, the patient was febrile, with blood pressure not recordable and tachycardia. A neurological examination revealed reduced power in all muscle groups (1/5), while all sensory modalities and reflexes were preserved. Bladder and bowel functions were not affected. Cardiovascular, respiratory, and abdominal examinations were unremarkable.

Details of routine investigation are depicted in Table 1.

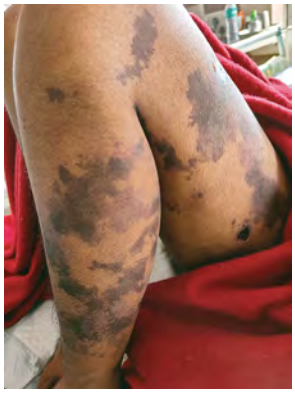

Fig. 1: Skin lesion over lower limb

Routine fever profile (dengue IgM, typhi dot IgM, scrub typhus IgM) and serology (HIV and hepatitis B, C) were negative. Urine examination and chest radiography showed no abnormalities. The coagulation profile was within the normal range. Urine culture, blood culture, myositis profile, antinuclear antibody (ANA) with an ANA profile, magnetic resonance imaging (MRI) of the bilateral lower limbs, electromyography (EMG), and muscle biopsy were scheduled.

A presumptive diagnosis of acute myositis of infective etiology with sepsis was made. The patient was initiated on empirical antibiotics with inotropic support and other conservative management. After 3 days of treatment, hemodynamic parameters improved, and fever and muscle pain subsided, but limb weakness persisted. Meanwhile, the blood culture report showed the growth of *Enterococcus*, and antibiotics were switched according to the sensitivity report, as detailed in Table 2. Despite the adjusted treatment regimen, no further improvement in symptoms was observed.

Follow-up investigations showed a total leukocyte count of 12,300/mm^3, a

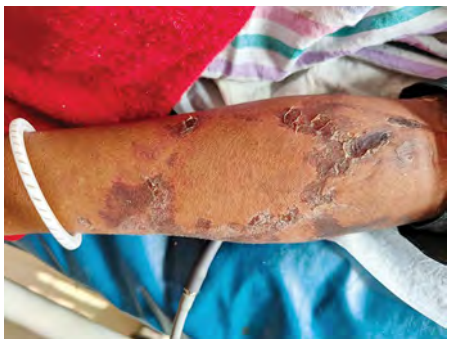

Fig. 2: Skin lesion over upper limb

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Table 1: Routine report

Investigation	*Initial report*	*Posttreatment report*	*Reference range*
Hemoglobin	10 gm/dL	9.8 gm/dL	12–15 gm/dL
Total leukocyte count	26,900/mm^3	12,300/mm^3	4,000–11,000/mm^3
Platelet count	4,57,000/mm^3	2,78,000/mm^3	1,50,000–4,00,000/mm^3
Urea	66 mg/dL	26 mg/dL	15–40 mg/dL
Creatinine	1.4 mg/dL	0.9 mg/dL	0.7–1.2 mg/dL
AST	453 IU/L	112 IU/L	0–40 IU/L
ALT	239 IU/L	85 IU/L	0–40 IU/L
Creatinine kinase	6,123 IU/L	561 IU/L	30–50 IU/L
Procalcitonin	10.2 mcg/L	2.1 mcg/L	0–0.5 mcg/L
Prothrombin time	13.6 seconds	13.9 seconds	11–15 seconds
Activated partial thromboplastin time	31 seconds	30 seconds	25–35 seconds
ANA with ANA profile	Negative		
Urine examination	Within normal limit	Within normal limit	

Table 2: Blood culture sensitivity report: blood culture shows growth of *Enterococcus* after 48 hours of incubation

Sensitive	*Resistant*
Vancomycin	Cotrimoxazole
Linezolid	Amikacin
Teicoplanin	Doxycycline
	Azithromycin
	Ciprofloxacin

Table 3: MRI of both thighs

Protocol	Multiplanar images of the both thighs taken in T1 and T2 weighted and STIR images
Findings	Altered intensity (hyper) on T2, STIR with atrophy noted involving anteromedial compartment of right thigh and all the compartments of left thigh muscles. Hamstring group of muscles at right side are not involved at present. Subcutaneous edema and soft tissue plane edema noted at bilateral gluteal region. Underlying bone appears normal
Impression	Features are suggestive of myositis as described above. Suggested other investigations and clinical correlation

Table 4: Myositis profile

Antibody	*Reports*
Anti-Mi-2	–
Anti-Ku	–
Anti-PM Scl 100	–
Anti-PM Scl 75	–
Anti-Jo 1	–
Anti-SRP	–
Anti-PL 7	–
Anti-Pl 12	–
Anti-Ro 52	–
Control	+++

Table 5: NCS of all four limbs

Motor NCS	Bilateral median, ulnar, tibia/ and peroneal CMAP are nonrecordable
Sensory NCS	Bilateral median, ulnar, and sural SNAP—are nonrecordable
"F" responses	All "F" responses are nonrecordable
"H" reflex	Bilateral H-reflex are nonrecordable
Impression	Bilateral symmetrical demyelinating with axonal type sensory-motor polyneuropathy

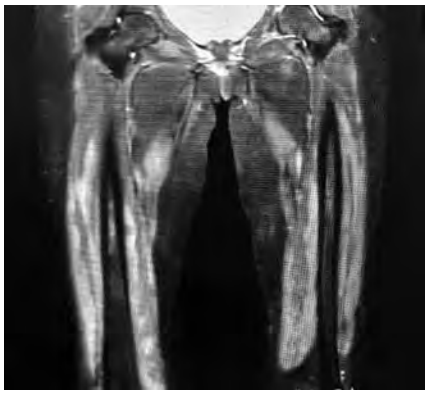

Fig. 3: MRI of thigh

platelet count of 2,78,000/mm^3, aspartate aminotransferase (AST) of 112 IU/L, alanine aminotransferase (ALT) of 85 IU/L, serum urea of 26 mg/dL, creatinine of 0.9 mg/dL, C-reactive protein (CRP) of 65 mg/dL, procalcitonin of 2.1 mcg/L, and creatine kinase of 561 IU/L. MRI of the lower limbs suggested myositis involving all groups of thigh muscles (Fig. 3), as detailed in Table 3.

Electromyography demonstrated polyphasic motor unit action potentials with spontaneous fibrillation activity, suggestive of myositis. However, muscle biopsy was inconclusive. The autoimmune myositis profile, as shown in Table 4, and the ANA profile were negative.

As limb weakness did not improve despite reductions in laboratory markers and updated antibiotic therapy, peripheral neuropathy was suspected. A repeat neurological examination revealed the absence of reflexes. A nerve conduction study (NCS), detailed in Table 5, and a cerebrospinal fluid (CSF) study were conducted. NCS findings indicated symmetrical bilateral demyelinating with axonal-type sensory-motor polyradiculoneuropathy of all four limbs. CSF analysis showed albumino-cytological dissociation (albumin: 79 mg/dL, cell count: 5/mm^3, all mononuclear).

A diagnosis of GBS was made, and the patient was started on intravenous immunoglobulin (IVIG) at 2 gm/kg in divided doses over 5 days. Limb weakness responded clinically, with muscle power improving to 4/5 within a week. Residual weakness was managed with physiotherapy, as advised by the Department of Physical Medicine and Rehabilitation.

The patient was discharged in a clinically stable condition with a final diagnosis of infective myositis with GBS caused by *Enterococcus* species.

Discussion

Enterococcus is a large genus of lactic acid-producing bacteria in the phylum Bacillota. Enterococci are gram-positive cocci that often occur in pairs (diplococci) or short chains, and it is not easy to differentiate them from streptococci. Two species are common commensals in the intestines of

humans: *Enterococcus faecalis* (90–95%) and *Enterococcus faecium* (5–10%). Rare infections may occur with other species, including *Enterococcus casseliflavus*, *Enterococcus gallinarum*, and *Enterococcus raffinosus*. Pérez-Rodríguez et al.[4] reported that *E. faecalis* is the causative organism of myositis among the species mentioned above.

Acute infective myositis is an uncommon manifestation of *Enterococcus* infection, where direct muscle infection or autoimmunity is likely the underlying pathogenesis. Fujinami et al.[5] stated that *Enterococcus* antigens may resemble muscle proteins (e.g., myosin, actin), leading to cross-reactivity of the immune system. This causes autoreactive T-cells and autoantibodies to attack muscle tissue, leading to persistent inflammation even after bacterial clearance. Infection-induced muscle damage releases self-antigens, which are then presented by activated antigen-presenting cells (APCs). This triggers autoreactive T-cell activation, further sustaining muscle inflammation. Case reports documenting *Enterococcus*-associated myositis in immunocompetent patients are sparse, based on a thorough review of the literature. Muscle pain and high serum creatine kinase levels (value >1,000 IU/L) are suggestive of acute myositis, according to Leverenz et al.[6] The laboratory diagnosis was confirmed by the presence of *Enterococcus* in blood culture, while other infective and autoimmune panels were unremarkable. MRI and EMG of the muscles suggested acute myositis.

Guillain-Barré syndrome is a rapidly progressive polyradiculoneuropathy in which patients present with limb weakness, typically preceded by an infection within the last 4 weeks. *Campylobacter jejuni* is the most common infective agent associated with GBS. GBS associated with *Enterococcus* infection has not yet been reported. Molecular mimicry is the proposed pathogenesis, where antibodies cross-react with antigens present on Schwann cells or axons of nerves. Following antibody binding, complement activation occurs, leading to the formation of the membrane attack complex, which damages the myelin sheath or axon.

The clinical characteristics of GBS classically include areflexic, ascending limb weakness without sensory or autonomic involvement. Diagnosis is confirmed through nerve conduction studies and CSF analysis. Treatment modalities include IVIG or plasmapheresis, and improvement is typically observed when treatment is initiated within 2–4 weeks of symptom onset.

Simultaneous occurrence of myositis and GBS has been reported in infections such as *Mycoplasma pneumoniae*, dengue viral fever, and cytomegalovirus. However, *Enterococcus* as a causative agent of concurrent myositis and GBS has yet to be reported. The improvement observed with IVIG suggests a possible autoimmune pathogenic mechanism.

Conclusion

The simultaneous occurrence of acute infective myositis and GBS is rare, with only a few cases documented in the literature, primarily associated with viral infections such as cytomegalovirus. Our case highlights an unusual presentation where *Enterococcus* was identified as the infectious etiology, further expanding the spectrum of potential causative agents. Early recognition and prompt management of both conditions are crucial to preventing severe complications and improving patient outcomes. This case underscores the need for a high index of suspicion in patients presenting with overlapping neuromuscular symptoms and calls for further research into the pathophysiological mechanisms linking infectious myositis and GBS.

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CASE REPORT

Type 4 Woolly Hair-palmoplantar Keratoderma Syndrome with a Novel Phenotype

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Abstract

Woolly hair with palmoplantar keratoderma (WH-PPK) is a group of four autosomal recessive syndromes. Type 4 WH-PPK is usually associated with KANK2 mutation and does not have cardiac morbidity among its features. Here we report a 25-year-old woman with woolly hair, palmoplantar keratoderma without any cardiac morbidity. However, she had sensorineural hearing loss and maculopathy. Thus, we present a patient with type 4 WH-PPK with a novel phenotype to highlight the rare WH-PPK syndromes. The association of woolly hair and palmoplantar keratoderma without cardiomyopathy, and with macular deposits and sensorineural hearing loss, has not been reported before.

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Introduction

Woolly hair (WH) is a rare congenital abnormality of scalp hair, characterized by tightly coiled hair involving a part of or the entire scalp.[1] Palmoplantar keratoderma (PPK) with woolly hair (WH-PPK) occurs as an autosomal recessive syndromes that affect the skin and hair with increased risk of cardiac morbidity. It is classified into four types.[2] Type 1 Naxos syndrome is characterized by woolly hair, PPK, and arrhythmogenic right ventricular cardiomyopathy. Type 2 Carvajal syndrome is characterized by woolly hair, PPK, and left ventricular dilated cardiomyopathy. Type 3 has a Naxos-like phenotype. Type 4 results in woolly hair and PPK, without cardiac involvement. Here, we report probably the first case presenting with woolly hair, PPK, without cardiac involvement, but with additional involvement of vision and hearing.

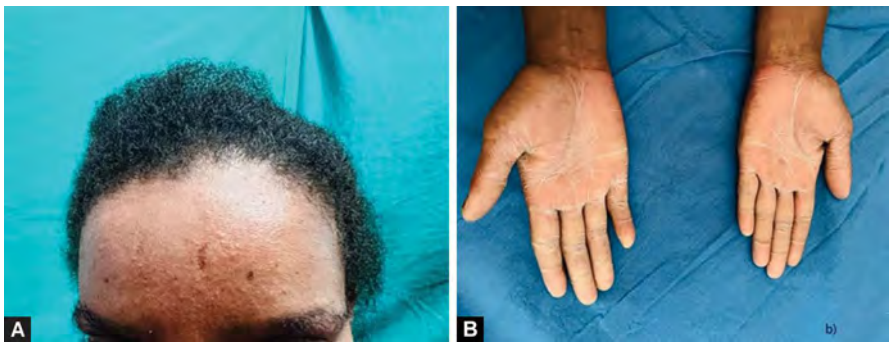
Case Description

A 25-year-old female born out of a third-degree consanguineous marriage presented with curly, fragile, brittle, and short hair over the scalp, eyebrows, and lashes since birth. There was thickening of palms and soles since the age of 7, and painful fissures over the bilateral feet. There was no history suggestive of cardiac issues. Similar complaints were reported in two of her three siblings; her mother had only thickening of palms and soles, and her maternal uncle had woolly hair. She also complained of diminished vision and hearing impairment in her right ear, which was not present in other family members. On examination, hair was sparse, curly, brittle, and lusterless over the scalp, eyebrows, and lashes (Fig. 1A). Diffuse thickening and scaling were present in both palms and soles (Fig. 1B). Oral mucosa and teeth were normal. Hair shaft examination was normal. Skin biopsy from keratoderma revealed hyperkeratosis, hypergranulosis, and acanthosis (Fig. 2A). Echocardiogram was within the normal limits. Ophthalmological examination revealed nystagmus, with bilateral nasal and temporal pterygium. Fundus examination revealed a chorioretinal scar with macular deposits (Fig. 2B). Audiometry revealed profound sensorineural hearing loss in the right ear and moderate sensorineural hearing loss in the left ear. Otoacoustic emission test revealed absent emission, confirming outer hair cell dysfunction. Genetic analysis could not be done due to financial constraints. A diagnosis of WH-PPK syndrome type 4 was made due to the presence of woolly hair, diffuse PPK without transgrediens, and absence of cardiac abnormality. She was prescribed topical keratolytics and emollients. Hearing aids were advised, and a guarded prognosis was advised pertaining to vision. Genetic counselling was done. The patient is on irregular follow-up.

Discussion

Woolly hair with palmoplantar keratoderma includes autosomal recessive inherited syndromes encompassing skin changes in the form of palmoplantar keratoderma and woolly hair, in association with cardiac manifestations. There are four autosomal recessive syndromes described in literature (Table 1). The first three are due to desmosomal protein mutations and are associated with cardiovascular morbidity.[3]

Type 4 WH-PPK is associated with a mutation in steroid receptor coactivator (SRC) interacting protein (SIP) and is not associated with cardiac abnormality.[3] SRC-2 and SRC-3 are coactivators of vitamin D receptor and are crucial for epidermal differentiation, production of sphingolipid, formation of permeability barrier, and normal



Figs 1A and B: (A) Short curly lusterless brittle hair on the scalp of the patient; (B) Thickening of the bilateral palms of the patient

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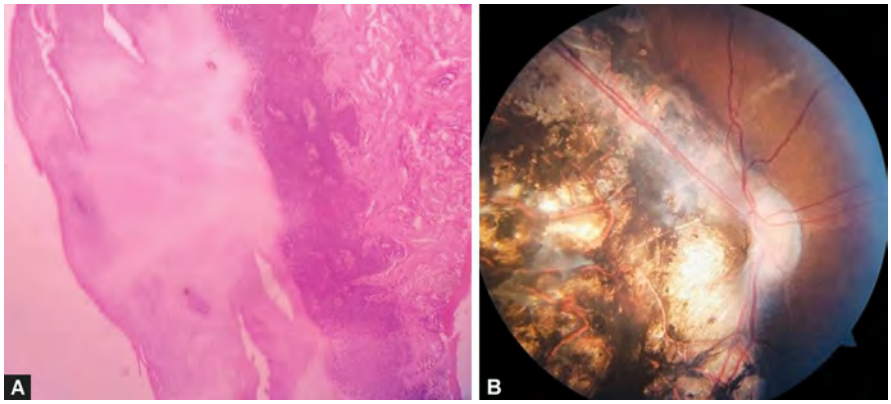
Table 1: WH-PPK syndromes and their features

Category	*Type 1* *Naxos syndrome*	*Type 2* *Carvajal syndrome*	*Type 3* *Naxos-like phenotype*	*Type 4*
Demography	Present in 2nd to 3rd decade of life	Present in early childhood		
Clinical features	Diffuse palmoplantar keratoderma, woolly hair, and arrhythmogenic right ventricular cardiomyopathy	Striate keratoderma, woolly hair, and dilated left ventricular cardiomyopathy	Arrhythmogenic right ventricular cardiomyopathy, woolly hair, and mild palmoplantar keratoderma	Woolly hair, keratoderma, pseudoainhum, leukonychia, without cardiac abnormality
Gene mutation	JUP gene	DSP gene	DSC2 gene	KANK2 gene
Prognosis	High risk of sudden death	Heart failure and sudden cardiac death in adolescents		Good prognosis



Figs 2A and B: (A) Histopathological examination of PPK showing hyperkeratosis and acanthosis (H&E, 40×); (B) Fundus examination showing chorioretinal scar

hair growth. SRCs are regulated by steroid receptor coactivator (SRC)-interacting protein (SIP), an ankyrin repeat-containing protein, which sequesters SRCs in cytoplasm and regulates transcription activation of steroid receptors. Type 4 WH-PPK occurs due to a mutation of KANK2, which encodes SIP. Hence, sequestering abilities of SIP are abolished, and vitamin D-induced transactivation is increased in patients' keratinocytes. In addition, SRCs are sequestered in the nucleus of basal keratinocytes in patients and cause altered transcriptional activation of nuclear receptors.[3] Our patient could have type 4 WH-PPK as she did not have cardiac issues. However, in a novel phenotype, she had sensorineural hearing loss and visual defects in addition to the woolly hair and palmoplantar keratoderma.

Type 4 WH-PPK has been reported by Ramot et al. in seven Arab patients belonging to two families with consanguinity, who had striate PPK and occasional pseudoainhum of the fifth toe, and with KANK2 mutation.[4] It was also reported by Hassanandani et al. in a patient in their late 30s with diffuse PPK with transgrediens and severe contractures and woolly hair, where genetic analysis was not done.[5] Another report of WH with diffuse PPK was by Mohanan et al.[6] in a 3-year-old female child. However, genetic analysis was not done; therefore, it may not be type 4 WH-PPK, as the patient may develop cardiomyopathy in the future.[6]

To conclude, we report a patient with a probable diagnosis of type 4 WH-PPK with a novel phenotype, having sensorineural deafness and maculopathy. We also stress the importance of cardiac screening in patients with the various syndromes of WH-PPK.

Acknowledgments

None.

Authors' Contribution

All authors were involved in conceptualization, data collection, and analysis. SS and SM wrote the manuscript, and all authors revised it for important intellectual content.

Take-home Message

- Woolly hair with PPK encompasses four different syndromes.
- WH-PPK syndromes are type 1 (Naxos syndrome), type 2 (Carvajal syndrome), type 3 (Naxos-like phenotype), and type 4.
- There are mutations in different proteins in these syndromes.
- Type 4 is not associated with cardiomyopathy. The other 3 are associated with cardiomyopathy.

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CASE REPORT

Unilateral Facial and Vestibulocochlear Nerve Palsy: A Case Report of a Rare Adverse Effect of Warfarin Therapy

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Abstract

Introduction: Intracranial hemorrhage, most often intraparenchymal hemorrhage, is an increasingly common and fatal complication of warfarin-induced coagulopathy. Warfarin remains the anticoagulant of choice in valvular atrial fibrillation. However, warfarin has a narrow therapeutic index. Extra axial hemorrhage due to warfarin-induced coagulopathy is a rare adverse event. We present a rare case of right vestibulocochlear and lower motor neuron (LMN) facial palsy secondary to an intracranial bleed along the cerebellopontine angle.

Case description: A 36-year-old woman presented with headache, giddiness, sudden onset of right-sided hearing loss, and left-sided deviation of the angle of the mouth. Symptoms had developed acutely over 4 hours. She was diagnosed with mitral stenosis at 8 years of age and had undergone mitral valve repair 2 years before presentation, after which she was started on warfarin. She was lost to follow-up for over a year and on presentation had right-sided sensorineural hearing loss along with features such as difficulty raising her right eyebrow, inability to close her right eye, and water drooling from the right side, all consistent with a right LMN facial palsy and vestibulocochlear nerve palsy. MRI brain showed an extra-axial hemorrhage at the right cerebellopontine angle cisterns.

Conclusion: Warfarin-induced intracranial bleeds without involving the parenchyma are a rare event, and through this case, we would like to highlight the importance of timely monitoring of the international normalized ratio (INR) of patients on warfarin therapy.

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Introduction

Oral vitamin K inhibitors (VKAs) [Coumatetralyl, warfarin (Coumadin), brodifacoum, phenprocoumon, dicoumarol, acenocoumarin, tioclomarol] remain the anticoagulants of choice in patients with valvular atrial fibrillation (Afib) and prosthetic valve replacement.[1] Among them, warfarin, one of the most widely used VKAs, has received FDA approval for treatment as well as prophylaxis of pulmonary embolism, venous thrombosis, valvular Afib or cardiac valve replacement related thromboembolic complications, reduction of mortality in recurrent myocardial infarction (MI), and post-MI related thromboembolic events (cerebrovascular accidents and systemic embolization).[2] Given its narrow therapeutic index, frequent monitoring with prothrombin time (PT) and the international normalized ratio (INR) is essential for balancing efficacy with the risk of bleeding. Among the various adverse effects, warfarin coagulopathy leading to significant hemorrhage remains the most devastating complication.[3]

Case Description

History and Presentation

A 36-year-old woman presented to the emergency department with complaints of sudden-onset headache, giddiness, and right-sided hearing loss, along with facial asymmetry. The symptoms had developed acutely over the past 4 hours. The patient also reported drooling from the right side of her mouth and difficulty closing her right eye. There was no history of trauma or similar prior episodes.

Her medical history was significant for mitral stenosis, diagnosed at the age of 8 years. She underwent balloon mitral valvotomy as a child and had undergone mitral valve replacement with a St. Jude's mechanical valve along with left atrial clot removal 2 years prior to presentation. She had been on long-term warfarin therapy (10 mg daily) but had been lost to follow-up for more than a year.

Examination

- Vital signs: Pulse rate of 86 beats/min, irregular.
- Apex pulse deficit: 12 beats/min
- Blood pressure: 130/80 mm Hg
- Neurological examination: Cranial nerve examination revealed right-sided lower motor neuron facial palsy, including difficulty raising her right eyebrow, inability to close her right eye, and deviation of the angle of the mouth to the left side.
- Hearing tests: Weber's test showed lateralization to the left side (unaffected ear).
- Rinne's test was positive on both sides (air conduction > bone conduction), but absolute bone conduction (ABC) was reduced on the right, indicating sensorineural hearing loss (SNHL).
- Vestibular signs: Gaze-evoked nystagmus with the fast phase directed toward the left was noted, consistent with a lesion in the right cerebellopontine angle.
- Glossopharyngeal nerve: The examination revealed an absent gag reflex and nasal intonation in speech, indicating glossopharyngeal nerve involvement.
- The rest of her neurological examination was normal.
- These findings pointed toward right-sided lower motor neuron involvement of both the facial and vestibulocochlear nerves, associated with right-sided sensorineural hearing loss, as well as additional glossopharyngeal nerve involvement.

Investigations

- International normalized ratio: 5.5, indicating supra-therapeutic anticoagulation.
- MRI of the brain: The imaging revealed an extra-axial hemorrhage located in the right cerebellopontine angle cistern, compressing the adjacent cranial nerves (Fig. 1).

Treatment

Warfarin therapy was discontinued immediately, and the patient was administered intravenous vitamin K (10 mg in 100 mL of normal saline). The INR was monitored, and after 3 days of treatment, it had fallen to 1.34. The patient's symptoms

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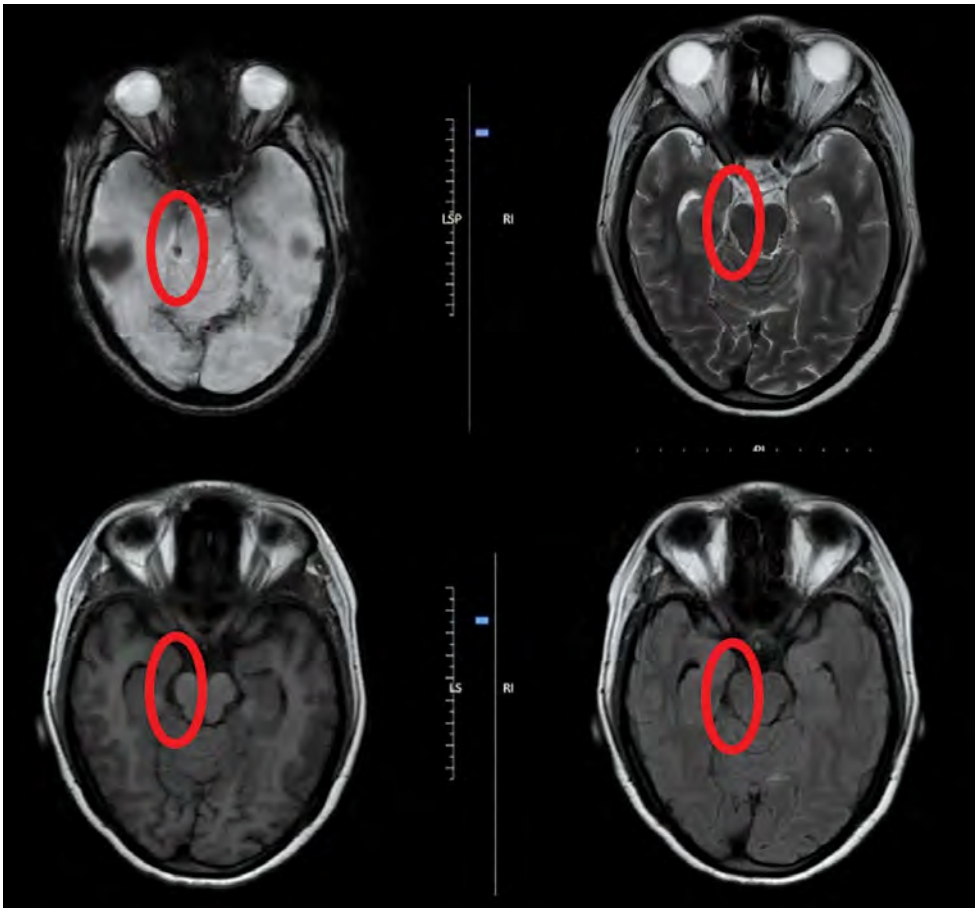

Fig. 1: MRI brain—Areas of altered signal intensity, which appear hyperintense on T2W, T1W, and FLAIR which demonstrates blooming on gradient images is noted in the extra-axial location in the prepontine, right cerebellopontine angle cistern tracking along the bilateral tentorial leaflets of maximum width 5.4 mm. Findings are most likely suggestive of extra-axial hemorrhage

remained stable without worsening. She was discharged after serial MRI monitoring and stabilization of her condition. She was started on low molecular weight heparin and bridged back to warfarin upon discharge.

Discussion

Warfarin is a competitive inhibitor of vitamin K epoxide reductase complex 1 (VKORC1), a key enzyme for activating vitamin K. This leads to the depletion of vitamin K and vitamin K-dependent clotting factors, namely II, VII, IX, and X, along with protein C and protein S (coagulation regulatory factors). Warfarin is administered orally, once daily. The dose is dependent on factors such as genetics, a diet rich in vitamin K, warfarin binding proteins, and interaction with drugs that induce/inhibit cytochrome P450 enzymes.[4]

The target INR for patients on warfarin therapy may vary based on the patient's presentation and the clinician's discretion. Target INR for mechanical mitral valves is specifically between 2.5 and 3.5.[5] Patients initiated on warfarin require close monitoring with INR. For admitted patients, INR should be repeated daily. Upon reaching a maintenance phase of warfarin therapy, INR can be monitored on a monthly basis. Additionally, in cases of supratherapeutic or subtherapeutic INR, frequent monitoring is necessary. In situations that warrant discontinuing or changing the dose of warfarin, frequent INR monitoring is required.

The risk of bleeding increases significantly when the INR reaches above 5.[4]

Warfarin-related adverse effects include nausea and vomiting, abdominal bloating, flatulence, abdominal pain, dysgeusia, bleeding, and, rarely, purple-toe syndrome. Among these, significant hemorrhage in the form of gastrointestinal (GI) bleeding, hematemesis, intraocular bleeding, intracranial hemorrhage, and hemarthrosis are serious complications.[4] Intracranial hemorrhage is one of the most devastating and life-threatening warfarin-related adverse effects. The most common locations for warfarin-related bleed are supratentorial and intraparenchymal, although bleed can happen at any location. Prolonged supratherapeutic levels of INR directly correlate with negative outcomes, including quality of life, size and growth of hemorrhage, and mortality.[6]

According to the 2012 ACCP guidelines, major bleeding, irrespective of INR levels, should be managed with prothrombin complex concentrate (PCC) and 5–10 mg of vitamin K1 IV. The immediate goal is to bring the INR down to less than 1.4 within the first 5 hours of presentation with INR monitoring every 4–6 hours up to 24 hours of presentation, and then daily for the next 5–7 days.[7]

Our case was unique as the patient presented with an extra-axial hemorrhage, which is highly unusual in warfarin coagulopathy. Also, the patient presented with LMN 7th and 8th cranial nerve palsy, which is often associated with lesions at the cerebellopontine angle such as schwannomas, meningiomas, congenital epidermoid inclusion cysts, and not commonly linked to anticoagulant use. Our initial diagnosis of warfarin coagulopathy was further confirmed by the fact that the patient had a stable disease after warfarin withdrawal,

vitamin K supplementation, and after an INR of 1.34 was achieved. Early identification of warfarin toxicity and prompt reversal of anticoagulation are crucial for preventing adverse neurological outcomes.

This case report presents a rare instance of cerebellopontine angle hemorrhage resulting in facial and vestibulocochlear nerve palsy due to warfarin-induced coagulopathy. It highlights the critical importance of regular INR monitoring in patients on long-term warfarin therapy. It is important to educate patients on chronic warfarin therapy for frequent follow-ups. Additionally, there is a need to study the safety and efficacy of other anticoagulants, especially in patients with valvular Afib and valve replacement.

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CASE REPORT

Elsberg Syndrome in Varicella Zoster Virus Infection

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Abstract

Elsberg syndrome (ES) is an acute-to-subacute onset, lumbosacral radiculitis, with or without myelitis, confined to lower spinal cord, often caused by herpes simplex virus (HSV)-2. We report a case of a 70-year-old lady with ES due to varicella zoster virus (VZV) reactivation, presenting as herpes zoster in right side L5–S2 dermatomes, with radiculitis in the respective roots and myelitis in the conus medullaris region. The diagnosis is often made by considering the clinical picture, as well as the investigations, such as magnetic resonance imaging (MRI) of the spine, cerebrospinal fluid (CSF) analysis, and electroneuromyography (ENMG), as a whole. Through this case report, we re-emphasize the fact that ES is an important differential to consider in patients presenting with acute-to-subacute onset lumbosacral radiculitis with/without myelitis, as the incidence of ES is around 10% in such cases.

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Introduction

An acute-to-subacute onset of lumbosacral radiculitis, with or without myelitis, confined to the lower spinal cord, often caused by herpes simplex virus (HSV)-2, is called Elsberg syndrome (ES). It is a self-limiting condition caused by primary infection or reactivation of the virus. We report a case of clinically definite ES due to varicella zoster virus (VZV) reactivation, which is a rarer etiology.

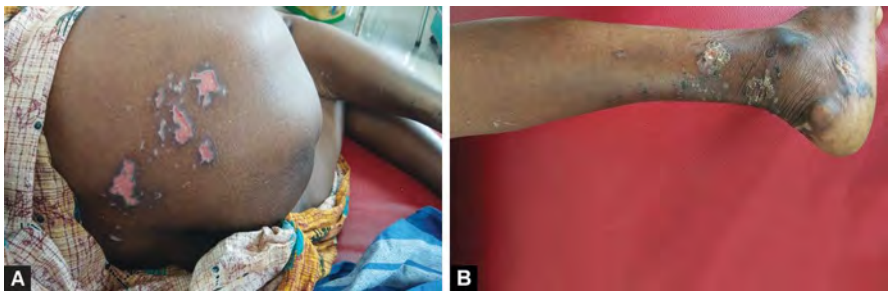
Case Description

A 70-year-old lady came with a 4-day history of skin lesions in the groin, right-sided buttock, and foot, followed by a burning sensation later in the same region. She also had complaints of urgency while micturition as well as increased frequency. 2 days later, she lost sensation of bladder fullness and developed urinary retention. On examination, she was conscious and oriented; there were grouped vesicles in the distribution of L5–S2 dermatomes (Fig. 1). Nervous system examination revealed normal cranial nerves; normal upper limb examination; spastic lower limbs bilaterally, with normal power, absent anal reflex on the right side (other superficial reflexes normal), brisk knee and ankle jerk, and extensor plantar bilaterally; pain, touch, and temperature reduced in the right L5–S2 dermatomal distribution. The possible structures involved are bilateral pyramidal tracts (below L1 level), bladder center in the spinal cord (S2–S4 levels, affecting the sensory perception as well as somatic control of voluntary micturition), and right-sided L5–S2 roots. The probable etiology is infectious, as she has typical vesicular lesions characterizing herpes zoster (due to reactivation of VZV). A clinical diagnosis of lumbosacral radiculitis with myelitis—ES was made.

Her complete blood count and metabolic work-up were normal. Magnetic resonance imaging (MRI) of the lumbosacral spine and whole-spine screening was normal. Cerebrospinal fluid (CSF) analysis showed elevated protein (68 mg/dL) and lymphocytic pleocytosis (20 cells/mm^3). CSF was negative for IgM HSV and VZV. The nerve conduction study was normal. Clinically and based on the laboratory studies, she is fitting into the diagnosis of clinically definite ES, as per the Savoldi diagnostic criteria. She was further investigated to rule out an immunocompromised status. Her blood sugar levels were normal; serology was negative for human immunodeficiency virus (HIV); peripheral smear not showing any atypical cells; computed tomography (CT) chest, abdomen, and pelvis normal (to rule out malignancy). She was treated with intravenous acyclovir for 14 days and intravenous methylprednisolone pulse therapy for 5 days, followed by a gradual taper. She improved symptomatically within 10 days of starting the treatment.

Discussion

Elsberg syndrome was first described in 1913. This clinical syndrome was found in five patients operated on by CA Elsberg, an eminent neurosurgeon, who described it as neuritis of cauda equina.[1] The exact cause was not known at that point. Later on, in the 1970s and 1980s, several case series were published with the same clinical description of lumbosacral radiculitis, with or without myelitis, the cause of which was attributed to HSV infection.[2–4] In 2017, Savoldi et al. proposed a formal case definition for ES and derived a classification based on the level of certainty of diagnosis (Table 1).[5] Our patient fit into the clinically definite level. In a retrospective study conducted by Savoldi et al. in the Mayo Clinic using data from 2000–2016, it was found that the ES is likely responsible for around 10% of all patients presenting with cauda equina syndrome and myelitis.[5] The most common cause is HSV-2, followed by VZV.[5,6] Other reported rarer causes include Epstein-Barr virus, cytomegalovirus, severe acute respiratory syndrome coronavirus-2, and *Angiostrongylus cantonensis*. Our patient has herpes zoster, which is a reactivation of the



Figs 1A and B: (A) Herpes zoster lesions over the right S2 and S3 dermatomal distribution (grouped vesicles eroded); (B) Herpes zoster lesions over the right L5 and S1 dermatomal distribution (grouped vesicles eroded)

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Table 1: Elsberg syndrome according to diagnostic certainty[5]

Categories	*Criteria*	*Assessment in the present case*
1. Laboratory-supported definite	(A1 or A2) and B5	
2. Clinically definite	A1 or A2; B1 and two of B2–B4; B1 and B2 (if concomitant)	✓
3. Clinically probable	A1 or A2; B1 and one of B2–B4	
4. Clinically possible	A1 or A2; one of B1–B4	
5. Excluded	Neither of A1 nor of A2; any of D1–D3	
A Required		
A1. Clinical symptoms and signs of cauda equina involvement: urinary hesitancy or retention; bowel incontinence, or severe constipation (erectile dysfunction is insufficient on its own)		✓
A2. MRI or electrophysiologic evidence of cauda equina involvement: enhancement of cauda equina; EMG evidence of radiculopathy		X
B Supportive but not required		
B1. Time course: acute or subacute onset; no relapse; progression over < 3 months		✓
B2. Coexisting or recently preceding symptoms of genital herpes infection or other clinical symptoms of herpes virus infection.		✓ (varicella zoster infection)
B3. Clinical (e.g., exaggerated reflexes and Babinski signs) or MRI evidence of myelitis in the conus		✓
B4. CSF pleocytosis		✓
B5. Documented herpes virus infection from CSF by PCR, culture, or detection of IgM serology.		X
C. Red flags		
C1. Relapses beyond 1 year from onset		–
D. Exclusionary		
D1. Myelitis extending rostral to T9		X
D2. Other neurologic symptoms suggestive of an alternate etiology: optic neuritis, brain/brainstem syndrome.		X
D3. Other etiologies proven or more likely for the syndrome: NMOSD, dural AV fistula, viral transverse myelitis, and other causes of myelopathy.		X

VZV infection, presenting with characteristic skin lesions in the right L5–S2 dermatomal distribution, complicated by radiculitis of the right L5–S2 roots and myelitis of the lower cord (ES). VZV, after a primary infection causing chicken pox, remains latent in the dorsal root ganglia. Reactivation occurs with factors such as immunosuppression, ageing, presenting as herpes zoster affecting one to two skin segments. Most often, these patients present with grouped vesicles in an erythematous skin base, in a dermatomal pattern, along with herpetic neuralgia. In rare cases, the patient develops nervous system complications such as radiculitis in the respective dermatomes, radiculomyelitis, polyradiculitis resulting in Guillain–Barré syndrome like presentation, Ramsay Hunt syndrome, meningoencephalitis, cerebellitis.[7]

The most common presenting complaint was loss of limb sensation (80% of the cases), followed by urinary retention (76.6%). Leg weakness and saddle anesthesia were each seen only in 50% of the cases.[5] Other rare presentations included bowel incontinence and constipation. The clinical syndrome, as we mentioned earlier, is that of a lumbosacral radiculitis with or without features of myelitis of the lower spinal cord. To confirm the diagnosis, electroneuromyography (ENMG), CSF analysis, and MRI spine are done. MRI spine is usually unremarkable, with only 36–40% of cases showing changes suggestive of radiculitis or radiculomyelitis.[5,6] MRI findings include nerve root thickening with smooth and continuous gadolinium enhancement, and T2 cord hyperintensity with or without gadolinium enhancement. More importantly, it helps to rule out other structural causes such as dural arteriovenous fistula and tumors having the same clinical presentation. ENMG evidence of radiculopathy is seen only in 40% of the cases.[5] CSF analysis shows lymphocytic pleocytosis (50% of cases), with elevated protein levels (mean 143 ± 131 mg/dL). 17.6% cases of the cases tested for viral polymerase chain reaction (PCR) were found to be positive in a case series by Savoldi et al.[5] The detection rate is the highest when the sample is obtained 3–14 days after symptom onset.[8] Hence, the diagnosis is often made considering the clinical picture as well as the laboratory parameters as a whole. No clear-cut guidelines are available regarding the treatment of ES. In previous case reports, patients are treated with intravenous acyclovir for 10–14 days and/or intravenous methylprednisolone high-dose pulse followed by a slow taper. Potential benefits of either are not clearly known.[5] Partial to complete recovery is seen in most of the cases. Relapse is reported in 6.7% of the patients in a case series by Savoldi et al.[5]

Conclusion

Elsberg syndrome is a common but rarely diagnosed treatable condition. It is pertinent for clinicians to consider it as a differential diagnosis in patients presenting with acute-to-

subacute-onset lumbosacral radiculitis with/without myelitis, even in patients without the clinical stigmata of infection. This aids in early diagnosis of the condition as well as prompt initiation of treatment.

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CASE REPORT

Coexistent Antiphospholipid Syndrome with Polycythemia Vera in a 25-year-old Lady Presented with Splenic Vein Thrombosis

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Abstract

A high risk of thrombosis is linked to myeloproliferative neoplasm (MPN) and antiphospholipid syndrome (APS). The systemic autoimmune disorder known as APS is characterized by persistently positive antiphospholipid antibodies [anticardiolipin (aCL), lupus anticoagulant, and antibeta 2 glycoprotein 1 IgG and IgM antibodies] in conjunction with obstetrical complications or thrombosis (Chayoua et al.). Polycythemia vera (PV) is a MPN that causes too many red blood cells (RBCs) in the blood and proinflammatory cytokines.

In this report, we present a case of a 25-year-old lady with a history of second-trimester abortion who presented with abdominal pain and hepatosplenomegaly. Owing to erythrocytosis, thrombocytosis, and moderate hepatosplenomegaly, workup for MPN was done along with prothrombotic workup including APS, and she turned out to be positive for both. Coexistence of MPN and APS is rare in the literature. The optimal management of patients with coexistent APS and MPN has not been defined so far. Immediate anticoagulation with specific treatment for MPN is essential to prevent further thromboembolic episodes and progression to catastrophic APS.

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Introduction

Antiphospholipid syndrome (APS) and myeloproliferative neoplasm (MPN) are associated with an increased risk of thrombosis. MPN and APS are two different conditions, but sometimes they can occur together. Polycythemia vera (PV) is a MPN that causes too many red blood cells (RBCs) in the blood and proinflammatory cytokines, whereas APS is an autoimmune disorder causing thrombotic events and pregnancy complications. Triple-positive APS is linked to the highest risk of thrombosis, while isolated existence of an anticardiolipin (aCL) antibody is linked to the lowest risk.[1] In contrast, patients who are just double-positive (aCL IgG and antibeta 2 glycoprotein 1) have a moderate risk of thrombosis. It is very rare to find PV and APS occurring together. The Janus kinase 2 (JAK2) V617F mutation, which is found in 95–98% of patients with PV, has been linked to thrombosis in a way that is similar to APS.[2] The optimal management of patients with coexistent APS and MPN has not been defined so far. Anticoagulants with vitamin K antagonist or direct oral anticoagulants can be continued. We thought of publishing this case owing to the rarity and the difficulty in the management of such coexisting disease.

Case Description

A 25-year-old lady presented with left-sided upper abdominal pain for 17 days, which was aggravated on deep inspiration. She was initially evaluated at a local hospital for similar complaints and was given symptomatic treatment. Her routine blood evaluation showed an elevated platelet count, and ultrasonography (USG) abdomen from outside revealed evidence of splenic vein thrombosis with splenomegaly, and she was referred to our institution.

She also had a history of recurrent headache since the past 7 years with bilateral papilledema. Her magnetic resonance (MR) angiogram and venogram were normal, suggesting the possibility of idiopathic intracranial hypertension. She conceived spontaneously after 1 year of marriage, but she had intrauterine fetal demise at 23 weeks of gestation. Her father had a history of seizure disorder, and internal carotid artery aneurysm was detected on angiographic evaluation.

On examination, she had a body mass index (BMI) of 15.8 kg/m^2. Her blood pressure was 110/80 mm Hg while sitting. Pulse rate was 80/minute, regular, with normal volume. Optic fundi were normal. General examination showed neither pallor nor lymphadenopathy. Abdominal examination revealed firm, nontender hepatomegaly, 10 cm below the right costal margin in the midclavicular line, and the spleen was palpable 9 cm below the left costal margin in the midclavicular line. Other systems were within normal limits.

Her complete blood count (CBC) showed increased RBC count (5.69×10^6/mm^3), normal hemoglobin level, and thrombocytosis (7.37 L/mm^3). Liver function test showed elevated liver enzymes, and renal function was normal. Lactate dehydrogenase (LDH) levels were elevated. Peripheral smear showed thrombocytosis (Fig. 1). Hemoglobin electrophoresis was normal.

The USG abdomen showed recently formed thrombus in the portal vein and its branches, superior mesenteric vein confluence, and retropancreatic splenic vein. There was no evidence of thrombosis in inferior vena cava or superior mesenteric vein. She had moderate splenomegaly and mild hepatomegaly. She underwent bone marrow biopsy in view of possible MPN and prothrombotic state, needing early anticoagulation. Bone marrow aspirate showed normal myeloid maturation, erythroid maturation without any abnormal cells, and bone marrow biopsy showed panmyeloid hyperplasia (Fig. 2).

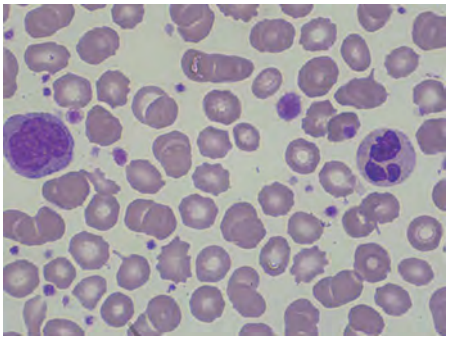

Fig. 1: Peripheral smear showing large megakaryocytes, erythrocytosis, and myeloid cells

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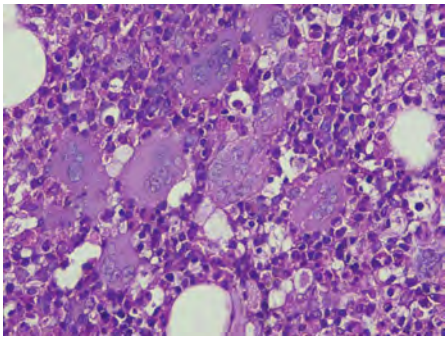

Fig. 2: Bone marrow showing panmyeloid hyperplasia

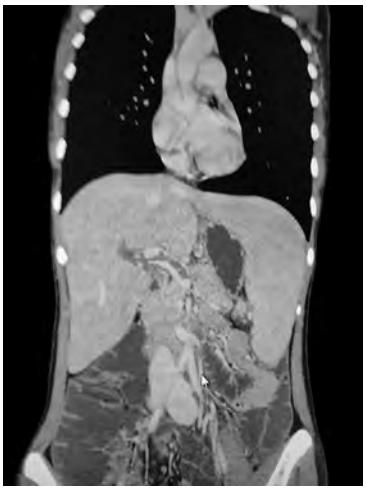

Fig. 3: CECT of the abdomen showing partial lumen filling thrombus involving main portal vein

After bone marrow study, she was started on injection low-molecular-weight heparin (LMWH) 0.4 mL subcutaneous every 12 hours in view of rapidly progressing venous thrombosis. She was given LMWH for 5 days and shifted to oral apixaban. Autoimmune workup showed a normal antinuclear antibody (ANA) profile. She was diagnosed to have possible APS progressing into catastrophic APS characterized by portal and pulmonary artery thrombosis.

She developed acute-onset dyspnea on 2nd day of admission without any hypoxia or hemodynamic instability. Hence, to assess the progression of venous thrombosis and involvement of lung parenchyma, a contrast-enhanced computed tomography (CECT) abdomen and thorax was done, which showed partial lumen-filling thrombosis involving the main portal vein, extending into right and left branches of portal vein, sectoral portal divisions in both lobes of liver, partial lumen-filling thrombus at the splenoportal confluence, and involving the entire length of splenic vein (Fig. 3). There was no evidence of thrombosis in superior mesenteric vein or inferior vena cava. She had a subsegmental pulmonary thromboembolism in the lower lobe of right lung (Fig. 4).

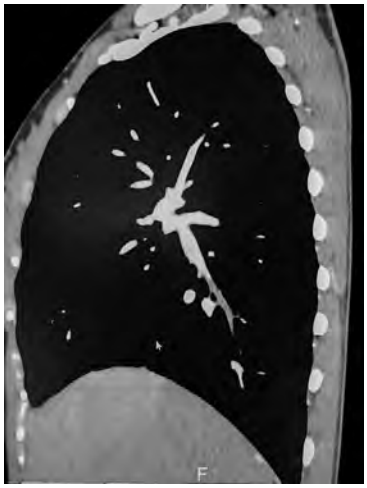

Fig. 4: Partial luminal thrombus noted in the subsegmental division of the pulmonary artery in the postero basal segment of right lower lobe

Her prothrombotic workup for serum homocysteine, antithrombin activity, paroxysmal nocturnal hemoglobinuria (PNH) profile, factor V Leiden mutation, protein C, and protein S was normal. Her antiphospholipid antibody (APLA) profile results showed elevated activated partial thromboplastin time (APTT) and dilute Russell's viper venom time (dRVVT); aCL IgG was weakly positive (32 GPL U/mL), and beta 2 glycoprotein 1 IgG was strongly positive 68 U/mL (positive >10), suggesting the positivity of APS. Lupus anticoagulant, beta 2 glycoprotein 1 IgM, and IgM cardiolipin were negative. In view of lack of efficacy of new oral anticoagulants (NOAC), apixaban was then changed to warfarin with target international normalized ratio (INR) 2–3. Her INR was brought up to 2.4, and injection LMWH was stopped, and she was continued on warfarin 5 mg/day. She remained hemodynamically stable during the course of hospital stay and was discharged after 10 days of hospital stay.

On follow-up, MPN reflex panel showed JAK2 V617F (exon 14) positivity. Anticoagulation was continued to a target INR of 2.5. She was evaluated by a hematologist for further management. APLA profile repeated after 12 weeks showed elevated APTT and dRVVT; aCL IgG was weakly positive (21 GPL U/mL), and beta 2 glycoprotein 1 IgG was strongly positive 57 U/mL (positive >10). Lupus anticoagulant, beta 2 glycoprotein 1 IgM, and cardiolipin IgM were negative, confirming the diagnosis of APS.

Our final diagnosis was primary APS, primary PV, type II portal vein thrombosis, and subsegmental pulmonary thromboembolism.

Discussion

The autoimmune condition known as APS is characterized by persistently positive antiphospholipid antibodies, arterial or venous thromboembolism, and/or pregnancy morbidity.[3] A potentially fatal form of APS, catastrophic APS is distinguished by its quick onset of symptoms, involvement of several organs, and thrombotic consequences, including both large and small vessels.[4] The kidney (74%) and brain (56%) are more commonly involved, while lungs, heart, skin, liver, peripheral arteries, and gastrointestinal tract are the other organ systems that are frequently involved.[5]

In our patient, she had recurrent headache during the past 7 years and was diagnosed as idiopathic intracranial hypertension, with a normal MR angiogram and venogram. People with APS will have headache due to migraine about 20%, seizure disorder, memory loss, transient ischemic attack, and stroke.[5] Our patient had papilledema, suggesting raised intracranial pressure, without any evidence of arterial or venous thrombosis.

She became pregnant after a year of marriage and resulted in intrauterine death in second trimester, which can occur in APLA syndrome.[3] She was not investigated at that time and was not treated with anticoagulants. Similarly, she had no features of any autoimmune disorders like systemic lupus erythematosus (SLE). As per the literature, 28% of patients with catastrophic APS were known to have previous history suggestive of SLE.[5] Hence, our patient was likely to have had a primary APLA syndrome.

Obstetric complications in APS include: (1) stillbirth or unexplained fetal death; (2) recurrent pregnancy loss, defined as three or more spontaneous abortions; (3) unexpected fetal demise in the second or third trimester; (4) the onset of severe preeclampsia before 34 weeks; (5) severe fetal development retardation that cannot be explained; and (6) chorea gravidarum. Thus, our patient had APS that had not been identified before, who now complained of 17 days of upper abdominal pain, with her USG abdomen revealing moderate hepatosplenomegaly and splenic vein thrombosis.

On the 2nd day of admission, she developed acute onset of dyspnea at rest without any hypoxia or hemodynamic instability. CECT of the abdomen and thorax showed partial lumen-filling thrombus in the portal vein extending to the right and left branches of the portal vein, sectoral portal vein divisions in both lobes of the liver, splenoportal confluence, and the entire length of the splenic vein, without any thrombosis in the superior mesenteric vein or inferior vena cava, and there was no evidence of bowel ischemia. It was clear that the thrombus rapidly progressed within a period of 4–5 days. CT thorax showed subsegmental

pulmonary arterial thromboembolism producing breathlessness at rest. Altogether, she was progressing to catastrophic APLA syndrome, requiring urgent anticoagulation.

The following criteria are used to classify APS as catastrophic[4]:

- Evidence of involvement of three or more organs, systems, or tissues.
- The onset of thrombotic symptoms either simultaneously or within 1 week.
- Histopathological confirmation of small-vessel blockage in at least one organ or tissue.
- Detection of antiphospholipid antibodies in the blood.

A diagnosis of definite catastrophic APS is made when all four criteria are met. Probable catastrophic APS is diagnosed under the following conditions:

- All four criteria are met, but only two organs, systems, or tissues are involved.
- All four criteria are met, but laboratory confirmation is lacking due to the patient's early death before antiphospholipid testing could be done.
- Criteria 1, 2, and 4 are met.
- Criteria 1, 3, and 4 are met, along with the development of a third event occurring >1 week but <1 month despite anticoagulation. In this case, criteria 1, 2, and 4 were present.

Before starting LMWH, she also underwent bone marrow biopsy to rule out any coexistent hematological illness, like MPN, owing to thrombocytosis, erythrocytosis, and hepatosplenomegaly, which can also result in portal vein thrombosis. Her CBC showed normal hemoglobin (13.6 gm/dL), increased RBC count ($5.69 \times 10^6/mm^3$), normal packed cell volume (PCV) (42.1%), normal white blood cell (WBC) count ($10,000/mm^3$, neutrophils 72%, lymphocytes 15%, eosinophils 2.9%), and thrombocytosis ($7.37 lakh/mm^3$), and peripheral blood smear showed marked thrombocytosis.

Her bone marrow aspirate showed normal myeloid maturation, erythroid maturation, without any abnormal cells. Bone marrow biopsy showed panmyeloid hyperplasia, and her MPN reflex panel was positive for JAK2 V617F (exon 14) on discharge after 5 days. Hematologist evaluated her and suggested that PV was more likely the primary pathology in view of the gene mutation and clinical setting than APLA syndrome, where the latter may be secondary to the former, and the malnourished physique of the patient masked the increase in hemoglobin levels.

After 5 days of LMWH, she was started on apixaban daily. NOAC was started as treatment for portal vein thrombosis.[6] She clinically presented as APS, and the patient was double positive (aCL IgG and antibeta 2 glycoprotein 1 IgG), carrying a moderate risk for thrombosis, which was further aggravated by coexistent JAK2 V617F mutation-associated MPN (PV). Triple-positive APLA, which is the simultaneous positivity of LA, aCL, and aβ2GPI antibodies, regardless of their isotype, is linked to the highest risk of thrombosis, whereas the solitary presence of aCL antibodies is linked to the lowest risk.[7] Conversely, the only single positivity linked to an increased risk of thrombosis is isolated LA positivity.[8] As the literature support was more in favor of warfarin,[9] and the risk for recurrent venous thrombosis and bleeding was common with apixaban,[10] it was replaced by warfarin, and the target INR was kept at 2–3. She remained hemodynamically stable.

After 12 weeks, a repeat APLA profile showed persistence of aCL IgG (21 GPL U/mL) and beta 2 glycoprotein 1 IgG (57 U/mL), confirming the diagnosis of primary APLA syndrome. Treatment for MPN (PV) was deferred at the moment, as she had normal PCV and normal cell count. Thus, she finally turned out to be a case of primary APS, primary PV causing type II portal vein thrombosis, subsegmental pulmonary thromboembolism, and second trimester intrauterine death.

Coexistent APS and MPN are very rare, and only a few case reports are in the literature. The JAK2 V617F expression has been linked to the formation of neutrophil extracellular traps (NETs) and further thrombus formation. They have a higher risk of thrombosis at multiple sites, with a chance for recurrence. Direct oral anticoagulants are not recommended at present for these patients. Warfarin is the mainstay of treatment. NOACs are being tried now, but current literature favors treatment with warfarin.[11]

Conclusion

Coexistent PV and APS are rare. They are at higher risk of thrombosis or recurrence. Adverse outcomes in pregnancy should be evaluated. A possibility of APS should not be missed, as the complication for such patients when they present as catastrophic APS is high and causes significant mortality and morbidity. Clinical examination should be thorough, and the laboratory findings should be correlated. Presence of polycythemia in a thrombotic patient requires careful monitoring of hemoglobin, hematocrit, and screening for JAK mutation.

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CASE REPORT

Complicated Seronegative Neuromyelitis Optica Longitudinally Extensive Transverse Myelitis in Elderly: A Diagnostic Dilemma

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Abstract

A 69-year-old gentleman without any previous comorbidities presented with complaints of acute-onset low-grade fever, one episode of loss of consciousness, and weakness of both legs with urinary and stool retention for 1 day. He had an episode of generalized tonic-clonic seizure 3 hours after admission. On examination, he had tachycardia and hypotension; Glasgow Coma Scale (GCS) was E3V2M4, and neurological examination was suggestive of bilateral lower limb upper motor neuron lesion in the shock stage. Blood investigation revealed severe hyponatremia, and magnetic resonance imaging (MRI) with contrast of the dorsolumbar spine revealed longitudinally extensive transverse myelitis (LETM). Blood investigation for antineuromyelitis optica (anti-NMO) antibody was negative. Other investigations revealed low serum osmolality, raised urine osmolality, and spot sodium. Cerebrospinal fluid (CSF) viral panel detected human herpesvirus 6 (HHV6). He was treated with a pulse dose of IV methylprednisolone, hypertonic saline, and IV levetiracetam. He had symptomatic improvement and was discharged with a tapering dose of oral prednisolone. He had a complete recovery after 3 months of regular follow-up. Thus, we report a case of HHV6-induced LETM complicated with cerebral salt wasting syndrome and hyponatremic seizures.

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Introduction

Longitudinally extensive transverse myelitis (LETM) is defined as a spinal cord lesion that extends over three or more vertebrae, as seen on magnetic resonance imaging (MRI) spine. Symptoms include paraparesis, sensory disturbances, gait imbalance, and bladder and bowel involvement.[1] Although LETM is suggestive of neuromyelitis optica (NMO), it can also be caused by a spectrum of other systemic and local disorders.[2]

Case Description

A 69-year-old gentleman without any comorbidities or previous addiction presented with low-grade fever, one episode of loss of consciousness, weakness of both legs, and urinary and stool retention for 1 day. There was no history of nausea, vomiting, photophobia, facial or neck swelling, cough, hemoptysis, chest pain, or yellowish discoloration of eyes and urine. There was no history of recent vaccination. He had a history of passing large volumes of urine, almost 4 L in the last 1 day.

On examination, Glasgow Coma Scale (GCS) was E3V2M4, pulse rate 110/minute, blood pressure (BP) 80/50 mm Hg, respiratory rate 28/minute, and pallor was present. On neurological examination of the lower limbs, there was reduced tone, power 2/5, and deep tendon reflexes were absent. The plantar reflex was absent. There was no neck stiffness; Kernig's and Brudzinski's sign were absent. Other systemic examinations were within normal limits.

About 3 hours postadmission, he had an episode of generalized tonic-clonic seizure.

Initial blood investigations showed hemoglobin 10.4, total leukocyte count (TLC) 3600, urea 64, creatinine 1.6, sodium 108, potassium 5.4, uric acid 4.5, and the liver function test was normal. Noncontrast computed tomography (NCCT) brain was normal. MRI dorsolumbar spine detected segmental altered signal intensity in the form of T2 short tau inversion recovery (STIR) hyperintensity with patchy heterogeneous postcontrast enhancement seen in the dorsal cord at D5–D7 level for a length of approximately 6 cm (Fig. 1). MRI brain with screening of cervical spine did not detect any acute lesion. Considering the differential diagnosis of such a presentation, an extensive workup was done.

Further blood and urine investigations and cerebrospinal fluid (CSF) studies were done. Blood parameters showed vitamin B12 768, thyroid-stimulating hormone (TSH) 3.1, serum cortisol 17, serum osmolality 230, human immunodeficiency virus (HIV) negative; antinuclear antibody (ANA) panel, anti-NMO and antimyelin oligodendrocyte glycoprotein (MOG) antibody, anticardiolipin antibody IgG and IgM, lupus anticoagulant, beta 2 microglobulin, and paraneoplastic antibody panel all negative; urine spot sodium 54 and urine osmolality 242—both were raised. COVID-19 reverse transcriptase polymerase chain reaction (RT-PCR) was negative. CSF studies showed: cell count 3—100% lymphocytes; sugar 74 (serum glucose was 130); protein 55; malignant cell cytology, TB Gene Xpert, fungal stain, oligoclonal bands/IgG antibody all negative; CSF comprehensive viral panel was positive for human herpesvirus 6 (HHV6) (Fig. 2).

He was initiated on IV fluids, hypertonic saline, and IV levetiracetam. Pulse dose of IV steroid methylprednisolone 1 gm for 5 days was also given. He had symptomatic improvement with the medications, with improvement of sensorium, and both lower limb power improved to 3/5. He was discharged with a

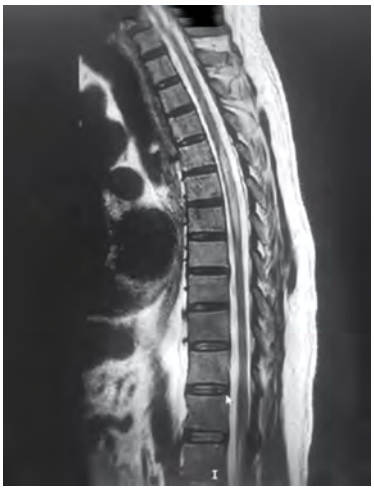

Fig. 1: MRI dorsolumbar spine with contrast

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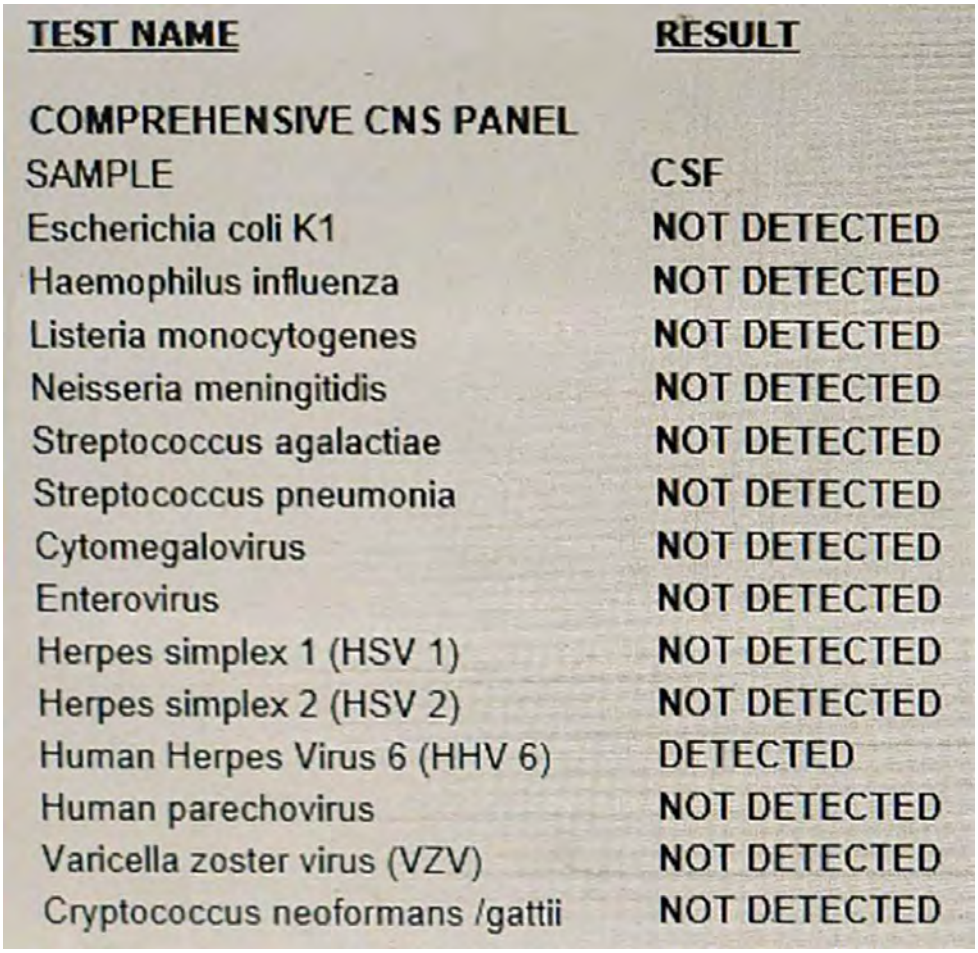

TEST NAME	RESULT
COMPREHENSIVE CNS PANEL	
SAMPLE	CSF
Escherichia coli K1	NOT DETECTED
Haemophilus influenza	NOT DETECTED
Listeria monocytogenes	NOT DETECTED
Neisseria meningitidis	NOT DETECTED
Streptococcus agalactiae	NOT DETECTED
Streptococcus pneumonia	NOT DETECTED
Cytomegalovirus	NOT DETECTED
Enterovirus	NOT DETECTED
Herpes simplex 1 (HSV 1)	NOT DETECTED
Herpes simplex 2 (HSV 2)	NOT DETECTED
Human Herpes Virus 6 (HHV 6)	DETECTED
Human parechovirus	NOT DETECTED
Varicella zoster virus (VZV)	NOT DETECTED
Cryptococcus neoformans /gattii	NOT DETECTED

Fig. 2: CSF viral panel report

tapering dose of oral steroids and levetiracetam. After 3 months of follow-up, he had lower limb power improvement to 5/5, was walking on his own, and had returned to his normal life.

Discussion

In our case, we did an urgent MRI of the spine, which was suggestive of LETM and was associated with severe symptomatic acute hyponatremia. Hence, an extensive workup was done.

Seronegative LETM was diagnosed on initial investigations. Seronegative LETM is caused by infectious myelitis (including viral, fungal, tuberculosis, parasitic, and bacterial); autoimmune conditions like neuropsychiatric lupus, neurosarcoidosis, Behçet's disease, Sjogren's syndrome, antiphospholipid antibody syndrome; malignancy and paraneoplastic syndromes; multiple sclerosis; and so on. Careful history taking, clinical examination, blood and CSF analysis, and diagnostic imaging are useful to differentiate among them. Treatment differs as per the etiology of the disease.[3]

In our patient, infective viral etiology of HHV6 was found. Neurological manifestations of HHV6 are encephalitis, seizures, and febrile seizures. It has also been implicated to play a role in multiple sclerosis and Alzheimer's disease. But HHV6 causing LETM is not well documented.[4] There has been a novel case report by Jumah et al.[5] where HHV6 was causing LETM in the background of COVID-19. Our patient was immunocompetent and did not have any significant medical history. He was diagnosed with seronegative NMO LETM as per the international consensus for NMO diagnostic criteria for 2015,[6] fulfilling the clinical and MRI criteria.

The HHV6 is a beta-herpes deoxyribonucleic acid (DNA) virus. It is closely related to cytomegalovirus and HHV7. The primary infection causes roseola. It is mainly prevalent in immunosuppressed individuals and very rare in immunocompetent adults. It can be diagnosed by viral culture, serology, or PCR.[7] Treatment of neurologic manifestations of HHV6 in immunocompetent adults is usually symptomatic with IV methylprednisolone. For immunosuppressed individuals, antivirals like cidofovir, foscarnet, or ganciclovir must be given.[8]

For evaluation of hyponatremia in our patient, there was hypotension with increased urine spot sodium, increased urine osmolality, increased serum potassium, and prerenal acute kidney injury. Given the clinical and laboratory findings, a diagnosis of cerebral salt wasting syndrome was made.[9] In LETM, rare patients may present with only features of hyponatremia. The proposed mechanism for the same is syndrome of inappropriate antidiuretic hormone (SIADH) secretion.[10] Cerebral salt wasting is usually seen with central nervous system lesions. However, in cases of hyponatremia in spinal cord lesions, a study by Kriz et al. has shown that many patients had features consistent with cerebral salt wasting syndrome, as was seen in our patient.[11] Cerebral salt wasting syndrome in LETM is not documented but was diagnosed in our novel case.

Acute severe hyponatremia of sodium levels below 115 mEq/L can cause seizures, which are usually generalized tonic-clonic seizures. Treatment of the same is by hypertonic saline, which causes symptomatic improvement.[12] It was found in our patient, and his seizures were controlled with treatment.

Conclusion

Hence, we report a rare novel case of HHV6 seronegative NMO LETM in an elderly

gentleman, which was complicated by cerebral salt wasting syndrome and hyponatremic seizures, which was treated conservatively with steroid, hypertonic saline, antiepileptics, and other supportive measures, and he had a complete recovery.

Patient Consent

Patient consent was taken.

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CASE REPORT

The Unlikely Duo: Tuberculous Lymphadenitis Leading to Secondary Amyloidosis in a Young Patient

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Abstract

Amyloidosis is an extremely rare condition with a variety of symptoms that, in extreme situations, can be fatal. Basically a protein misfolding disorder, it is characterized by deposition of insoluble polymeric protein fibrils in tissues and organs. There are different types of amyloidosis; here, we see a case of secondary amyloidosis, which is usually a consequence of a chronic disease. The case is unique, as there are many research projects showing the link of tuberculosis (TB) and secondary amyloidosis, but it is rarely documented because of extrapulmonary TB, which here is tuberculous lymphadenitis, and also here the patient is younger than the mean age.

The clinical manifestations of this disease are seen mainly in the renal system, gastrointestinal system, and reticuloendothelial system. For which the management is mainly supportive, along with treatment of the underlying cause.

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Introduction

Amyloidosis is an extremely rare condition with a variety of symptoms that, in extreme cases, can be fatal. Essentially a protein misfolding disorder, it is characterized by the deposition of insoluble polymeric protein fibrils in tissues and organs. The term amyloidosis was coined by Rudolf Virchow in 1854 due to its striking resemblance to starch polymers under light microscopy.

Different forms of amyloidosis exist and are classified based on whether they are primary or secondary, inherited or acquired, and according to various clinical patterns. Amyloid light-chain (AL) type amyloidosis is the most commonly diagnosed form, with an incidence of 4.5 cases per 1,00,000 population. Secondary amyloidosis is usually a consequence of chronic disease; however, in 30% of cases, the etiology remains unidentified. For secondary amyloidosis, the reported male-to-female ratio is 1.6:1.[1]

Extrapulmonary tuberculosis (TB) most commonly presents as tuberculous lymphadenitis. Up to 43% of peripheral lymphadenopathy in developing countries is caused by TB. The purpose of this case report is to highlight the well-established link between TB and secondary amyloidosis, which is rarely documented in cases of extrapulmonary TB—specifically, tuberculous lymphadenitis.[2]

Most patients diagnosed with amyloidosis are over 40 years of age. The mean age of diagnosis is 50–55 years,[1] likely due to the prolonged period of chronic inflammation required for the disease to develop. The uniqueness of this case lies in the early age of presentation at 30 years and the rapid progression of the disease.

In the case discussed, we examine an uncommon presentation of secondary AA-type amyloidosis. It is characterized by the extracellular deposition of fibrils produced from serum amyloid A (SAA) protein and can arise in any chronic inflammatory condition.[3] The clinical manifestations primarily affect the renal, gastrointestinal, and reticuloendothelial systems. Management is mainly medical, with supportive care tailored to the systems involved.

Case Description

A 30-year-old male without any comorbidities was brought to the emergency department of our tertiary care hospital. The patient presented with chief complaints of bilateral pedal edema for 15 days, abdominal distention for 15 days, and bouts of cough with minimal whitish sputum for 1 week. There were no complaints of periorbital puffiness, yellowish discoloration of skin or sclera, abdominal pain or diarrhea, low-grade fever, or weight loss. The patient was addicted to alcohol for 7 years with around 45 mL daily intake. No similar complaints were present in any family members, and no significant past history was elicited.

On general examination, the patient was moderately built and nourished. There was bilateral pitting-type pedal edema to both the knees. A swelling was also seen on the right side of the neck, which developed around 2 years ago. On palpation, it appeared to be level Ib, II, and III lymph nodes, which had a firm consistency and were conglomerate and matted, suggestive of tubercular lymphadenitis. On per-abdomen examination, the abdomen was distended without guarding and rigidity. Shifting dullness could be elicited, which was suggestive of moderate ascites. The rest of the systemic examination was unremarkable.

Investigations were done in view of the above presentation, which were as follows—hematology, biochemistry, and ascitic fluid analysis (Tables 1 and 2).

Chest X-ray was performed, which showed mild blunting of bilateral costophrenic angles, suggestive of bilateral pleural effusion. Ultrasonography (USG) of the chest showed mild pleural effusion bilaterally. Sputum acid-fast bacilli (AFB) and cartridge-based nucleic acid amplification test (CBNAAT) were sent for screening for pulmonary TB, which were negative.

Ultrasound of kidney, ureter, and bladder (USG-KUB) was suggestive of mildly enlarged kidneys with preserved corticomedullary differentiation. Urinalysis was suggestive of albuminuria, following which quantification of urinary protein was done, and the urine protein creatinine ratio was 7.58 mg/gm, suggestive of nephrotic-range proteinuria. Then, histopathological examination, as a part of the evaluation of nephrotic syndrome, was done by taking the biopsy specimen from the kidney, which under light microscopy showed an increase in the size of the glomeruli, expanded mesangium, organized deposits, basement membrane thickening, and open capillary loops (Fig. 1). The deposits showed periodic acid–Schiff (PAS) positivity and stained positively with Congo red stain, with an apple-green

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Table 1: Biochemical analysis of serum sample

Parameter	*On admission*	*At 3rd month of treatment*	*At 6th month of treatment*	*Reference range*
S. urea	39	38	24	15–40 mg/dL
S. creatinine	0.77	0.89	1.02	0.6–1.2 mg/dL
S. total bilirubin	0.80	0.7	0.8	0.1–1.2 mg/dL
S. direct bilirubin	0.30	0.3	0.2	0.1–0.4 mg/dL
S. indirect bilirubin	0.50	0.4	0.6	0.1–0.8 mg/dL
S. alanine aminotransferase (ALT)	12	20	26	0–40 IU/L
S. aspartate aminotransferase (AST)	28	24	35	0–40 IU/L
S. alkaline phosphatase (ALP)	130	113	142	25–140 IU/L
S. total protein	4.14	5.12	5.8	6–8 gm/dL
S. albumin	2.06	2.6	3.1	3.3–5 gm/dL
S. globulin	2.08	2.52	2.7	2.5–3.5 gm/dL
S. sodium	133	136	140	135–145 mEq/L
S. potassium	3.10	3.4	4.1	3.5–5.0 mEq/L
S. albumin/globulin ratio	0.99	1.03	1.14	1–2
C-reactive protein	82.5	64	14	1–6 mg/L
Erythrocyte sedimentation rate (ESR)	138	76	32	<15 mm/hour
Hemoglobin	10.7	11.2	12.1	13.5–16.5 gm/dL
Total counts	10,600	7,600	6,400	4,000–11,000 cells/mm^3
Differential count (N/L/E/M/B)	78/20/2/0/0	75/23/2/0/0	70/28/2/0/0	N: 55–70% L: 20–40% E: 1–6% M: 2–8% B: 0–1%
Platelet counts	3,69,000	2,40,000	3,20,000	1.5–4 lakh/mm^3
Red cell distribution width (RDW)	17	13	14	10–15%
S. cholesterol	192	180	164	150–200 mg/dL
S. triglyceride	200	134	129	0–150 mg/dL
S. high-density lipoprotein (HDL)	54	48	52	40–100 mg/dL
S. low-density lipoprotein (LDL)	98	76	70	60–100 mg/dL
S. very-low-density lipoprotein (VLDL)	40	27	26	12–30 mg/dL

Table 2: Analysis of ascitic fluid

On admission		*Reference range*
Color	Pale yellow	–
Quantity	3 mL	
Total count	40	<250 cells/mm^3
Differential count	40% polymorphs 60% lymphocytes	–
On wet mount	WBC/high power field seen and very occasional RBCs seen	–
Total protein	0.65	<2.5 gm/dL in transudates >2.5 gm/dL in exudates
Serum ascitic albumin gradient (SAAG)	0.9	>1.1 in transudative effusion <1.1 in exudative effusion and nephrotic syndromes
Ascitic fluid adenosine deaminase (ADA)	13	<40 IU/L (In TB >40 IU/L)

birefringence under polarized microscopy (Fig. 2); that was typical of amyloidosis. Immunofluorescence (IF) microscopy showed IgM patchy staining in the glomeruli and SAA protein deposition, which was suggestive of secondary amyloidosis due to a chronic inflammatory state, in this case, tuberculous lymphadenitis.

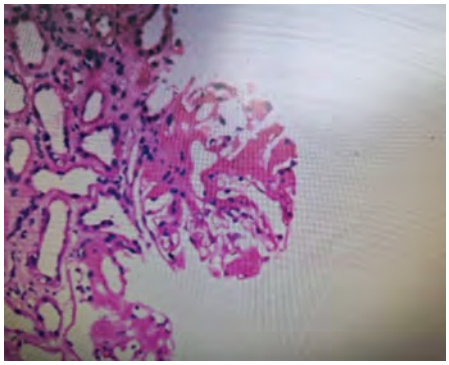

Fig. 1: Biopsy specimen under light microscopy

The otorhinolaryngologist also ordered fine-needle aspiration cytology (FNAC) of the neck swelling, which confirmed a firm, nontender swelling that had cheesy material on aspiration. Under microscopy, it revealed caseous necrosis, degenerated granuloma with few lymphocytes, and AFB positivity, which was typical of tuberculous lymphadenitis. The CBNAAT of the biopsy

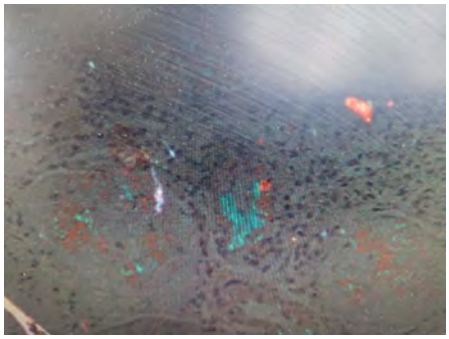

Fig. 2: Biopsy specimen stained with Congo red stain and under polarized microscopy

sample showed *Mycobacterium tuberculosis* sensitive to rifampin.

The patient was managed on angiotensin-converting enzyme (ACE) inhibitors (enalapril) for proteinuria, IV furosemide for edema, statins for dyslipidemia, and was given prophylaxis for deep vein thrombosis with inj. low-molecular-weight heparin and other supportive treatment. After CBNAAT positivity in FNAC, a diagnosis of tuberculous lymphadenitis was made, and the patient was started on anti-Koch therapy (AKT), fixed-drug combination (FDC), four tabs/day. The edema started resolving with furosemide, and subsequently the patient was discharged.

Follow-up visits were scheduled monthly for proteinuria *via* urine protein to creatinine ratio (UPCR), which decreased to 1.5 mg/mg at the end of the 3rd month and 0.9 mg/mg at the end of the 6th month, when the patient completed his AKT therapy. Mild pedal edema was present at the end of 6 months, and the patient was continued on an ACE inhibitor for nephroprotection. The patient, as of the last follow-up at 6 months, was much better, with almost complete resolution of all symptoms except for mild pedal edema.

Discussion

The incidence of amyloidosis is higher in men and typically occurs in individuals aged 50 years or older. Several comorbidities have been associated with this disorder, including diabetes, renal disease, peptic ulcer, and malignancy.[4] Epidemiological studies estimate the incidence of systemic amyloidosis at 8–12 cases per million person-years, with higher prevalence in populations with chronic inflammatory conditions.[5]

Amyloidosis may be either inherited or acquired, and it can present as a systemic or localized disease. There are several types of amyloidosis, including senile amyloidosis, organ-specific amyloidosis, dialysis-related amyloidosis, hereditary amyloidosis, as well as AL and AA amyloidosis.[6] Senile systemic amyloidosis is linked to wild-type transthyretin deposition, dialysis-related amyloidosis arises from β2-microglobulin accumulation, while hereditary forms include mutations in transthyretin, fibrinogen, apolipoprotein AI, and gelsolin.[7] In this case, amyloidosis presented with nephrotic syndrome, a classic manifestation of renal involvement. Among the inflammatory causes are ankylosing spondylitis, bronchiectasis, cystic fibrosis, familial Mediterranean fever, hairy cell leukemia, Hodgkin's lymphoma, multiple myeloma, rheumatoid arthritis, systemic lupus erythematosus, and—most commonly—TB, which remains the most prevalent chronic inflammatory process leading to this condition. In developing countries, TB remains the leading etiology of secondary (AA) amyloidosis, while autoimmune conditions dominate in developed nations.[8] In this case, the underlying cause was tuberculous lymphadenitis, which is a recognized but relatively rare trigger for systemic amyloid deposition.[9] The pathophysiology of TB leading to systemic amyloidosis involves the release of inflammatory mediators—mainly interleukin-1, interleukin-6, and tumor necrosis factor—as part of the immune response against the bacterium. These cytokines stimulate the hepatic production of SAA, an acute-phase reactant, which undergoes misfolding into β-pleated sheet fibrils and subsequently deposits in tissues.[10] Preferential organ involvement such as the kidneys, liver, and heart is thought to be related to their vascularity and reduced clearance mechanisms.[11] To investigate amyloidosis, the presence of λ light chains or monoclonal immunoglobulin κ in deposits can help distinguish AL amyloidosis using IF. Staining for these proteins aids in differentiating AA from AL amyloidosis. Additional diagnostic techniques include immunogold labeling, mass spectrometry, and immunohistochemistry (IHC). An IHC antibody panel is considered a sensitive and reliable tool for identifying amyloid proteins, though mass spectrometry has emerged as the diagnostic gold standard.[12] Confirmation is further obtained using polarizing microscopy on Congo red-stained tissue, which demonstrates apple-green birefringence.[1] Laboratory findings, when combined with clinical features, support the diagnosis of amyloidosis. Clinical symptoms include pulmonary manifestations due to TB, while symptoms of amyloidosis vary depending on the organ or system involved. Common features include arthralgia, breathlessness, easy fatigability, macroglossia, limb dysesthesias, and weight loss. Cardiac involvement may result in congestive heart failure or restrictive cardiomyopathy, while renal involvement typically manifests as nephrotic syndrome. Gastrointestinal symptoms can include anorexia, diarrhea, abdominal pain, and malabsorption, while neurological features may include autonomic dysfunction, sensorimotor neuropathy, and ataxia.[7,8] The primary treatment for this condition is antitubercular therapy (ATT). Patients may achieve remission but more commonly progress to chronic renal failure with persistent proteinuria, as seen in this case. Once the kidneys are significantly involved, regression of amyloid deposits is rare despite effective ATT. Patients who develop end-stage renal disease (ESRD) may require hemodialysis or renal transplantation. Recurrence of amyloidosis in transplanted kidneys can occur if the underlying cause (AL or AA) is not adequately treated, though this often takes years to manifest. Recently, eprodisate has shown promise in treating AA amyloidosis by binding to glycosaminoglycan sites on amyloid fibrils, thereby reducing polymerization and deposition.[13] In addition, biologics such as IL-6 inhibitors (e.g., tocilizumab) and colchicine in familial Mediterranean fever represent targeted approaches in secondary amyloidosis.[14]

Conclusion

This case highlights tubercular lymphadenitis presenting as nephrotic syndrome secondary to amyloidosis, a relatively underreported association. It underscores the importance of screening for amyloidosis in patients with TB and considering extrapulmonary TB, particularly lymphadenitis, in patients diagnosed with amyloidosis.

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CASE REPORT

Poncet's Disease—A Rare Complication of Tuberculosis: A Case Report

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Abstract

Objectives: We present a rare case of Poncet's disease, a sterile reactive arthritis associated with active tuberculosis (TB), mimicking seronegative spondyloarthritis in a young diabetic male. We aim to highlight the diagnostic challenges and emphasize the importance of considering Poncet's disease in patients with inflammatory arthritis, especially in the context of subclinical TB.

Methods: We present a detailed case report of a 28-year-old male with poorly controlled diabetes mellitus type 2 [glycated hemoglobin (HbA1c) 13.9%] who presented with a 3-week history of bilateral ankle pain, swelling, and redness. The pain progressed to involve multiple small joints of the hands, wrists, elbows, and knees, significantly impacting his mobility, with no history of trauma, fever, rash, or urinary symptoms. Physical examination revealed tenderness and swelling in the affected joints with limited range of motion. Laboratory investigations showed an elevated erythrocyte sedimentation rate (ESR) of 74 mm/hour and C-reactive protein (CRP) of 104 mg/L. Chest X-ray revealed bilateral hilar lymphadenopathy, and computed tomography (CT) scan confirmed multiple enlarged lymph nodes in the mediastinum and bilateral hilar regions, suggestive of pulmonary TB. Despite the absence of acid-fast bacilli in bronchoalveolar lavage (BAL), the clinical presentation, imaging findings, exclusion of other causes of reactive arthritis, and a dramatic response to anti-TB therapy within days of initiation strongly supported the diagnosis of Poncet's disease. The patient completed 6 months of anti-TB therapy and achieved complete resolution of joint pain and swelling, regaining his full range of motion.

Results: The patient's symptoms, including joint pain, swelling, and inflammatory markers, significantly improved within weeks of starting anti-TB therapy. Serial CRP and ESR readings showed a downward trend, confirming the response to treatment.

Conclusion: This case report highlights the importance of considering Poncet's disease in the differential diagnosis of seronegative spondyloarthritis, particularly in patients with underlying TB. A high index of suspicion and prompt initiation of anti-TB therapy can lead to rapid improvement in symptoms and prevent unnecessary investigations and potentially harmful immunosuppressive medications.

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Introduction

Tuberculosis (TB) is one of the most prevalent and notorious infections known to mankind. Despite pulmonary TB being the most frequently encountered presentation, extrapulmonary manifestations such as lymphadenitis, peritonitis, pleuritis, spondylosis, and arthritis are also frequently encountered in clinical practice.[1]

We report a rare extrapulmonary manifestation of TB known as Poncet's disease or tuberculous rheumatism, a sterile reactive arthritis caused by immune-mediated mechanisms without direct mycobacterial invasion. It is a type of reactive symmetric polyarthritis that occurs during acute TB, in which no other cause of the arthritis or any mycobacterial involvement can be detected.[2] Poncet's disease is a diagnosis of exclusion, supported by the drastic response in arthritis upon starting antitubercular medication.[3]

Case Description

A 28-year-old male was admitted to our hospital after returning from a recent trip to Australia. He presented with bilateral ankle pain for the past 3 weeks without any history of trauma. There was accompanying swelling and redness in both ankles as seen in Figure 1. He was brought to our hospital in a wheelchair due to severe pain that prevented him from walking.

The patient's joint pain began gradually, symmetrically involving the ankles and then progressing to the small joints of the hands [proximal interphalangeal (PIP), distal interphalangeal (DIP), and metacarpophalangeal (MCP) joints, along with the wrists and elbows) and later involving large joints such as the knees. A total of 18 joints were involved over the course of 2 months. The range of motion was limited in both active and passive movements, and all movements of a particular joint were painful. There was tenderness over the joint line on examination, along with swelling. Pain worsened with activity and was not associated with joint stiffness. There was no history of mouth ulcers, genitourinary symptoms, skin rash, photosensitivity, diarrhea, burning micturition, or conjunctivitis.

The patient also complained of fatigue, dry cough for 1.5 months, and intermittent low-grade fever with an evening rise in temperature. He had a history of significant weight loss of about 15 kg in the past year. He had been vaccinated with Bacillus Calmette–Guérin (BCG) at birth. There was no family history of TB or any rheumatological disease.

The patient was a known case of uncontrolled diabetes mellitus type 2 since 2023 and was on metformin. His HbA1c value was 13.9%.

He had no known allergies or asthma. There was no history of hypertension or hypothyroidism, and he was not taking any long-term medications.

The patient noted that he had been treated for the same complaints with nonsteroidal anti-inflammatory drugs

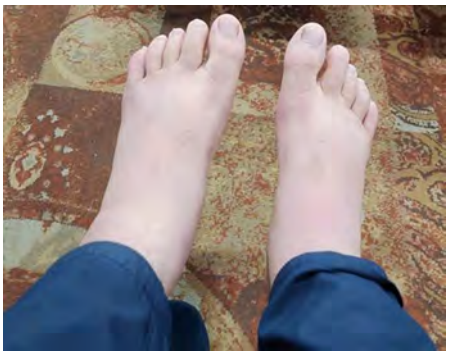

Fig. 1: Swelling and redness of both ankles, subtalar joints and metatarsophalangeal joints

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(NSAIDs) and steroids before coming to us, with no resolution of symptoms.

On examination, the patient had no acute distress and his vital signs were within normal limits. On musculoskeletal examination, there was tenderness on palpation in both ankles and multiple small joints of the hands. No lymphadenopathy or erythema nodosum was noted. No adventitious sounds were found on chest auscultation.

The patient's laboratory findings were significant for an elevated erythrocyte sedimentation rate (ESR) of 74 mm/hour and C-reactive protein (CRP) of 104 mg/L when he first came to us, suggesting an inflammatory etiology. Vasculitis was suspected; however, his vasculitis profile [proteinase 3 (PR3), myeloperoxidase (MPO), glomerular basement membrane (GBM)] was negative. On serial testing, the ESR was 80 mm/hour and the CRP was 150 mg/L. His total leukocyte count (TLC) was 11.1 × 10^3 cells/µL (with 75% neutrophils and 18% lymphocytes). Complete blood count (CBC) showed hemoglobin of 13 g%; his kidney and liver function tests were normal.

Chest X-ray showed bilateral bulky hilar lymph nodes (LNs) (Fig. 2).

Sarcoidosis was considered as a differential diagnosis but was effectively ruled out based on normal serum calcium levels, imaging findings, and the absence of systemic features.

A Contrast Enhanced Computed Tomography (CECT) chest was performed in view of intermittent fever and cough. The scan revealed multiple enlarged lymph nodes in the bilateral hilar and mediastinal regions. These affected areas included the pretracheal, paratracheal, prevascular, and perivascular spaces, as well as the aorto-pulmonary window and the pre/subcarinal regions.

Additionally, the imaging showed tiny nodules in the bilateral parahilar regions. Small focal patches of nodular consolidation were also present in the posterior basal segments of both lower lobes and the medial basal segment of the left lower lobe. These findings suggested an infective pathology, most likely pulmonary Koch's (Figs 3 and 4).

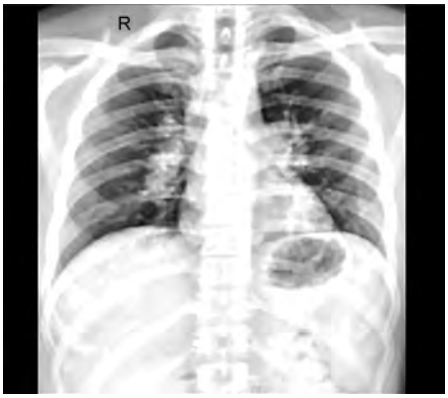

Fig. 2: Chest X-ray

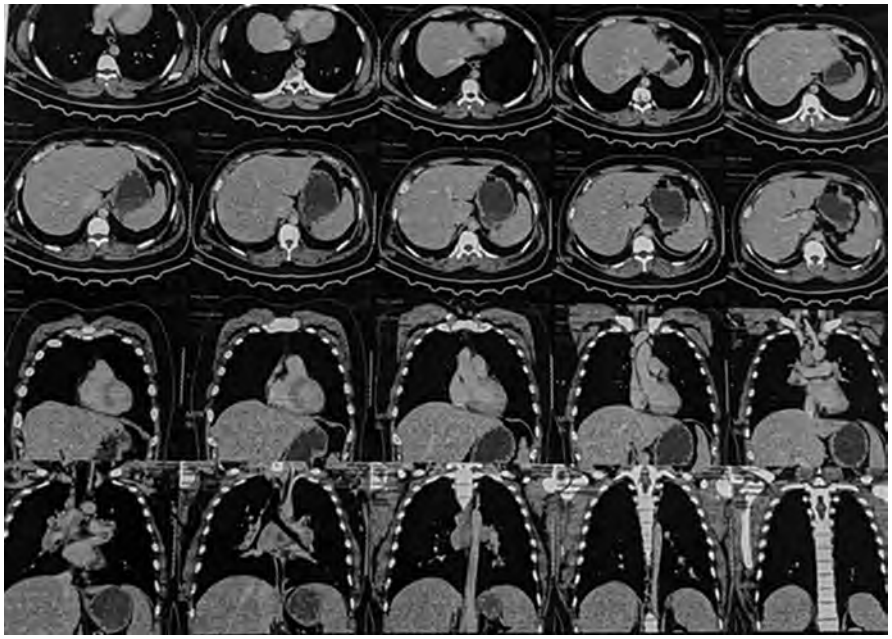

Fig. 4: Coronal and Axial CECT reconstructions showing the extent of lymph node enlargement and parahilar involvement

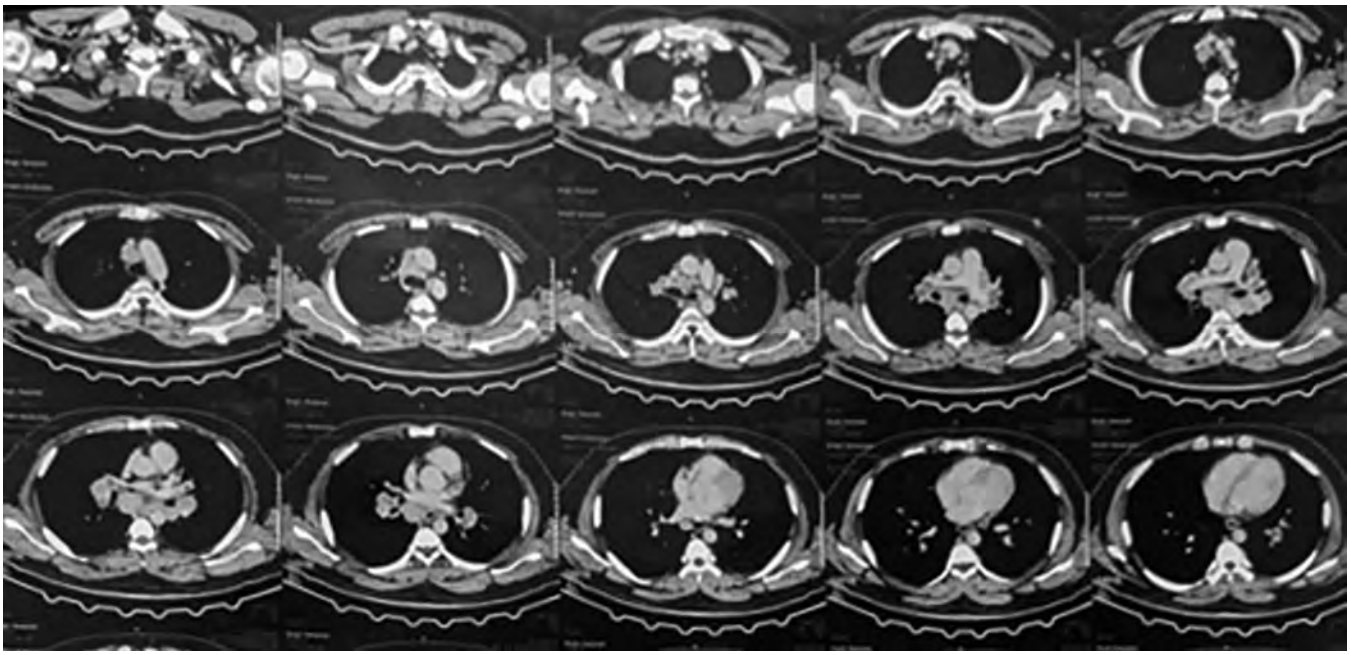

Fig. 3: Axial CECT (Mediastinal Window) showing subcarinal and hilar lymphadenopathy

A pulmonology consultation was obtained. Endobronchial ultrasound (EBUS) was initially planned but was deferred due to desaturation during preprocedural bronchoscopy. However, a bronchoalveolar lavage (BAL) was performed, and relevant samples were collected. Acid-fast bacilli were not detected in BAL. Standard antituberculosis therapy (ATT) with 4-drug regimen (isoniazid, rifampicin, ethambutol, and pyrazinamide) along with pyridoxine supplementation was started based on the high-resolution computed tomography (HRCT) report with a presumptive diagnosis of active TB. His symptoms improved drastically within a few days of starting ATT. His fever resolved, and serial CRP and ESR values reduced over the course of the next few weeks, as shown in the graphs plotted (Figs 5 and 6).

Fig. 5: Serial CRP readings

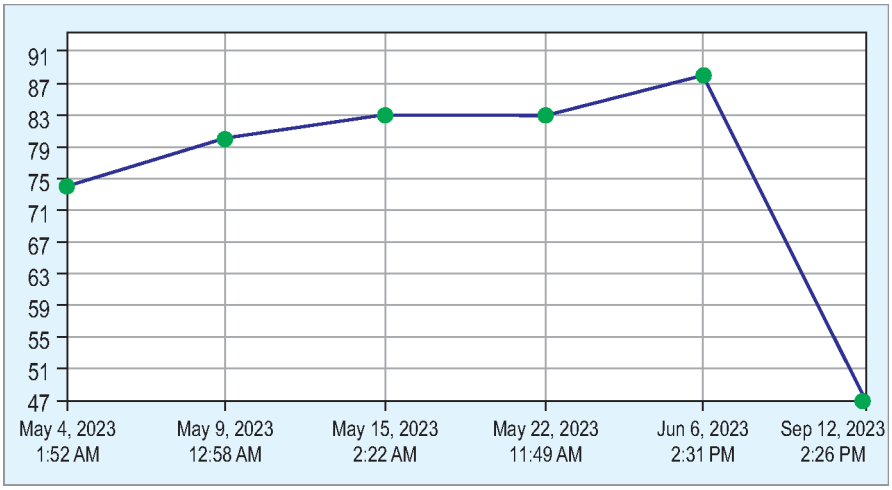

Fig. 6: Serial ESR readings

Table 1: Diagnostic criteria for Poncet's disease

Diagnostic criteria	
Essential criteria	Inflammatory, nonerosive, nondeforming arthritis, exclusion of other causes of inflammatory arthritis
Major criteria	Concurrent diagnosis of extra-articular tuberculosis Complete response to antitubercular therapy
Minor criteria	Mantoux positivity Associated hypersensitivity phenomenon, such as erythema nodosum, tuberculids, or phlyctenular keratoconjunctivitis Absence of sacroiliac and axial involvement
For diagnosis	
Definite	Essential + two major
Probable	Essential + one major + three minor
Possible	Essential + one major + two minor, or essential + three minor

The patient was followed closely and continued on ATT for 6 months, during which his joint pain and swelling completely resolved, allowing him to resume normal activities. Although joint imaging was unavailable, the diagnosis was clinically evident, supported by characteristic symptomatology, a rapid response to anti-TB therapy, and the exclusion of alternative causes. Based on these findings, he was diagnosed with Poncet's disease, a rare form of reactive arthritis associated with TB infection.

Discussion

Tuberculosis is an infection caused by *Mycobacterium tuberculosis* that presents with a great disease burden, leading to significant mortality and morbidity in developing countries such as ours. India alone houses nearly one-third of the total global cases of TB.[4] With an enormous caseload spread over a significantly large population, various presentations are encountered in daily clinical practice, out of which a prominently drawn-out association is that of TB and rheumatologic diseases.

Four different categories have been established for the same:

1. TB directly involving the musculoskeletal system such as osteomyelitis or septic arthritis.
2. *M. tuberculosis* causing an infection in rheumatologic patients.
3. Rheumatologic diseases caused by anti-TB treatment, including tendinopathy and drug-induced lupus.
4. Reactive immune reactions such as reactive arthritis.[5]

One of the less frequently reported reactive arthritides associated with active TB is Poncet's disease. A type of sterile polyarthritis, it predominantly affects patients suffering from extrapulmonary TB. It has a female preponderance and is usually seen to affect young patients, mostly involving large joints.[6] The disease is seen to symmetrically involve large joints, such as the knees, wrists, and ankles, along with skin changes like erythema nodosum.

Poncet's is a diagnosis of exclusion and has no standard criteria for diagnosis; however Sharma et al. proposed diagnostic criteria in 2015 after conducting a study of 23 patients with Poncet's disease as stated in Table 1.[7]

Other differentials, such as osteoarticular TB, should ideally be ruled out by identifying

M. tuberculosis in the synovial joint aspirate, but our patient refused the invasive investigation. TB of the joints does not respond as rapidly to ATT as Poncet's disease does, and this was therefore a significant clincher in order to rule it out. Other differentials such as reactive arthritis and rheumatoid arthritis were also ruled out based on the symptomatology and investigations, the lack of classic history of any eye or urinary tract involvement for reactive arthritis, and a negative rheumatoid factor for rheumatoid arthritis.

Poncet's disease is hypothesized to be an immune response to TB proteins, causing joint space inflammation by antigen-induced activation of T cells, which leads to cross-reactivity with cartilaginous proteoglycans. It has been linked to HLA-DR3 and HLA-DR4 haplotypes.[8]

Although it is a rare entity to diagnose, the possibility of TB, even if subclinical, triggering a reactive condition should be kept in mind by clinicians, as missed cases of this disease enable the possibility of careless use of steroids, immunosuppressants, and biologics, which might further cause immunocompromise and exaggerate TB.[9]

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CASE REPORT

A Rare Case of Reverse Variant of Takotsubo Cardiomyopathy in a Postpartum Female and How to Differentiate It from Peripartum Cardiomyopathy

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Abstract

Takotsubo cardiomyopathy (TCM) is a type of disorder of cardiomyocytes in which there is apical akinesia and ballooning, whereas the base is hyperkinetic. Reverse Takotsubo cardiomyopathy (rTCM) is a rare variant of TCM in which the base of the heart is akinetic and ballooned out rather than the apex, which is hyperkinetic.

Takotsubo cardiomyopathy is usually seen in postmenopausal women, but a rising number of cases of the reverse variant are being reported in peripartum women. We present a case of a 24-year-old primigravida at 37 weeks of gestation, who presented with an acute onset of breathlessness just after cesarean delivery. A 2D echocardiogram revealed changes of rTCM with an overall ejection fraction of 40%. She was treated for the same, and a 2D echocardiogram repeated after 1 week showed improvement in the ejection fraction to >60%, which supported our diagnosis of peripartum rTCM.

Another important objective of this study is to differentiate TCM occurring in the peripartum period from peripartum cardiomyopathy (PPCM), both of which are clinically indistinguishable but have different etiopathogenesis, treatment, and prognosis. While rTCM treatment mostly includes the management of heart failure, such as oxygen supplementation, diuretics, and noninvasive mechanical ventilation, the management of PPCM also includes bromocriptine, along with treating heart failure. The outcome of rTCM is excellent, with recovery of left ventricle function in almost all cases, while a few patients of PPCM have irreversible heart failure, making it imperative to differentiate between the two clinical entities.

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Introduction

Takotsubo cardiomyopathy (TCM), also known as "broken heart syndrome," is an uncommon disorder of the heart that affects mainly postmenopausal women and is often exacerbated by emotional or physical stressors.[1] In TCM, there is acute and reversible dysfunction of the left ventricle, marked by distinctive ballooning of the left ventricular apex.[2] Reverse takotsubo cardiomyopathy (rTCM), an uncommon variant of TCM, in which there is ballooning at the base of the heart, while the apex is hyperkinetic.[3] rTCM is usually observed in young women, compared to TCM, which usually occurs in postmenopausal women[1] but TCM is now increasingly reported in peripartum women.[2]

Peripartum TCM (PTCM) is clinically similar to peripartum cardiomyopathy (PPCM), both cause acute heart failure with low ejection fraction (EF) in young women without any prior cardiac history. Differentiating between PTCM and PPCM is important because of the differences in management and prognosis- PTCM has a better prognosis with quicker normalization of LV systolic function.[2–4]

We present a rare case of a reverse variant of TCM in a peripartum female. This case report describes a rare case of rTCM in the peripartum period and highlights the importance of distinguishing it from peripartum cardiomyopathy. Expanding the literature on such rare variants is crucial for enhancing diagnostic accuracy and developing management strategies tailored to each patient's unique situation. More research is needed to deepen our understanding of this uncommon condition and differentiate it from other cardiac syndromes, such as PPCM.

Case Description

A 24-year primigravida with 37.4-week gestational age, known case of beta thalassemia trait, came with a nonreassuring nonstress test (NST) and was admitted under the Obstetrics and Gynecology Department for safe confinement. Emergency lower segment caesarean section (LSCS) was performed on 9th June, 2023. 2 days after the delivery, on 11th June, the patient complained of sudden onset dyspnea at rest, which increased on lying down and relieved in the propped up position. She had no other complaints of fever, angina, or cough. Her examination revealed tachycardia with a heart rate of 118/min and blood pressure of 116/92 mm Hg. She was tachypneic with a respiratory rate of 28/min and hypoxic with a saturation of 86%. Her jugular venous pulse (JVP) was elevated. Her respiratory system examination was significant for bilateral basal crepitations. Her cardiac examination was unremarkable. A clinical diagnosis of heart failure was made.

The patient was started on 3 liters of O_2 with nasal prongs and shifted to the ICU.

Her investigations were significant for anemia with hemoglobin of 8.9 gm/dL, mild leukocytosis with total leukocyte count of 12,400/mm^3, sinus tachycardia and poor R wave progression on ECG (Fig. 1), bilateral haziness in lung fields suggestive of pulmonary edema on chest X-ray, hypoxia (PaO_2 50.1 mm Hg), hypocarbia ($PaCO_2$ 26.3 mm Hg) and acidosis (HCO_3^- 17.6 mEq/L) with a compensated pH of 7.444. Her creatinine was 0.8 mg/dL, and electrolytes (Na/K/Cl) were 141/4.2/108 mEq/L. Routine urine examination was normal. D-dimer was 1575 mg/L, and NT Pro-BNP was 5295.5 pg/mL. 2D echocardiography revealed basal hypokinesia (of the basal septum and basal lateral wall) with hypercontractile mid septum, apical septum, mid lateral wall, apical lateral wall, and apex (Fig. 2). Her left ventricle ejection fraction (LVEF) was 40% without any associated valvular dysfunction. Her right atrium and ventricle were normal in size and function. A diagnosis of heart failure

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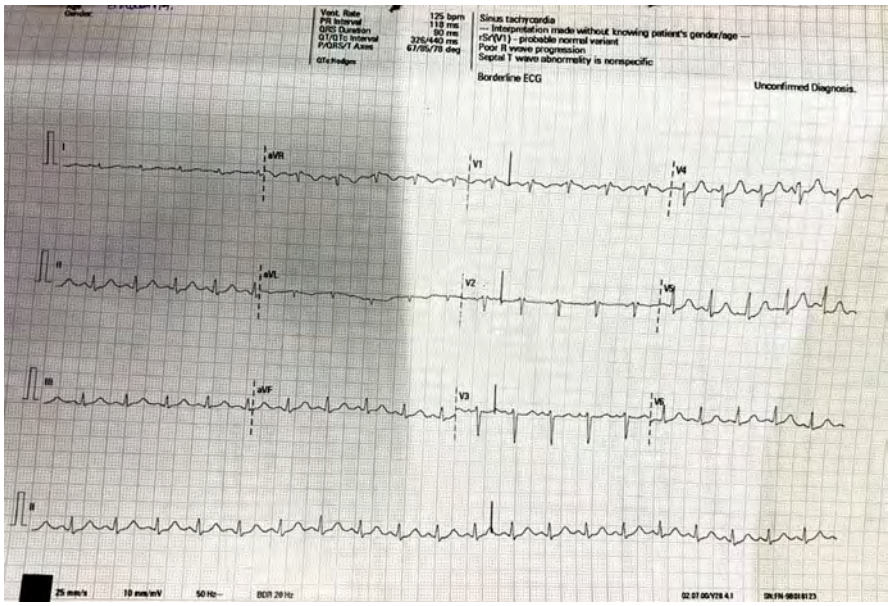
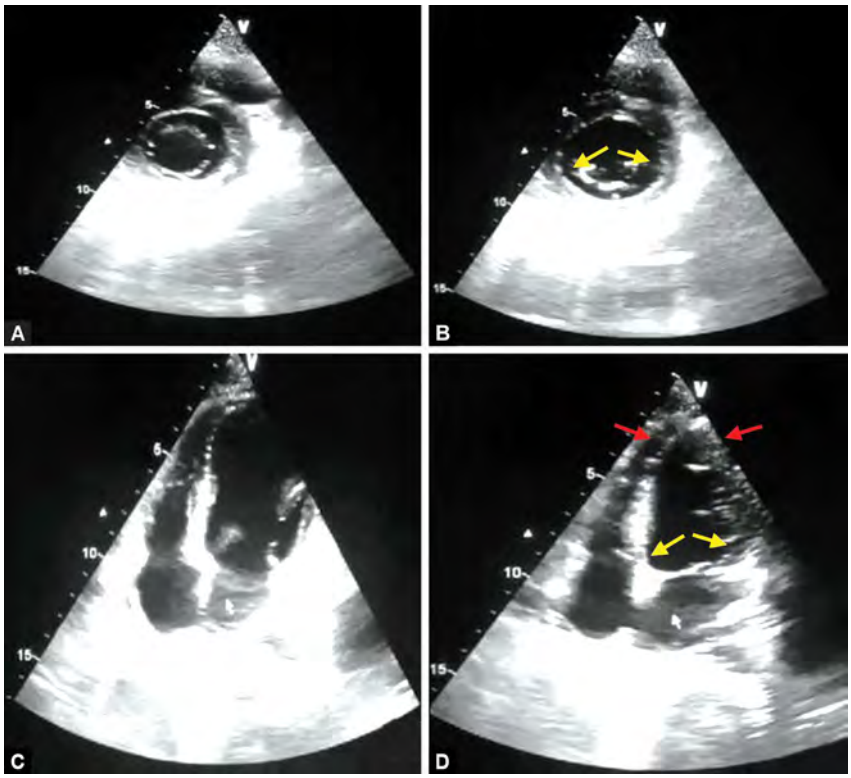


Fig. 1: ECG showing sinus tachycardia and poor R-wave progression in chest leads



Figs 2A to D: Two-dimensional echocardiography images in the basal short-axis view in diastole (A) and systole (B) showing akinetic basal segments without systolic shortening (yellow arrows). Apical four-chamber view showing diastolic (C) and systolic (D) frames where the apex contracts in systole (red arrows), but the basal segments do not show shortening or endocardial thickening suggestive of akinesia (yellow arrows)

with a reduced ejection fraction due to reverse variant of TCM was made. Coronary angiography could not be performed in this patient due to financial constraints of the patient.

The patient was started on intravenous furosemide and subcutaneous enoxaparin. She improved clinically, and symptoms of dyspnea and orthopnea reduced with maintenance of adequate negative balance. The patient was started on enalapril and metoprolol, and on the next day on oral spironolactone/furosemide combination therapy. Patient was advised to keep a salt-restricted diet and maintain fluids <1 L/day. She improved gradually and was weaned off oxygen support. She was shifted out of the intensive care unit in 2 days. She was monitored in the ward for another 5 days. A repeat 2D echocardiography done 1 week later on 21st June showed complete reversal of the changes with normal cardiac function of 60% and no regional wall motion abnormality, which confirmed the diagnosis (Fig. 3).

Discussion

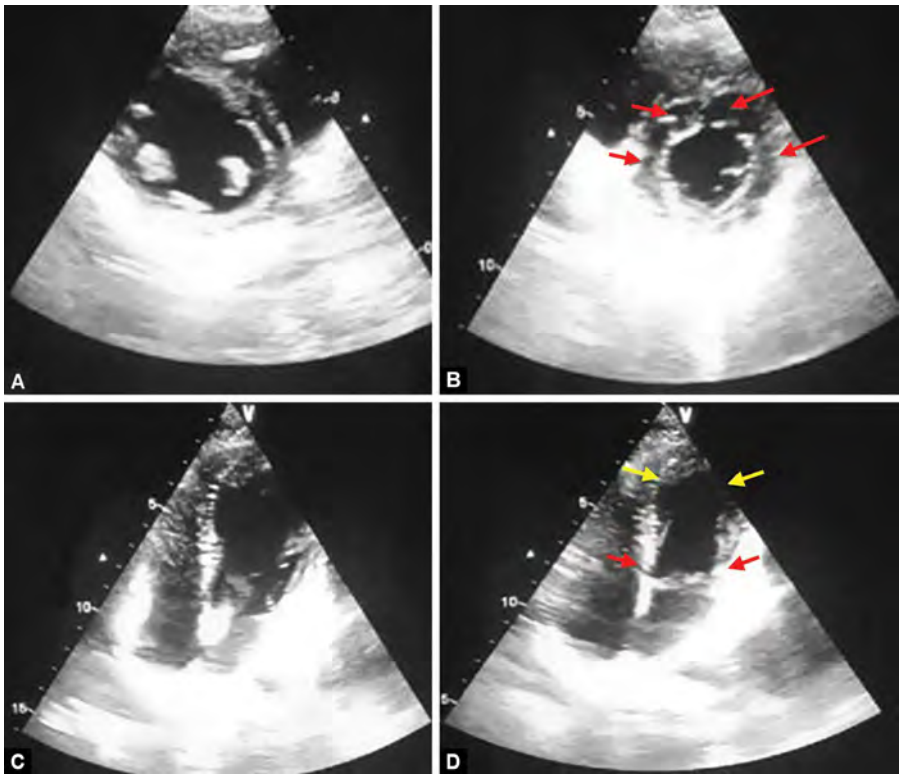
Takotsubo cardiomyopathy is a rare cardiac condition that has acute and transient left ventricular dysfunction, usually set off by a physical or emotional stressor.[2] It presents with ballooning and akinesia of the LV apex with hyperkinetic LV base (the so-called "octopus trapping pot").[3] Historically, TCM primarily affected postmenopausal women aged 60–70 years,[1,2] but recently increasing cases among young peripartum women are reported.[2] A less common variant, known as rTCM, involves ballooning at the basal segments of the heart, while the apex is hypercontractile.[3] rTCM commonly affects younger patients and is generally associated with less severe hemodynamic compromise.[4]

Our patient was a young female admitted due to a nonreassuring NST and had to be taken for emergency LSCS due to fetal distress. The significant stress of the baby's poor heartbeat and the possibility of the baby requiring NICU after delivery most likely caused the patient to go into rTCM just after delivery.

The occurrence of TCM is higher among Asian women.[2] Moreover, women in the postpartum period after cesarean section are at higher risk of TCM than those with vaginal deliveries, as was the case in our patient. In contrast, PPCM is associated with hypertensive disorders in pregnancy, multiparity, age of mother over 30 years, and black race.

Recovery of LV systolic function occurs within approximately 2 weeks in TCM.[5] Unlike PPCM, where persistent myocardial dysfunction and heart failure are not uncommon, TCM has a relatively transient course.[5] The findings in our patient align with this observation, the ejection fraction normalized within a week.

The underlying mechanisms of TCM (and rTCM) involve coronary artery spasm, catecholamine-induced cardiotoxicity, microvascular dysfunction, and less understood neuroendocrine interactions affecting the hypothalamic-pituitary-



Figs 3A to D: Two-dimensional echocardiography images in the basal short-axis view in diastole (A) and systole (B) showing systolic contraction of the basal segments (red arrows), suggestive of recovery to normal cardiac function. Apical four-chamber view showing diastolic (C) and systolic (D) frames where the apex contracts in systole (yellow arrows) and the basal segments show shortening and endocardial thickening (red arrows), suggestive of recovery of cardiac function compared to the previous figure

adrenal axis.[6] Additionally, rTCM is often exacerbated by a lack of estrogen.[1] The etiopathogenesis of PPCM is still unclear, but it is thought to involve genetic and hormonal factors triggering myocardial inflammation and vascular dysfunction.[7,8] Estrogen deficiency in postmenopausal females leads to endothelial dysfunction and sympathetic overactivity. After delivery, a rapid decline in estrogen levels after placental expulsion has similar effects.[2] Moreover, the heightened emotional and physical stress of labor may cause a rise in catecholamine levels in TCM.[1,2] Our patient had significant stress before her delivery due to fetal distress and going in for an emergency LSCS, which correlates with the mechanism of catecholamine-induced cardiotoxicity and vasospasm, along with declining levels of estrogen after delivery, causing the postpartum worsening of her cardiac function.

Both TCM and rTCM present similarly with symptoms such as angina-like chest pain, dyspnea, syncope, sweating, and/or epigastric pain.[1] TCM can clinically resemble acute coronary syndrome (ACS), classically in women with no previous cardiac history, and does not show obstructive lesions on coronary angiography.[1,2] ECG changes such as ST-elevation, T-wave inversion, new bundle branch block, or prolonged QTc interval may be present.[1] Typically, the cardiac troponin and brain natriuretic peptide (BNP) are raised.[1]

A transthoracic 2D echocardiogram clinches the diagnosis, revealing hypokinesia and ballooning of the LV apex in TCM, while a normal coronary angiogram helps rule out ischemic heart disease.[1] Cardiac catheterization with left ventriculography can often provide an accurate diagnosis.[1] Cardiac magnetic resonance imaging (MRI) helps quantify left ventricular (LV) and right ventricular (RV) function, visualize regional wall motion abnormalities (RWMA), and complications such as RV and LV thrombi, pericardial effusion. It also aids in distinguishing reversible injury (inflammation, edema) from irreversible damage (necrosis, fibrosis) using delayed enhancement of gadolinium. Also, it helps in ruling out ACS and myocarditis. Although cardiac MRI and coronary angiography help in ruling out ACS, we could not perform these investigations in our patient due to their financial constraints.

Based on the distribution of RWMA on 2D Echo, TCM can be categorized into typical and atypical variants (the latter being rare and including midventricular, reverse, isolated right ventricular, focal, and global). In the commoner typical variant, there is apical ballooning and akinesia with basal hypercontractility, while in the reverse atypical variant, there is basal akinesia with apical hyperkinesia. Patients with the reverse variant are usually younger (mean age of 30 years) and are more likely to develop pulmonary edema and cardiogenic shock. They often exhibit ST depression, longer QTc intervals, and less impaired ejection fraction. However, recurrence rates and long-term prognosis are similar to those of typical TCM.

Mayo diagnostic criteria for rTCM includes four points—all four should be present:[1] (1) transient regional wall motion abnormality such as hypokinesia/akinesia of the LV basal segments, extending beyond the distribution of a single epicardial vessel; (2) absence of obstructive lesions on coronary angiography; (3) new-onset ECG changes or rise in level of cardiac troponins; and (4) absence of pheochromocytoma or myocarditis. Hence, without a coronary angiogram, one cannot make a diagnosis of rTCM according to this criterion.

Regardless of the TTC variant, management is similar, supportive measures and treatment of the underlying process that has caused a catecholamine surge or stress trigger.[9] Beta-blockers are administered to decrease the contractility of the affected cardiac segment. Treatment of pulmonary edema, if present, involves a propped-up position, oxygen therapy, and diuretics.[1] Angiotensin receptor blockers and ACE inhibitors tend to decrease the recurrence rate.[10] Treatment of PPCM includes managing pulmonary edema and bromocriptine.

In summary, while peripartum rTCM and PPCM share similarities in clinical presentation, they differ in their etiopathogenesis, diagnosis, management, and prognosis. Understanding these distinctions is crucial for accurate diagnosis and appropriate management of the patient (Table 1).

Limitations

Unavailability of a cardiac MRI machine at our institute. A coronary angiogram could not be performed due to financial constraints of the patient.

Table 1: Highlighting major differences between PPCM and rTCM

	Peripartum cardiomyopathy (PPCM)	*Reverse Takotsubo cardiomyopathy (rTCM)*
Definition	Heart failure from third trimester to 6th month postpartum[9] (diagnosis of exclusion)	Basal ballooning and akinesia with apex hypercontractility secondary to an emotional or physical stressor
Risk factors	Multipara, multifetal gestation, maternal age >30, black race, hypertensive disorders in pregnancy, use of tocolytics	Delivery by caesarean section, Asian women
Etiopathogenesis	Prolactin-mediated inflammation, genetic predisposition, immune damage to mother's myocytes by fetal antigens, and Titin mutations in 15% of patients[9]	Neuroendocrine storm (catecholamines), reduced estrogen levels (most cases present just after delivery)
Echocardiograph features	Global hypokinesia (systolic dysfunction—LVEF nearly always <45%),[10] left ventricular and right ventricular dilatation and/or dysfunction, functional mitral and/or tricuspid regurgitation, pulmonary hypertension, and left atrial or biatrial enlargement	Left ventricular basal dysfunction (hypokinesia, akinesia, or dyskinesia) and apical hyperkinesia
Electrocardiograph features	Normal ECG, sinus tachycardia, pathologic Q-waves, ST depression, T-wave abnormalities (nonspecific)	Acute: ST-segment elevation, ST-segment depression, and QTc prolongation, late features: T-wave inversion
Management	Oxygen, NIV, diuretics, role of bromocriptine[9] (inhibits prolactin)	Oxygen, NIV, diuretics, role of ACE inhibitors, and beta blockers
Average time for recovery	Recovery in fewer patients (sometimes partial recovery only)	LVEF normalcy within 30–60 days (most recover within 2 weeks)
Long-term prognosis	Poor	Fair

Conclusion

This study highlights the importance of recognition of reverse TCM in peripartum women, which is critical to avoid misdiagnosis. Doctors must be aware of the rising cases of the rTCM among peripartum women. Echocardiogram shows ballooning of the cardiac base and increased contractility of the apex. Management is mostly supportive: O_2 supplementation and diuretics for pulmonary edema, and beta-blockers to decrease the contractility of affected segments where dynamic left ventricle obstruction is present. The differential diagnosis of peripartum cardiomyopathy should also be considered, as it has different pathophysiological, therapeutic, and prognostic implications.

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