Vol No. 74 Issue No. 6 June 2026 ISSN: 0004-5772

Journal of
The Association of Physicians of India

Supplement Copy

Editor-in-Chief: **Prof. Dr. Nandini Chatterjee**

JAPI

www.japi.org app: myJAPI

Published on 1st of every month

JAPI JOURNAL OF THE ASSOCIATION OF PHYSICIANS OF INDIA
Editor-in-Chief: **Prof. Dr. Nandini Chatterjee**

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Subscription Information
Journal of The Association of Physicians of India is published monthly. The annual subscription is ₹15,000 (India). The Journal is dispatched within India by surface mail.

Business Correspondence
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Published and Edited by
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Supplement Copy on

Case Reports

Contents

CASE REPORT

Seizures as Presenting Complaint of Cerebral Cortex Involvement in Leprosy

Vishnu Sharma[1], Naman Modi[2*], Vansh Bagrodia[3], Ankit Alria[4]

Received: 31 August 2024; *Accepted:* 07 April 2026

Abstract

Leprosy, recognized as one of the ancient diseases, predominantly affects the integumentary system and peripheral nerves. Nevertheless, central nervous system (CNS) involvement is a rare occurrence, with cortical manifestations being exceedingly infrequent. We present a case that aligns with this rarity, showcasing diffuse hyperintensities on magnetic resonance imaging (MRI) within the cortical region of the brain. The patient's clinical presentation was marked by seizures, necessitating targeted therapeutic interventions.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1533

Introduction

Leprosy, a chronic infectious disease caused by *Mycobacterium leprae*, primarily impacts the peripheral nervous system, skin, and various anatomical structures, including the reticuloendothelial system, bones, joints, mucous membranes, eyes, testes, muscles, and adrenals.[1] Ridley and Jopling introduced the comprehensive "five-group TT-LL" classification, encompassing tuberculoid (TT), borderline-tuberculoid (BT), borderline (BB), borderline-lepromatous (BL), and lepromatous (LL) categories.[2]

Within the lepromatous leprosy spectrum, patients exhibit a prominent Th2 immune response, fostering a permissive environment for *M. leprae* proliferation. This clinical subtype is characterized by multibacillary (MB) leprosy, an incapacity to generate specific Th1 cell responses against *M. leprae*, elevated antibody titers targeting *M. leprae* antigens, and compromised granuloma formation marked by a profusion of bacilli within lesions.[3]

Clinically, lepromatous leprosy manifests as distinctive red-brown nodular infiltrates, termed lepromas, prominently observed on the skin and mucous membranes, particularly affecting the face and auricles, resulting in a characteristic "leonine facies." Additionally, a noteworthy clinical feature includes the typical loss of eyelashes and eyebrows. Notably, nerve involvement is a pervasive feature in all forms of leprosy, even when devoid of apparent skin lesions. In lepromatous leprosy (LL), the perineural inflammatory process exhibits an initial, less pronounced presentation compared to tuberculoid forms, accompanied by the detection of numerous mycobacteria within Schwann cells. The clinical trajectory is marked by distal symmetrical peripheral polyneuropathy.[4]

This article contributes a rare case wherein a lepromatous leprosy patient presented with seizures and functional neurological disorder, shedding light on potential central nervous system involvement in this disease. This unique clinical presentation expands our understanding of the varied neurological manifestations associated with lepromatous leprosy.

Case Description

A female patient in her forties presented to the emergency department in a state of altered mental status, following a recent generalized tonic–clonic seizure witnessed by her attendants approximately an hour prior to admission. Vital signs recorded upon arrival were all normal. General physical examination revealed diffuse, erythematous, poorly defined, and anesthetic plaques distributed bilaterally across the face, while the rest of the examination was unremarkable.

The patient had received a diagnosis of lepromatous leprosy 2 months ago and has been undergoing multidrug therapy for the same since then. Upon further inquiry, the patient reported no prior history of seizures, and there was no familial precedent for such events. Notably, this seizure episode represented the inaugural occurrence of such an event in the patient's medical history.

The investigations conducted at the patient's initial presentation, including a random blood glucose level and electrolyte levels, were all within physiological limits. Additionally, a complete blood count and peripheral blood film analysis revealed no abnormalities. Liver function tests, renal function tests, and arterial blood gas analysis demonstrated unremarkable results.

Further investigations included an electrocardiogram (ECG), a 2D echocardiogram, and a chest X-ray, all of which revealed no abnormalities. Fundoscopy exhibited a healthy optic disk. Serological tests for hepatitis B virus (HBV), human immunodeficiency virus (HIV), and hepatitis C virus (HCV) were negative.

Lumbar puncture indicated normal opening pressure with clear cerebrospinal fluid (CSF). Analysis of CSF components revealed elevated protein levels, while other parameters, including cells and glucose, fell within the normal range. Polymerase chain reaction (PCR) assays for Japanese encephalitis (JE), Epstein–Barr virus (EBV), and cytomegalovirus (CMV) in the CSF were negative. Bacterial culture and KOH mount yielded negative results, ruling out bacterial or fungal infections.

Electroencephalogram (EEG) findings demonstrated generalized spikes or sharp waves, indicating abnormal electrical activity in the brain. Autoimmune markers, including antinuclear antibodies (ANA) and antidouble-stranded DNA (dsDNA) antibodies, were negative. Prolactin levels were elevated at 42 ng/mL (normal range: <25 ng/mL).

Magnetic resonance imaging (MRI) revealed cortical hyperintensities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences in the left high parietal and left high frontal lobes, extending into the underlying subcortical white matter (Figs 1 and 2). Importantly, there was no evidence of diffusion restriction.

The differential diagnosis for the presented spells encompasses a spectrum of conditions, including seizures, syncope, intracranial space-occupying lesions (ICSOL), migraine auras, intracranial hypertension, and psychogenic nonepileptic seizures (PNES). To systematically exclude potential

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How to cite this article: Sharma V, Modi N, Bagrodia V, *et al.* Seizures as Presenting Complaint of Cerebral Cortex Involvement in Leprosy. J Assoc Physicians India 2026;74(6):7–9.

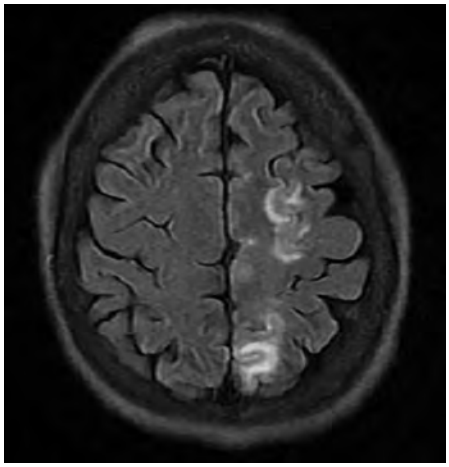

Fig. 1: Transverse MRI image revealing T2-weighted and FLAIR cortical hyperintensities in the left high parietal and left high frontal lobes of the patient's brain

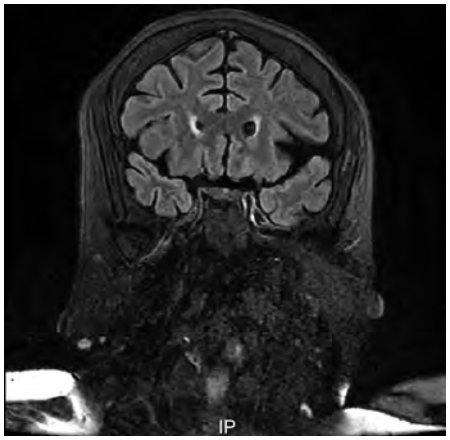

Fig. 2: Coronal MRI image displaying T2-weighted and FLAIR subcortical hyperintensities in the patient's brain

causes, a thorough diagnostic approach was undertaken. Migraine was ruled out as the patient did not meet the diagnostic criteria. Intracranial hypertension was negated by normal lumbar puncture opening pressure, and elevated prolactin levels ruled out the possibility of PNES.

A comprehensive investigation into potential etiologies for seizures was pursued. Vascular, infective, traumatic, autoimmune, neoplastic, and metabolic causes were all excluded through relevant investigations, turning out to be normal as mentioned above.

After an exhaustive evaluation, since none of the conventional causes could account for the observed seizures in this patient, it was concluded that the seizures were attributed to CNS involvement by leprosy, including the findings on MRI, highlighting the importance of considering leprosy as a possible etiology for seizures.

In light of the diagnosed CNS involvement by leprosy and the occurrence of seizures, the patient's management plan was initiated promptly. Levetiracetam was prescribed to address the seizure activity in the patient, administered at a dosage of 500 mg twice daily. Concurrently, the patient was maintained on a multidrug therapy regimen consisting of rifampicin, dapsone, and clofazimine to manage the underlying lepromatous leprosy.

The patient's progress at the 1-month follow-up was marked by the absence of seizure episodes. The patient was continued on levetiracetam for seizure management and multidrug therapy for lepromatous leprosy. We advised the patient to undergo an additional MRI following the treatment; however, due to financial constraints, she opted not to proceed with the imaging, as she was asymptomatic.

Regular follow-up appointments will be crucial to monitor the patient's response to the prescribed medications, assess any potential side effects, and ensure the ongoing effectiveness of the treatment plan.

Discussion

Leprosy, also called Hansen's disease, is most commonly found in India, Brazil, and Indonesia. It mainly affects the skin and the peripheral nervous system. While the precise route of transmission remains elusive, nasal droplet infection is thought to be most likely. The progression of disease is intricately linked to the immune response of the individual host.[4]

The damage to peripheral nerves caused by neurotropic tendencies of *M. leprae* is well-recognized. However, our understanding of *M. leprae*'s impact on the CNS remains limited.[5] Hansen, the pioneer in leprosy research, maintained the belief that leprosy never impacted the brain. Yet, postmortem discoveries of adhesions between the dura mater and brain prompted discussions on the potential involvement of leprosy bacilli in the brain, steering the conversation toward considering CNS manifestations of leprosy.[6]

Polavarapu et al. conducted an imaging study that highlighted eight cases of leprosy exhibiting central nervous system (CNS) involvement. Among these cases, two patients showed lesions in the brainstem, with one displaying a lesion in the nucleus ambiguus, while another exhibited enhanced facial nuclei and nerves. Additionally, they detailed a case involving multiple lower cranial nerve impairments.[5] Other studies have similarly showcased the involvement of cranial nerves and the brainstem through imaging investigations.[5,7–9]Generally, among the cranial nerves affected, the facial and trigeminal nerves are the most commonly observed.[7] The hypothesis suggests that the bacteria might traverse along these cranial nerves to access the brainstem.[8] The case described in our report exhibited diffuse cortical lesions without evident brainstem or cranial nerve involvement. This distinct pattern of neurological manifestation highlights the specific nature of the CNS involvement in lepromatous leprosy for this particular patient.

An autopsy study by Aung et al. unveiled vacuolar changes in motor neurons located in the medulla oblongata and spinal cord. Significantly, this study detected *M. leprae*-specific DNA specifically within the brainstem, indicating the presence of this bacterium within the brainstem area.[8]

The most conclusive diagnosis of leprosy often necessitates a biopsy of the affected regions. However, accessing intricate areas within the CNS is not always feasible. As far as our current understanding goes, there exists only one case report offering both histopathological and molecular evidence demonstrating CNS involvement by leprosy in a living patient.[10] In our patient, the intracranial lesion manifested as a diffusely distributed lesion, introducing inherent uncertainties regarding the potential diagnostic yield of a brain biopsy. Notably, the patient exhibited a discernible lack of confidence in undergoing the procedure, attributable to explicit aversions, ultimately resulting in the withholding of consent.

Early treatment often leads to complete recovery without lasting effects. Paucibacillary forms of leprosy typically involve a treatment regimen of rifampicin and dapsone for a minimum of 6 months. On the other hand, multibacillary leprosy necessitates treatment for at least 12 months, with the addition of clofazimine. It is important to note that leprosy reactions occurring during treatment can significantly worsen the progression of the disease.[4]

Conclusion

When neurological symptoms such as seizures manifest in a patient with leprosy, swift investigation using imaging techniques is crucial. If imaging reveals a lesion, biopsy should be considered, whenever feasible, to establish a definitive diagnosis. Leprosy has shown the potential to affect not just the brainstem, cranial nerves, brachial plexus, and ganglia, but also the cerebral cortex itself. While the precise mechanism causing CNS lesions remains unclear, further research is imperative to elucidate and understand these mechanisms conclusively. Since the cortical involvement in leprosy is not described in the literature, specific treatment guidelines do not

exist. Treatment, as in our case, was based on the multidrug regimen for leprosy.

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CASE REPORT

Recurrent Hemothorax in a Patient with von Willebrand's Disease: Case Report and Literature Review

Vishnu Sharma[1], Naman Modi[2*], Vansh Bagrodia[3], Shraddha Gupta[4]

Received: 25 November 2024; *Accepted:* 23 May 2025

Abstract

Von Willebrand disease (vWD) type 3 is the most severe and rare form of vWD, often underdiagnosed due to clinical overlap with other bleeding disorders such as hemophilia A. We present a unique case of a woman in her thirties with confirmed vWD type 3 who experienced multiple episodes of spontaneous internal bleeding, including recurrent hemoperitoneum and, notably, spontaneous hemothorax—an extremely rare complication in adults. Her prior misdiagnosis delayed appropriate treatment, highlighting the diagnostic complexity of vWD. Laboratory findings revealed undetectable vWF levels and severely reduced factor VIII activity. She was managed conservatively with factor replacement therapy and antifibrinolytics, avoiding invasive procedures. This case brings attention to an unusual bleeding manifestation in vWD and emphasizes the need for heightened clinical suspicion to guide early and accurate diagnosis.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1551

Introduction

Von Willebrand disease (vWD) is a bleeding disorder caused by either a qualitative or quantitative defect in the von Willebrand factor (vWF), a key protein involved in blood clotting.[1] It is the most prevalent inherited bleeding disorder, with literature reporting prevalence rates between 0.01 and 1.30%.[2]

Von Willebrand disease can occur either as an inherited disorder or through acquisition. The inherited forms of vWD are categorized into the following phenotypes:

1. Type 1: This type involves a partial quantitative deficiency of vWF and is inherited in an autosomal dominant (AD) pattern, with incomplete penetrance seen in about 60% of cases. It accounts for the majority of vWD cases.
2. Type 2: Also inherited in an AD manner, type 2 is associated with qualitative abnormalities in vWF. It is subdivided into four variants: 2A (AD or autosomal recessive), 2B (AD), 2N (autosomal recessive), and 2M (AD), with type 2A being the most common among these subtypes.
3. Type 3: This rare autosomal recessive disorder results from a complete absence of vWF, leading to a severe bleeding phenotype.

The clinical manifestations of vWD vary across the different types. Patients may experience mild to moderate symptoms such as epistaxis, gingival bleeding, and easy bruising. Those with type 3 vWD, however, can present with more severe symptoms, including internal bleeding and hemarthrosis, although this type remains exceedingly rare.[3]

The diagnosis of vWD is multifaceted and involves several laboratory investigations. Initial evaluations include a detailed bleeding history, complete blood count, and vWD profile tests (vWF:Ag, vWF:RCo, and FVIII:C), alongside ABO blood group typing. If the preliminary results indicate vWD, additional tests such as vWF multimer analysis, vWF:CBA, vWF:FVIIIB, ristocetin-induced platelet aggregation (RIPA), and genetic testing may be performed to confirm the diagnosis or determine the specific subtype.[3]

Treatment for vWD primarily focuses on replenishing the deficient vWF protein. Management strategies include nonreplacement therapy with desmopressin, replacement therapy using vWF concentrates, and adjunctive therapies like antifibrinolytic agents.[3] Notably, desmopressin is ineffective in managing type 3 vWD due to the complete absence of vWF in these patients.[1]

Case Description

We present the case of a female in her late thirties with a known history of vWD type 3, who was admitted to the emergency department with complaints of chest pain and dyspnea for 2 days. She had been in consultation with us since late 2018.

Her family history was notable for bleeding tendencies in two of her three siblings, though no such history was reported in her parents or grandparents. Until 2018, she had been misdiagnosed and treated as a case of hemophilia A at her local center.

She reported having attained menarche at the age of 13 years and subsequently experienced occasional episodes of menorrhagia, some of which required blood transfusions. In June 2009, she delivered a healthy child but developed a second-degree postpartum hemorrhage, necessitating a subtotal hysterectomy followed by internal iliac and uterine artery embolization. Two months postdischarge, in October 2009, an ill-defined pelvic mass with fluid collection was noted on ultrasonography. Aspiration confirmed the presence of hemoperitoneum. A follow-up scan 1 month later revealed a pelvic stump hematoma. The patient reported that she was managed conservatively at that time.

After an extended uneventful period, she presented to her local center again in February 2018 with a complaint of abdominal pain and an ill-defined pelvic mass noted on examination. Ultrasound revealed an acute hyperdense pelvic hematoma, hemorrhagic ovarian follicles, moderate hemoperitoneum, and mild splenomegaly. Additionally, she complained of chest pain and dyspnea and a chest X-ray revealed moderate left-sided pleural effusion, which was found to be hemorrhagic on aspiration. Basal lung atelectasis was also observed. This was the first episode of hemothorax in the patient's history. The patient was managed conservatively with factor VIII replacement, tranexamic acid, and FFP under the pretext of the episode occurring as a result of her hemophilia.

Nine months later, she experienced another such episode, during which a large stump hematoma was visualized on ultrasonography. Given her extensive bleeding history, she was referred to our tertiary care

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How to cite this article: Sharma V, Modi N, Bagrodia V, *et al.* Recurrent Hemothorax in a Patient with von Willebrand's Disease: Case Report and Literature Review. J Assoc Physicians India 2026;74(6):10–12.

Fig. 1: Chest X-ray showing bilateral pleural effusions (minimal on the right, gross on the left)

center. On careful review of her medical history, her primary diagnosis was reconsidered and investigations were ordered with a suspicion of vWD. Laboratory investigations revealed vWF levels <5 IU/dL (normal: 50–200 IU/dL), factor VIII activity at 1% (normal: 50–150%), and absent RIPA—findings consistent with vWD type 3. At the same time, her brother was also investigated and found to have been suffering from vWD rather than hemophilia A.

The patient was counseled and started on ferrous sulfate, tranexamic acid, oral contraceptive pills, and plasma-derived factor VIII/vWF concentrate (Immunate) as needed. Her episodes of hemoperitoneum were understood to be due to excess bleeding at the time of ovulation, and thus the patient was put on ovarian suppression.

The patient had two more episodes of hemothorax, one in 2020 and the other in 2021, both of which were treated with Immunate along with tranexamic acid 500 mg twice daily, with no need for thoracocentesis. During the current admission, the patient's chest X-ray showed features of bilateral pleural effusions (minimal on the right, gross on the left) (Fig. 1). Aspirate revealed it to be hemorrhagic, thus making it the fourth episode of hemothorax in the patient in 6 years. On taking the history predisposing to such episodes, the patient reported having blunt chest trauma before the first episode of hemothorax. On subsequent occasions, while there was no history of any significant trauma, the patient had experienced violent coughing due to a URI in the days leading up to the hemothorax. Our interpretation was that these episodes led to neovascularization, which led to pleural thickening, thus increasing the risk of recurrent hemothorax with every episode. The patient was counseled accordingly so that further such episodes may be prevented. Like previous episodes, similar treatment was done with Immunate and tranexamic acid, and the patient reported resolution of symptoms; CXR showed clear lung fields within 3 days.

Discussion

In 1926, Finnish physician Erik Adolf von Willebrand first characterized VWD after encountering a young girl with recurrent bleeding episodes that differed clinically from hemophilia.[4]

Despite being the most common inherited bleeding disorder, vWD is frequently difficult to diagnose due to a number of issues. The illness is frequently incorrectly diagnosed, overdiagnosed, or overlooked, which puts more load on the healthcare system and causes avoidable difficulties for patients.

In severe instances, such as type 3 vWD, low FVIII activity can lead to a misdiagnosis of hemophilia A if vWD testing is entirely disregarded. This diagnostic challenge is particularly significant in patients without a family history of severe hemophilia A, especially in males, where milder presentations frequently go unrecognized or are overlooked.[5] In our case, the patient was initially incorrectly diagnosed with hemophilia A.

Our patient experienced bleeding episodes from various sites throughout her illness. Notably, she had complications involving hemoperitoneum and hemothorax. Hemoperitoneum in patients with vWD may be due to ovarian follicle rupture. On the contrary, mild bleeding from follicular rupture is common in healthy females and usually occurs in the middle of the menstrual cycle.[6] Replacement therapy with intermediate-purity factor VIII concentrates, guaranteeing minimum factor VIII levels of 50%, is the recommended treatment for severe bleeding episodes during ovulation in female patients with type 3 vWD.[7] Long-term use of combined oral contraceptive medication until menopause is another effective strategy that is essential for controlling and preventing severe bleeding issues.[8] Our patient was well managed on oral contraceptives for years, and her bleeding issues related to uterine and peritoneal bleeding occurred after she discontinued the medication.

Another noteworthy finding in this patient is recurrent spontaneous hemothorax, which poses significant management challenges and has not been documented in the literature.[9–11] Pleural fluid with a hematocrit higher than 50% of the patient's blood is known as spontaneous hemothorax, and it occurs when blood builds up in the pleural space without any trauma or other causes.[12] To determine the rate of blood loss and avoid complications from developing clots and possible surgical intervention when problematic, hemothoraces of any size should be treated with tube thoracostomy.[12] The management of any hemorrhagic episode is usually more cautious than for individuals without vWD because of the increased risk of procedure-related bleeding in these patients.

We conducted a literature review focusing on the management of spontaneous hemothorax in patients with hemophilia, given the similarity in bleeding risks and clinical presentations between hemophilia and vWD. While there is some literature on spontaneous hemothorax in hemophilia patients, only two case reports—one from 1969 and another from 2021—describe spontaneous hemothorax in pediatric patients with vWD.[9,11] As far as the authors are aware, this case is the first time that repeated recurring spontaneous hemothorax in vWD has been reported in an adult patient. A review by Tripoppoom and Leelayuwatanakul suggests that conservative management can yield favorable clinical outcomes. It has been shown that conservative approaches such as replacing fresh plasma and plasma-derived factor VIII concentrate work well. Bleeding stopped entirely in patients treated with these treatments, and no more interventions were needed.[13]

Although the best way to drain a hemothorax in vWD patients is still unknown, we think that the type and timing of intervention should be tailored to each patient's unique circumstances, taking into account hemodynamics and the severity of the condition. But in these situations, it is important to weigh the potential risk of bleeding from aggressive operations with the potential challenges that stem from a conservative strategy. The hemothorax in this patient was mild and did not make stability difficult to maintain. However, we have chosen to use factor replacement treatment in conjunction with tranexamic acid to achieve hemostasis, followed by therapeutic thoracentesis, due to the probable danger of bleeding from an intrusive surgery and the concerns regarding sequelae of retained hemothorax.

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CASE REPORT

A Curious Case of Emphysema and Fibrosis

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Received: 15 January 2026; *Accepted:* 22 May 2026

Abstract

Rheumatoid arthritis (RA) is a systemic autoimmune disease with frequent extra-articular manifestations, of which pulmonary involvement is the most common and clinically significant. Combined pulmonary fibrosis and emphysema (CPFE) is a distinct clinic-radiological syndrome characterized by the coexistence of upper-lobe emphysema and lower-lobe fibrosis and is increasingly recognized in patients with connective tissue diseases, including RA.

We describe the case of a 50-year-old nonsmoking woman who presented with a 3-year history of progressive exertional dyspnea and chronic dry cough, preceding the onset of inflammatory polyarthritis by nearly 2 years. She later developed symmetrical involvement of small and large joints with prolonged morning stiffness, along with constitutional symptoms including low-grade fever and weight loss. Physical examination revealed grade IV digital clubbing and bibasilar inspiratory crackles. Laboratory evaluation showed elevated inflammatory markers with negative rheumatoid factor and anticyclic citrullinated peptide antibodies, consistent with seronegative RA. High-resolution computed tomography of the thorax showed upper lobe emphysema and lower lobe honeycombing, confirming the diagnosis of CPFE. Pulmonary function testing showed relatively preserved airflow with mildly reduced diffusion capacity, along with severe exercise-induced desaturation. Echocardiography revealed mild pulmonary hypertension.

This case highlights an uncommon presentation of rheumatoid arthritis-associated combined pulmonary fibrosis and emphysema (RA-CPFE), where pulmonary manifestations preceded articular disease, emphasizing the need for a high index of suspicion. Early recognition through high-resolution computed tomography (HRCT) and comprehensive pulmonary evaluation is crucial, as RA-CPFE is associated with significant morbidity, pulmonary hypertension, and poor prognosis. Multidisciplinary management incorporating immunosuppressive therapy, consideration of antifibrotics in progressive disease, and supportive care remains essential. Further studies are required to better define optimal treatment strategies and prognostic markers in RA-CPFE.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1586

Case Description

A 50-year-old lady with no addiction presented with mMRC grade III dyspnea progressively increased over 3 years, accompanied by a persistent nonproductive cough. Over the past 1 year, she developed symptoms of symmetrical polyarthritis involving the proximal interphalangeal and metacarpophalangeal joints of both hands, as well as the ankles, feet, and larger joints, including the elbows and shoulders. The joint pain was associated with morning stiffness for more than 60 minutes, which improved with activity. There were no subcutaneous nodules on examination.

She reported intermittent low-grade fever and an unintentional weight loss of 6 kg over the preceding year. There were no sicca symptoms, dysphagia, Raynaud's phenomenon, proximal muscle weakness, recurrent oral ulcers, alopecia, or dermatological manifestations. She was not receiving any regular treatment for these symptoms.

On examination, pulse was 102/min, blood pressure was 110/72 mm Hg, respiratory rate was 28/min, and her oxygen saturation was 92% on ambient air. She had grade IV digital clubbing on general examination. There was no pallor, icterus, cyanosis, clubbing, pedal edema, or lymphadenopathy. On respiratory system examination, bilateral fine end-inspiratory crackles were heard on chest auscultation. On cardiovascular examination, there was loud P2; no other abnormality was detected. On musculoskeletal examination, there were no skin changes or deformity, but there was evidence of movement restriction in small joints of the hands and shoulder joints. The movement restriction was similar on both sides. Chest radiograph findings are depicted in Figure 1. A summary of laboratory investigations is presented in Table 1.

High-resolution computed tomography (HRCT) of the thorax was performed, as shown in Figure 2. Transthoracic two-dimensional (2D) echocardiography demonstrated normal left ventricular function with an estimated pulmonary artery systolic pressure of 39 mm Hg, suggestive of mild pulmonary hypertension.

Pulmonary function testing was attempted multiple times but was technically suboptimal despite repeated efforts. Spirometry showed a forced vital capacity (FVC) of 1.07 L (45% predicted), forced expiratory volume in one second (FEV1) of 0.87 L (44% predicted), and an FEV1/FVC ratio of 81.7. Total lung capacity (TLC) was 3.16 L (72% predicted), and diffusion capacity for carbon monoxide (DLCO) was 71% predicted. A 6-minute walk test demonstrated severe exercise-induced desaturation, with oxygen saturation dropping to 78% on room air and a total walking distance of 240 meters.

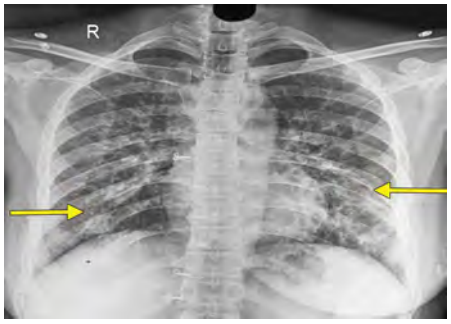

Fig. 1: Chest radiograph showing reticular opacities in bilateral lung fields, predominantly in the middle and lower zones (yellow arrow)

Table 1: Blood investigations of the patient

Blood investigation	*Values*
Hemoglobin	11.3 gm/dL
Total leukocyte count	9.2×10^3/mm^3
Platelet count	1.62×10^5/mm^3
Urea/creatinine	25/0.7 mg/dL
Total bilirubin	0.7 mg/dL
Alanine transaminase	21 U/L
Aspartate transaminase	41 U/L
Rheumatoid factor	Negative
Anti-citrullinated cyclic peptide	Negative
Antinuclear antibody (ELISA)	21.36 U
Alpha-1 antitrypsin levels	142 mg/dL

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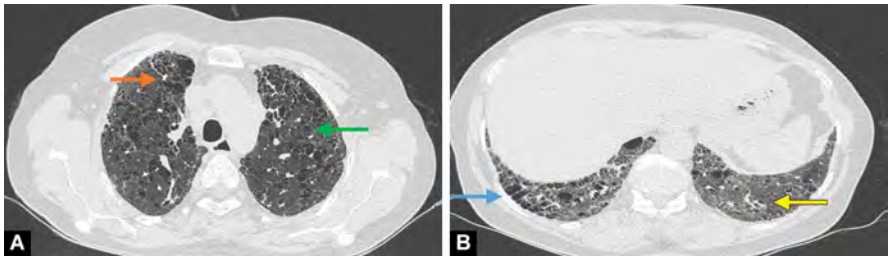
How to cite this article: Joshi S, Gothi D. A Curious Case of Emphysema and Fibrosis. J Assoc Physicians India 2026;74(6):13–16.



Figs 2A and B: High-resolution computed tomography thorax of the patient showing: (A) paraseptal emphysema (orange arrow) and centriacinar emphysema (green arrow), predominantly involving the upper lobes; and (B) interlobular septal thickening with traction bronchiolectasis (yellow arrow) and honeycombing (blue arrow), consistent with fibrotic changes in the lower lobes

Question

What is the likely diagnosis? What are the HRCT thorax findings?

Answer

The likely diagnosis is rheumatoid arthritis-associated combined pulmonary fibrosis and emphysema (RA-CPFE).

The diagnosis of rheumatoid arthritis (RA) is primarily clinical and supported by classification criteria. The 2010 EULAR classification criteria for RA encompass four key domains: (1) joint involvement, (2) serology (including RF and anti-CCP antibodies), (3) acute-phase reactants, and (4) symptom duration. Serological positivity, although helpful, is not mandatory, and RA can be diagnosed in seronegative patients based on clinical features and inflammatory markers. A cumulative score of 6 or more confirms the diagnosis.[1]

In this patient, the presence of symmetrical involvement of small and large joints, symptom duration exceeding 1 year, and elevated acute-phase reactants fulfilled the criteria, yielding a total score of 6 and confirming the diagnosis of RA.

High-resolution computed tomography of the thorax findings are characteristic of combined pulmonary fibrosis and emphysema. Figure 2A demonstrates paraseptal emphysema (orange arrow) and centriacinar emphysema (green arrow), predominantly involving the upper lobes. Figure 2B shows interlobular septal thickening with traction bronchiolectasis (yellow arrow) and honeycombing (blue arrow), consistent with fibrotic changes in the lower lobes.

Discussion

Rheumatoid arthritis is a long-term systemic autoimmune disease that predominantly affects synovial joints, leading to chronic inflammation and progressive joint damage. Extra-articular manifestations are common and contribute significantly to disease-related morbidity and mortality. Among these, pulmonary involvement is the most frequent and clinically important. RA can involve all compartments of the lung, including the interstitium, airways, pleura, and pulmonary vasculature.[2]

Pulmonary manifestations typically occur concurrently with or following the onset of articular disease. However, in approximately 10–20% of cases, extra-articular features may precede joint symptoms, as seen in the present case, often leading to diagnostic delay.[2]

Rheumatoid factor and anticitrullinated protein antibodies (ACPAs) are the most sensitive and specific serological markers for RA. Nevertheless, a subset of patients remains seronegative. Several other autoantibodies have been implicated in RA, particularly in those with extra-articular involvement. These antibodies, as summarized in Table 2, were not available for testing in the present case.[3]

Combined pulmonary fibrosis and emphysema (CPFE) is a recognized clinical and radiological syndrome defined by the coexistence of upper-lobe predominant emphysema and lower-lobe pulmonary fibrosis on HRCT. CPFE has a multifactorial pathogenesis. CPFE is classically seen in men (85%) with a high smoking index.[4,5] It is uncommon in nonsmoking women. Other risk factors include advancing age (most commonly presenting in the sixth decade), occupational and environmental exposures such as silica and coal dust, autoimmune diseases including RA and systemic sclerosis, and genetic predisposition. Mutations involving telomere-related genes (TERT and TERC), as well as ABCA3 and MUC5B, suggest a role for inherited susceptibility and familial clustering.[4]

Clinically, patients with CPFE typically present with progressive exertional dyspnea, chronic cough, and hypoxemia. Physical examination often reveals digital clubbing, fine end-inspiratory crackles, and signs of pulmonary hypertension, such as a loud and accentuated pulmonic component of the second heart sound. Digital clubbing is not seen in emphysema or RA; it usually indicates lung fibrosis. Whereas fine end-inspiratory crackles may be seen both in emphysema and fibrosis. HRCT remains the cornerstone of diagnosis, demonstrating the characteristic distribution of emphysema and fibrosis.[4]

Combined pulmonary fibrosis and emphysema is increasingly considered a clinical syndrome rather than a purely radiological diagnosis. CPFE criteria as per the American Thoracic Society (ATS), 15% of the lung showing emphysema; preserved lung with reduced DLCO; pulmonary hypertension not fully explained by emphysema (FEV1 > 60%) alone or fibrosis alone (FVC >70%).[4]

Preserved lung volumes with markedly reduced DLCO are regarded as hallmarks of CPFE, and the pattern varies depending on the relative severity of emphysema and interstitial lung disease. The coexistence of emphysema and fibrosis results in a counterbalancing physiological effect, wherein the hyperinflation and airway obstruction caused by emphysema offset the restrictive changes due to fibrosis. Consequently, spirometric indices such as FEV1, FVC, and TLC may appear relatively preserved, while gas exchange is severely impaired. DLCO and transfer coefficient are therefore disproportionately reduced (Table 3).[4] In the present case, spirometry showed a preserved FEV1/FVC ratio with reduced FEV1, FVC, TLC, and DLCO. The reduced lung volumes may partly reflect suboptimal test performance. In our case, DLCO was only mildly reduced because of poor breath-holding time. The severe impairment in gas exchange was evidenced by marked exercise-induced desaturation during the 6-minute walk test.

At present, no single parameter has been validated for assessing disease severity in CPFE. Reduced DLCO remains the most consistent marker, reflecting extensive alveolar-capillary membrane destruction. Some studies have suggested that a ratio of percentage predicted FEV1 to percentage predicted FVC greater than 1.2 may independently predict mortality, although it is not suitable for severity assessment. The FVC/DLCO ratio has been used to predict pulmonary hypertension in interstitial lung disease and may have potential utility in CPFE, although data remain limited. The pulmonary hypertension in this case is likely to be due to either due to CPFE or obstructive airway disease as the fibrosis was though more 5% but not extensive. The RV/TLC ratio may assist in diagnosis and management but can underestimate disease severity.[5]

Table 2: Prevalence of antibodies in rheumatoid arthritis

Antibodies	*Type of antibodies*	*Antibodies against an antigen*	*Prevalence*	*Characteristics and relevance*
Citrullination-associated antibodies	ACPA	Vimentin, fibronectin, actin, HSP90, histones, α-enolase, eEF1a, CAP-1, CapZalpha-1, asporin, cathepsin D, histamine receptor, PDI, ER60 precursor, ALDH2, collagen type I and II, eIF4GI, aldolase, PGK1, calreticulin, HSP60, FUSE-BP1 and 2, ApoE, MNDA, hnRNP-A2/B1	Up to 80%	Severe joint destruction and bone erosion. Extra-articular manifestations are higher, like rheumatoid arthritis-interstitial lung disease and higher cardiovascular morbidity
–	Anti-PAD 2/3/4	Peptidyl arginine deiminase	25–45%	Higher radiographic disease severity. It can be seen in systemic lupus erythematosus (SLE) also
Antibody to chemically modified antigens	Anticarbamylated protein	Alpha-1 antitrypsin and others	45%	Associated with juvenile idiopathic arthritis. May have higher disease activity
–	Anti-malondialdehyde and anti-malondialdehyde-acetaldehyde (MAA) antibodies	Unknown	10%	RA with other systemic comorbidities such as diabetes mellitus and chronic liver disease
Nonspecific RA antibody	Rheumatoid factor	IgG (Fc)	50–90%	High titers of rheumatoid factor have been associated with worse prognosis, more aggressive articular disease, increased disease activity, reduced rates of remission, higher prevalence of extra-articular manifestations, and increased morbidity and mortality, especially when in combination with ACPA
–	Anti-RA-33 or anti-hnRNP A2 antibodies	hnRNP-A2 (heterogeneous nuclear ribonucleoprotein)	15–35%	Less severe disease

ACPA, anti-citrullinated protein antibody; ALDH2, mitochondrial aldehyde dehydrogenase; ApoE, apolipoprotein E; CAP-1, adenylyl cyclase-associated protein 1; CapZalpha-1, F-actin-capping protein subunit alpha-1; CarP, carbamylated protein; eEF1a, elongation factor 1-alpha; eIF4GI, eukaryotic translation initiation factor 4G1; ER60, endoplasmic reticulum resident protein 60 precursor; FUSE-BP, far upstream element-binding protein; hnRNP, heterogeneous nuclear ribonucleoprotein; HSP, heat shock protein; IgG, immunoglobulin G; MAA, malondialdehyde-acetaldehyde; MNDA, myeloid nuclear differentiation antigen; PAD, peptidyl arginine deiminase; PDI, protein disulfide-isomerase; PGK1, phosphoglycerate kinase 1; PTM, post-translational modification; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis

Table 3: Showing possible pulmonary function abnormalities in CPFE

Spirometry variable	*Abnormalities seen in PFT*
FVC	Normal or decreased
FEV1	Normal or decreased
FEV1/FVC	Variable (normal, decreased, or increased)
Total lung capacity (TLC)	Variable (normal, decreased, or increased)
Functional residual capacity (FRC)	Variable (normal, decreased, or increased)
Residual volume	Variable (normal, decreased, or increased)
DLCO	Disproportionately reduced
Transfer coefficient for carbon monoxide	Severely reduced
Saturation during exercise	Severe desaturation

Management of CPFE associated with connective tissue disease, particularly RA, is challenging due to limited evidence. Immunomodulatory therapy remains the cornerstone of treatment and includes corticosteroids, mycophenolate mofetil, and azathioprine. In patients with established progressive pulmonary fibrosis, antifibrotic therapy should be considered in addition to anti-inflammatory treatment.[2] Nintedanib is a tyrosine kinase inhibitor, whereby it inhibits fibroblast growth factor, vascular endothelial growth factor, and platelet-derived growth factor, whereas pirfenidone acts by inhibiting transforming growth factor-beta 1 (TGF-β1), thus reducing fibroblast proliferation, myofibroblast differentiation, and collagen synthesis.[6,7] Evidence from the INBUILD and RELIEF trials supports the use of antifibrotic agents in slowing FVC decline in patients with progressive fibrosing interstitial lung diseases, including CTD-associated ILD.[6,7] Progression of fibrosis in any connective tissue disorder, including RA, is difficult to predict. However, there are certain biomarkers which may help, e.g., bronchoalveolar lavage lymphocytosis, KL-6, SP-D remain investigational.[8]

Comorbid conditions such as pulmonary hypertension and lung cancer must be actively screened for and managed, as they significantly affect prognosis. Supportive care measures—including pulmonary rehabilitation, vaccination against influenza, pneumococcus, and COVID-19, inhaled bronchodilators for symptomatic relief, long-term oxygen therapy when indicated, and early referral for lung transplantation in eligible patients—are essential components of comprehensive management.[4]

Conclusion

Rheumatoid arthritis-associated combined pulmonary fibrosis and emphysema represents a distinct and severe extra-

articular manifestation characterized by progressive disease, substantial symptom burden, and increased risks of pulmonary hypertension, lung cancer, and mortality. Early recognition through HRCT and pulmonary function testing, combined with a multidisciplinary management approach incorporating immunosuppressive and antifibrotic therapies, is crucial for improving outcomes. Given its poor prognosis and limited therapeutic evidence, further research is needed to elucidate disease mechanisms and establish optimal treatment strategies for RA-CPFE.

Author Contributions

Conceptualization and writing: SJ and DG; review and editing: DG and SJ.

Conflicts of Interest

None.

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CASE REPORT

When It's Not Just "That Time of the Month": Identifying Thoracic Endometriosis in the Context of Recurrent Pleural Effusion

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Received: 10 October 2024; *Accepted:* 16 December 2024

Abstract

Recurrent hemorrhagic pleural effusion presents as a challenge for both the clinician and the patient, with common causes being tuberculosis, malignancy, and collagen vascular diseases. Among uncommon causes of recurrent hemorrhagic effusion is catamenial hemothorax, which is a part of thoracic endometriosis syndrome (TES). Endometriosis is the extrauterine growth of endometrial glands and stroma. It is relatively common among women of reproductive age-group, with reported incidence of around 11%. Although rare, the thorax is the most common extraabdominal site for endometriosis. Here we present a rare case of recurrent hemorrhagic pleural effusion due to thoracic endometriosis in a young female with infertility. A 33-year-old female housewife presented with dyspnea on exertion modified Medical Research Council (mMRC) grade 2 and dry cough occasionally for 6 months. She had a history of tubercular cervical lymphadenopathy for which she was on treatment. Therapeutic thoracocentesis was performed thrice in 4 months. Routine microscopy showed predominantly lymphocytes, mesothelial cells, and numerous foamy histiocytes, some pigment laden. There were no malignant cells or acid-fast bacilli (AFB) detected in the fluid. Pleural fluid amylase and lipase were normal. Contrast-enhanced computed tomography (CT) thorax showed moderate right-sided pleural effusion without any evident parenchymal lesions, pleural lesions, or mediastinal lymphadenopathy. Ultrasonography (USG) abdomen and pelvis showed mild ascites which was nontappable. As we had not reached a definitive diagnosis, medical thoracoscopy was performed. It showed moderate hemorrhagic pleural fluid in the pleural cavity and a small raised erythematous glandular tissue on the parietal pleural surface from which biopsy was taken. Histopathology showed an island of endometrial stroma with a single gland. Immunohistochemistry was performed on this section, which was PAX8 and CD10 positive, confirming the diagnosis of thoracic endometriosis. Pleurodesis with talc slurry was done to prevent further refilling of the effusion. Gynecology opinion was sought, and patient was started on monthly subcutaneous injections of gonadotropin-releasing hormone (GnRH) analogue for 3 months. Chest X-ray after 3 months showed no refilling of pleural effusion. Catamenial hemothorax is the second commonest manifestation of TES, occurring in approximately 14% of cases. It affects the right side in about 80% of the cases. Diagnosis is based on high degree of suspicion and is often delayed. Video-assisted thoracic surgery (VATS) remains the gold standard for diagnosis and management of TES. Medical thoracoscopy is a viable alternative in resource-poor settings or when diagnosis is not confirmed. On histology, diagnosis is confirmed by the presence of endometriotic glands or stroma, which may also show stromal arterioles, erythrocytes, and pigmented histiocytes. In difficult-to-diagnose cases, CD10 immunohistochemical staining can help in diagnosis of endometrial tissue. There are various treatment modalities considered in the management of catamenial hemothorax, like surgical resection, medical management along with pleurodesis, combination therapy, or in some cases, simple observation. Currently, VATS with GnRH analogue therapy is considered the gold standard of management.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1018

Introduction

Recurrent hemorrhagic pleural effusion presents as a challenge for both the clinician and the patient, of which the common causes are tuberculosis, malignancy (either primary or metastatic), and collagen vascular diseases. If the underlying lung parenchyma shows no mass lesions or signs of infection, then uncommon causes of recurrent hemorrhagic effusion should be considered.

The proliferation of endometrial glands and stroma outside the uterus is known as endometriosis. With a reported frequency of about 11%, it is relatively frequent among women in the reproductive age range.[1] The most frequent extraabdominal location for endometriosis, although rare, is the thorax,[2] presenting with a variety of manifestations, referred to as thoracic endometriosis syndrome (TES).[3]

The four reported entities that make up TES are: catamenial pneumothorax (commonest, approximately 73% of published cases), catamenial hemothorax (14% cases), catamenial hemoptysis (7% cases), and endometriotic lung nodules (6% cases).[4] Because of the overwhelming prevalence of catamenial pneumothorax, the entity was further divided into three separate subgroups: endometriosis-proven catamenial pneumothorax, nonendometriosis-proven catamenial pneumothorax, and noncatamenial but endometriosis-related pneumothorax.[4]

Given that catamenial hemothorax is a very rare cause of recurrent hemothorax, diagnosing and treating TES—especially nonpneumothorax entities—requires a high level of clinical suspicion.[5] Approximately 80% of these cases present with right-sided effusion,[6] with bilateral and left-sided effusion also being reported.

Clinical criteria are frequently used to make the diagnosis, while computed tomography (CT) scans may reveal pleural-based lesions. The gold standard of care is video-assisted thoracic surgery (VATS) with gonadotropin-releasing hormone (GnRH) analogue therapy; other treatments include pleurodesis and thoracoscopy, as well as cutting-edge techniques like diaphragmatic patch.[2,7,8]

Here we present a rare case of recurrent pleural effusion due to thoracic endometriosis in a young female with infertility.

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How to cite this article: Kamath A, Nair JP, Sinha T, *et al.* When It's Not Just "That Time of the Month": Identifying Thoracic Endometriosis in the Context of Recurrent Pleural Effusion. J Assoc Physicians India 2026;74(6):17–19.

Case Description

A 33-year-old female housewife presented to the outpatient department with dyspnea on exertion [modified Medical Research Council (mMRC) grade 2] and occasional dry cough for 6 months. She had a history of tubercular cervical lymphadenopathy, for which she had been receiving treatment for the last 6 months at her local hospital. She also had a history of therapeutic thoracocentesis thrice during this period (a total of 3.8 L in three sittings), which was hemorrhagic, exudative, with predominantly lymphocytes and a low adenosine deaminase (ADA) level. Her menstrual history was significant for menorrhagia along with dyspnea since menarche. She also had a history of primary infertility, which had not yet been evaluated.

Due to the nonresolution of the effusion on antitubercular treatment, she was referred to our hospital. She denied any history of hemoptysis or chest pain. Clinical examination was significant for moderate pleural effusion on the right side, which was corroborated by chest X-ray (Fig. 1). Routine blood investigations revealed anemia (Hb: 10.3 gm/dL), normal total (9,900/mm^3), and differential WBC counts (N: 68, E: 04, B: 00, L: 25, M: 03). Physical observation of pleural fluid obtained after a diagnostic as well as therapeutic thoracocentesis revealed a deep brownish-red hemorrhagic fluid.

Pleural fluid had a hematocrit under 50% of blood. The pleural fluid had a total cell count of 400/mm^3, of which 60% were lymphocytes with an abundance of red blood cells. It was a low ADA lymphocytic effusion. Routine microscopy showed predominantly lymphocytes, mesothelial cells, and numerous foamy histiocytes, some pigment-laden. The fluid revealed neither acid-fast bacilli (AFB) nor malignant cells. Pleural fluid amylase and lipase were normal. Contrast-enhanced CT thorax revealed a substantial pleural effusion on the right side, but no pleural lesions, parenchymal abnormalities, or mediastinal lymphadenopathy were identified. Ultrasonography (USG) abdomen and pelvis showed mild ascites, which was nontappable.

As we had not reached a definitive diagnosis, medical thoracoscopy was performed with a semirigid thoracoscope. The pleural cavity had considerable hemorrhagic pleural fluid, and a small raised erythematous glandular tissue on the parietal pleural surface, from which a biopsy was taken (Fig. 2).

Histopathology showed an island of endometrial stroma with a single gland. Immunohistochemistry was performed on this section, which was PAX8 and CD10 positive (Fig. 3).

The diagnosis of pleural endometriosis was established based on the histology, clinical characteristics, and investigative findings.

Pleurodesis with talc slurry was done to prevent further refilling of the effusion. A gynecology opinion was sought, and the patient was started on monthly subcutaneous injections of GnRH analogue for 3 months. Chest X-ray after 3 months showed no refilling of pleural effusion (Fig. 4).

Discussion

Catamenial hemothorax is the second most common manifestation of TES, occurring in approximately 14% of cases.[4] It is right-sided in about 80% of the cases.[6] In a study on

Fig. 1: Chest radiograph on presentation revealing moderate right sided pleural effusion

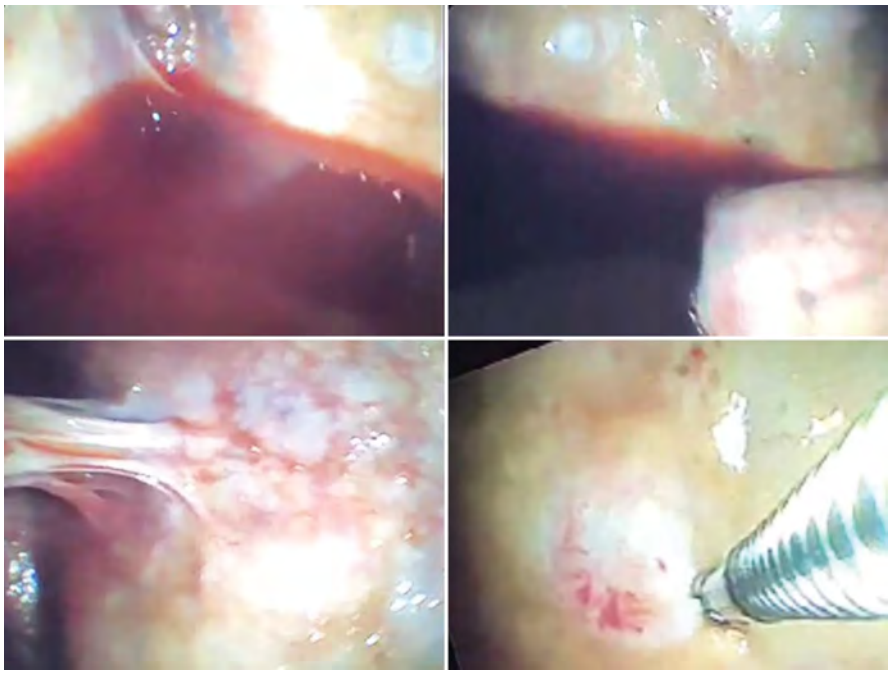

Fig. 2: Thoracoscopic images showing pleural cavity with hemorrhagic effusion with lesions on parietal pleura from which biopsy was taken

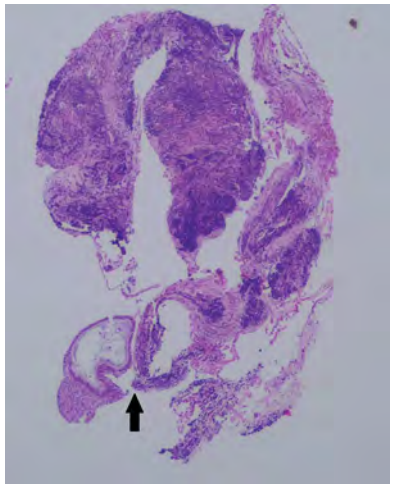

Fig. 3: Histopathology showing an island of endometrial stroma with a single gland

Fig. 4: Chest radiograph after 3 months showing no refilling of effusion after talc pleurodesis and GnRH analogue therapy

110 patients, the mean age at presentation was 35 ± 0.6 years (range 15–54 years), which is 5 years later than that for pelvic endometriosis.[9] Our patient is 33 years old and is near the mean age of presentation. Additionally, catamenial hemothorax has an 82.8% association with concurrent pelvic endometriosis, with 76.7% being infertile/nulliparous.[10]

The pathophysiology of TES has been suggested by a number of theories, including the notion of retrograde menstruation, lymphatic or hematological spread, prostaglandin theory, and coelomic metaplasia.[2,11] The most widely acknowledged of these is the notion of retrograde menstruation, which also explains why TES is more common on the right side.[12] However, the exact pathophysiology of the various manifestations of TES still remains unknown.

Patients with catamenial hemothorax present with a variety of symptoms, such as cough, dyspnea, chest pain, and shoulder pain, with chest pain being the most common presentation.[2,4] The diagnosis is frequently delayed and relies on a high level of suspicion. The main purpose of a CT scan is to rule out alternative effusion causes. Although MRI is thought to be better, it is frequently not done because of suspicions of other pathologies.[5]

The gold standard for diagnosing and treating TES is still VATS.[8] In situations with limited resources or when a diagnosis is uncertain, medical thoracoscopy is a good substitute. Medical thoracoscopy is useful in visualization of the lesions, which are more commonly seen on the diaphragmatic pleura as dark red to blue nodules or cysts.[6] On histology, diagnosis is confirmed by the presence of endometriotic glands or stroma, which may also show stromal arterioles, erythrocytes, and pigmented histiocytes.[13] In difficult-to-diagnose cases, CD10 immunohistochemical staining helps in the diagnosis of endometrial tissue.[13]

Treatment options for catamenial hemothorax include combination therapy, medicinal management in conjunction with pleurodesis, surgical resection, and, in certain situations, simple observation.[14] While surgical resection of the nodules/cysts is considered the definitive treatment, recurrences can still occur, often arising from concomitant abdominopelvic endometriosis, and require planned surgical management of both sites.[8] Lobectomy may be needed in some refractory cases. Medical therapy consists of various agents like GnRH analogs, GnRH antagonists, progestogens, and newer, more selective estrogen receptor modulators (SERM) and selective progestogen receptor modulators (SPRM).[15–17] However, a consensus drug of choice is still debated. Currently, VATS with GnRH analog therapy is considered the gold standard of management.

Patient Consent Statement

The author(s) have obtained written informed consent from the patient for the publication of the case report details and related images.

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CASE REPORT

Successful Management of Milroy's Disease: A Rare Condition Complicated by Tuberculous Pericardial Effusion

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Received: 15 May 2025; *Accepted:* 11 June 2025

Abstract

Milroy's disease is a rare hereditary primary lymphedema, typically presenting at birth or early infancy with chronic lower limb swelling due to mutations in the *FLT4* gene encoding VEGFR-3. While congenital lymphedema is the hallmark, its association with tubercular pericardial effusion leading to tamponade is extremely rare. We report an 18-year-old female with longstanding bilateral lower limb lymphedema who presented with progressive dyspnea and fever. Evaluation revealed tubercular pericardial effusion, and genetic testing confirmed an *FLT4* mutation. The patient improved with antitubercular therapy and supportive care. This case emphasizes the need to consider rare systemic complications in congenital lymphedema syndromes to optimize early diagnosis and management.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1536

Introduction

Milroy's disease, also known as hereditary lymphedema type I, is a rare autosomal dominant condition with variable penetrance caused by mutations in the vascular endothelial growth factor receptor 3 (*VEGFR3*) gene, which is essential for lymphatic vessel development.[1,2] It is a familial form of primary congenital lymphedema that usually develops shortly after birth, but sometimes it may develop later in life. It typically affects the lower extremities.[2] It was first described by Nonne and Milroy.[3,4] While lymphedema is the hallmark of Milroy's disease, the involvement of other systems, such as the cardiovascular system, is rare. Its occurrence with tubercular pericardial effusion, a rare complication in a rare disease, has not been previously reported. This case report presents a unique case of Milroy's disease with concurrent tubercular pericardial effusion, highlighting the diagnostic and therapeutic complexities of this rare association.

Case Description

An 18-year-old female presented with a 1-month history of progressive breathlessness, which worsened over the past 4 days (NYHA grade I to III). The patient also reported a dry cough for 15 days, low-grade fever without chills or rigors, and general malaise for 4 days. She was previously diagnosed with a case of congenital lymphedema (Milroy's disease) with vaginal hypoplasia, which was hereditary, as her family history revealed a similar condition in one of her aunts.

There was no history of trauma, surgery, infections, or chronic venous insufficiency or varicose veins. Similarly, she gave no history of living in or traveling to areas endemic for filariasis, nor did she have a history of systemic diseases such as ischemic heart disease, kidney disease, liver disease, hypertension, diabetes mellitus, or heart failure. She neither had a history of cancer nor malignancies in the past, nor had she received any radiation therapy.

Upon evaluation, the patient's pulse rate was 110 beats per minute, blood pressure (BP) was 92/50 mm Hg, and respiratory rate was 32/min. Jugular venous pressure (JVP) was elevated, and bilateral edema was observed in both lower and upper limbs (left > right). Cardiac examination revealed muffled heart sounds without murmurs or rubs. There was no pallor, icterus, cyanosis, clubbing, or puffiness of the face.

The patient's investigations revealed a hemoglobin level of 13.3 gm%, a leukocyte count of 9400/mm^3, and a platelet count of 1.95×10^5/mm^3. The peripheral smear was normal. Serum urea was 20 mg/dL, creatinine was 0.91 mg/dL, sodium was 135 mEq/L, potassium was 4.0 mEq/L, SGOT was 29 IU/L, SGPT was 11 IU/L, alkaline phosphatase was 152 IU/L, and total bilirubin was 0.73 mg/dL. A chest X-ray suggested pericardial effusion, and an electrocardiogram showed low voltage complexes.

2D echocardiography revealed massive pericardial effusion with early tamponade, while the left ventricular ejection fraction was normal at 60%. A pigtail catheter was inserted under fluoroscopic guidance with all aseptic precautions, and pericardial fluid was aspirated for diagnostic testing and therapeutic purposes. In the first attempt, 850 mL of yellowish pericardial fluid was removed, and later, 8 hourly fluid was removed according to the amount of fluid present in the sac. The fluid analysis showed 80 leukocytes, with 95% lymphocytes on differential count, a pH of 7.4, a sugar level of 70 mg/dL, a protein level of 3.9 gm/dL, and a lactate dehydrogenase (LDH) level of 970 IU/L. The adenosine deaminase (ADA) test was positive. The fluid was yellow in color, and a cobweb formation was observed on prolonged standing.

Culture and cytology of the pericardial fluid were negative.

Based on the above examinations and investigations, the patient was diagnosed as a known case of congenital lymphedema (Milroy's Disease) with vaginal hypoplasia complicated by tubercular pericardial effusion and cardiac tamponade. And so, she was treated with broad-spectrum antibiotics (cefotaxime and vancomycin) for 7 days, along with antitubercular therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol) as per standard guidelines. She showed significant clinical improvement and tolerated the treatment well, and so was discharged after 12 days of treatment, as shown in Figures 1 and 2.

Discussion

Lymphedema is a chronic condition caused by impaired transportation or drainage, or blockage, or imbalance between development and drainage of lymph resulting in accumulation of protein-rich fluid and water in the interstitium.[1,5] It is characterized by painless swelling of one or more limbs and occasionally the face, trunk, and genitalia.[1,5,6]

Nonne and Milroy originally defined it as congenital, bilateral or unilateral chronic

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How to cite this article: Khan K, Quazi T, Jalgaonkar P, *et al.* Successful Management of Milroy's Disease: A Rare Condition Complicated by Tuberculous Pericardial Effusion. J Assoc Physicians India 2026;74(6):20–21.

Fig. 1: Upper limb edema

Fig. 2: Lower limb edema

hereditary edema in lower extremities, and never above the inguinal ligament; but, later, the clinical spectrum was expanded, and edema of genitalia, upper limbs, face, and, infrequently, involvement of pleura, peritoneum, and pericardium was also included under the same heading.[7–9]

Lymphedema is broadly divided into primary and secondary lymphedema. Primary has three clinical subtypes as demonstrated in Table 1.[1,10]

Lymphedema is usually painless and symptomless except for chronic, dull, heavy sensation in the lower limbs. The main concern of patients is the appearance of their leg/s. Years of persistent lymphedema can cause immunological and inflammatory reactions that include the infiltration of fibroblasts, adipocytes, and mononuclear cells, which results in the deposition of collagen and adipose tissue in the skin and subcutaneous tissues. This causes pitting edema to change to nonpitting edema. Additionally, as the tissues become fibrotic and indurated, the limb takes on a woody texture.

Table 1: Demonstrating types of lymphedemas and the age of occurrence

Types of primary lymphedema	*Age of occurrence*
Congenital lymphedema (Milroy's disease) (hereditary lymphedema type I)	Appears shortly after birth
Lymphedema praecox (Meige's disease) (hereditary lymphedema type II)	Onset at the time of puberty
Lymphedema tarda	Usually begins after the age of 35 years

There is no cure for Milroy disease, and treatment focuses on minimizing swelling and preventing complications such as infection. Key treatments include massage techniques, compression stockings, and exercise, guided by a lymph therapist for skin care and hosiery use. Though there is no current cure, research on regrowing lymphatic vessels, showing promise in mice, raises hope for future human gene therapies. Skin hygiene is vital to prevent cellulitis and lymphangitis, with emollients recommended for dryness. Decongestive physiotherapy, manual lymphatic drainage, and compressive bandages help maintain edema reduction, with pneumatic compression devices used at home if needed. Diuretics are contraindicated due to the risk of volume depletion and metabolic abnormalities. Liposuction combined with physiotherapy is an option for severe cases, such as postmastectomy lymphedema. Future therapies, including gene transfer, are being explored in clinical trials. The lymphatic system also plays a crucial role in cardiovascular diseases such as obesity, atherosclerosis, and hypertension.[11,12]

The association of Milroy's disease with pleural effusion or pericardial effusion, particularly of tubercular origin, is exceedingly rare. Pericardial effusion of tubercular origin is often due to direct infection of the pericardium, leading to the accumulation of exudative fluid. Suspicion and work-up to rule out these conditions in Milroy's disease should be the routine practice, as these conditions could be fatal. Management of these situations more often requires the use of diuretics, so considering the co-existence of Milroy's disease and tubercular pericardial effusion in this patient underscores the complexity of managing rare diseases with multiple system involvement. It also raises questions about the potential relationship between impaired lymphatic drainage and susceptibility to infections such as tuberculosis.[8,12]

Conclusion

This case report presents the first documented case of Milroy's disease associated with tubercular pericardial effusion, emphasizing the need for heightened clinical awareness of such rare associations. Early detection and effective treatment are essential for favorable outcomes in these complex cases. Further research is needed to explore the potential links between genetic lymphatic disorders and susceptibility to infections.

Conflicts of Interest

The authors declare no conflicts of interest related to this case report.

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CASE REPORT

Synchronous Uterine Leiomyosarcoma and Pulmonary Adenocarcinoma: A Rare Oncological Puzzle

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Received: 14 April 2025; *Accepted:* 13 October 2025

Abstract

Introduction: The occurrence of dual primary malignancies is an uncommon clinical phenomenon. This case report details a 65-year-old female presenting with both uterine leiomyosarcoma (LMS) and pulmonary adenocarcinoma, initially misdiagnosed as a metastatic spindle cell tumor.

Case description: The patient presented with foul-smelling vaginal discharge, irregular menses, lower limb swelling, and a nonproductive cough. Imaging and biopsies revealed a necrotic uterine mass diagnosed as LMS and a left upper lobe lung mass identified as adenocarcinoma. Genetic testing of the lung tumor showed an epidermal growth factor receptor (EGFR) exon 19 deletion mutation. Treatment included chemotherapy targeting both malignancies, surgical resection of the uterine tumor, and targeted therapy for the lung adenocarcinoma.

Conclusion: This case underscores the importance of thorough diagnostic evaluation in patients with multiple tumors to distinguish between metastatic disease and dual primary malignancies, as treatment strategies differ significantly.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1531

Introduction

The occurrence of multiple primary malignancies in a single patient is rare, with an incidence ranging from 2.3 to 5.2% among all cancer patients.[1] The development of synchronous malignancies can be attributed to various genetic, environmental, and treatment-related factors, including inherited cancer syndromes, exposure to carcinogens, immunosuppression, and previous chemotherapy or radiotherapy.[2] Distinguishing between true dual primary malignancies and metastatic disease is crucial, as the latter often necessitates palliative care, whereas synchronous primaries require site-specific management strategies.[3]

Leiomyosarcoma (LMS) is a rare, aggressive mesenchymal tumor that arises from smooth muscle cells and accounts for approximately 1% of all uterine malignancies.[4] In contrast, pulmonary adenocarcinoma is the most common subtype of nonsmall cell lung cancer (NSCLC), frequently associated with genetic mutations such as epidermal growth factor receptor (EGFR) alterations, particularly in nonsmoking female patients.[5] The co-occurrence of these malignancies poses significant diagnostic and therapeutic challenges, as illustrated in the present case.

This case report describes a 65-year-old female diagnosed with both uterine LMS and pulmonary adenocarcinoma, initially suspected to be a metastatic lesion. The report emphasizes the importance of meticulous histopathological and genetic evaluation in distinguishing between metastatic and synchronous tumors, which ultimately influences treatment decisions and patient prognosis.

Case Description

A 65-year-old female presented to the outpatient department on September 29, 2023, with complaints of foul-smelling vaginal discharge, irregular menses for 1 year, lower limb swelling, loss of appetite, general weakness, and a nonproductive cough. Her medical history included treatment for uterine fibroids 23 years prior, an unsuccessful *in vitro* fertilization attempt, and a 25-year history of schizophrenia. She was a nonsmoker and did not consume alcohol.

Physical examination revealed pitting pedal edema without supraclavicular lymphadenopathy. Abdominal examination was unremarkable. Pelvic examination showed a necrotic mass protruding from the vagina with purulent discharge. Digital rectal examination was negative for blood.

Ultrasound imaging identified a well-defined pelvic solid organ lesion measuring approximately 105 × 76 mm, originating from the uterus with minimal vascularity. Pelvic computed tomography (CT) scan confirmed a large pedunculated submucosal uterine fibroid prolapsing into the endocervical and vaginal canal, along with an intramural fibroid in the uterine fundus.

On October 3, 2023, the patient underwent examination under anesthesia with biopsy and drainage of pyometra. Subsequent imaging on October 11, 2023, including contrast-enhanced CT of the chest and abdomen, revealed a focal heterogeneous enhancing nodule with lobulated margins in the apicoposterior segment of the left upper lung lobe, suggestive of a neoplastic lesion. Additionally, a bulky uterus with subserosal fibroids and heterogeneous fluid collection in the endometrial and endocervical regions were noted, along with mild ascites, hepatic steatosis, and cholelithiasis.

A whole-body positron emission tomography–computed tomography (PET–CT) scan on October 21, 2023, showed metabolically active lesions in both the left upper lung lobe and the uterus, raising suspicion for neoplastic changes at both sites (Fig. 1). Biopsies were performed, confirming moderately differentiated adenocarcinoma of the left lung on October 27, 2023, and LMS of the endometrial polypoid mass on November 9, 2023.

Genetic testing of the lung tumor on January 9, 2024, revealed an EGFR exon 19 deletion mutation. The patient received four cycles of chemotherapy with liposomal doxorubicin, followed by a type B radical hysterectomy on March 4, 2024. Histopathology indicated high-grade malignancy with mixed carcinoma and sarcoma elements, consistent with LMS. Postoperatively, from April 11 to April 23, 2024, she underwent radical radiotherapy for the lung adenocarcinoma.

She was treated with adjuvant chemotherapy followed by radiotherapy, which was completed in April 2024.

A PET-CT scan done before the initiation of treatment on October 21, 2023, and again on July 18, 2024, after completion of chemoradiation, demonstrated an interval response (Fig. 2).

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How to cite this article: Arpan, Kaur A, Dutta A, *et al.* Synchronous Uterine Leiomyosarcoma and Pulmonary Adenocarcinoma: A Rare Oncological Puzzle. J Assoc Physicians India 2026;74(6):22–24.

Fig. 1: Positron emission tomography–computed tomography done before treatment on October 21, 2023

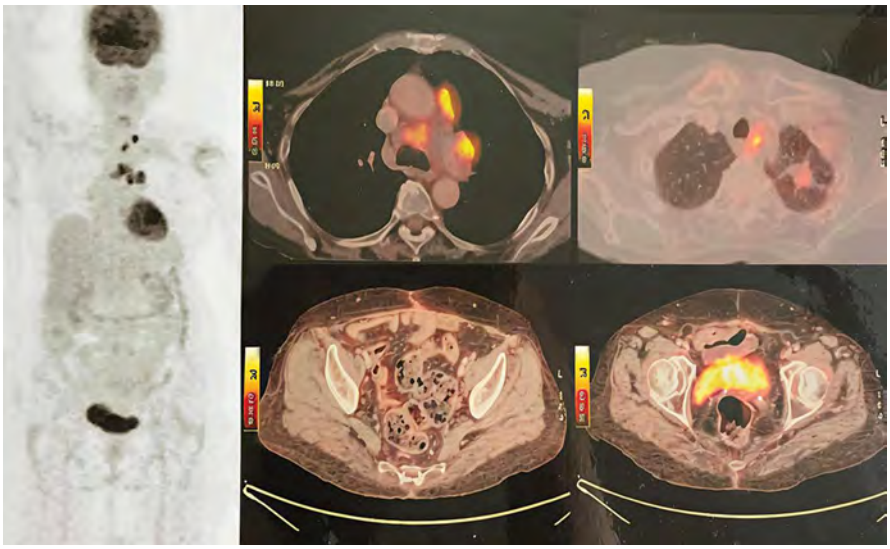

Fig. 2: Positron emission tomography–computed tomography done on July 18, 2024 (postchemoradiotherapy)

The latest PET-CT conducted on February 6, 2025**,** revealed a mildly metabolically active, heterogeneously enhancing residual mass lesion with spiculated margins in the apical-posterior segment of the left upper lobe of the lung (Fig. 3). This was consistent with a residual mildly metabolically active soft tissue density mass, suggestive of partial response to treatment compared with previous imaging. Additionally, there was metabolically active multiple mediastinal lymphadenopathy, indicative of residual metastatic mediastinal lymph node infiltration, also suggesting partial response to treatment. Importantly, there was no significant metabolically active mass or lesion in the pelvic cavity, thus ruling out any residual or recurrent primary malignant lesion in this region.

The patient is currently under regular follow-up and is improving clinically.

Discussion

The diagnosis and management of dual primary malignancies require a comprehensive approach involving histopathological differentiation, immunohistochemical analysis, and genetic profiling. In this case, both tumors exhibited distinct morphological features and genetic alterations, supporting their classification as separate primary malignancies rather than metastatic disease.

Leiomyosarcoma of the uterus is known for its aggressive nature and poor prognosis, with a five-year survival rate ranging from 25 to 50%, depending on the stage at diagnosis.[6] Common metastatic sites include the lungs, liver, and peritoneal cavity. The presence of a lung lesion in a patient with uterine LMS often raises suspicion of metastatic spread, but the histological confirmation of adenocarcinoma in the lung tumor ruled out this possibility in our case.[7]

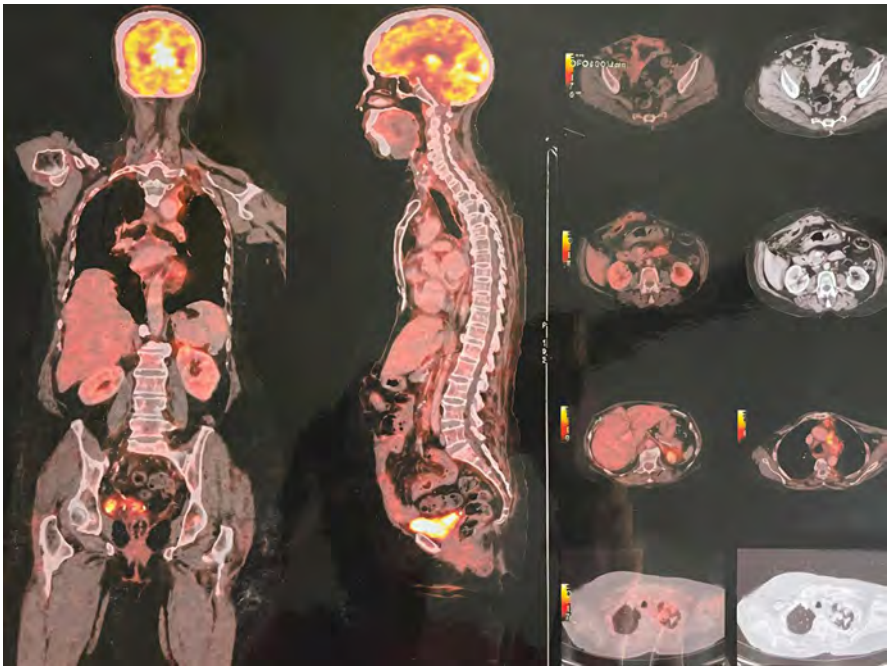

Fig. 3: Positron emission tomography–computed tomography done at latest follow-up on February 6, 2025

Pulmonary adenocarcinoma is frequently driven by mutations in genes such as *EGFR*, *ALK*, *KRAS*, and *MET*, which influence therapeutic strategies.[8] In our case, the identification of an EGFR exon 19 deletion mutation guided the initiation of targeted therapy with tyrosine kinase inhibitors (TKIs), which have demonstrated superior efficacy compared to conventional chemotherapy in EGFR-mutant NSCLC.[9]

The management of synchronous malignancies requires a multidisciplinary approach. The treatment plan for this patient included systemic chemotherapy with liposomal doxorubicin to target both malignancies, followed by surgical resection of the uterine tumor and subsequent radiotherapy for lung adenocarcinoma. Studies have shown that neoadjuvant chemotherapy can improve surgical outcomes in uterine LMS, while adjuvant radiotherapy has been associated with improved local control.[10] For lung adenocarcinoma, EGFR-targeted therapy has significantly improved progression-free survival, particularly in patients with activating mutations.[11]

Despite advances in cancer therapy, patients with dual primary malignancies face a complex disease trajectory with increased morbidity and treatment-related toxicity. Prognosis depends on the stage at diagnosis, tumor biology, and treatment response. Regular surveillance and early detection through imaging and biomarker analysis are crucial for optimizing outcomes.[12]

This case highlights the necessity of thorough diagnostic evaluation in patients with multiple tumors to differentiate between metastatic disease and dual primary malignancies. It also underscores the role of personalized treatment strategies incorporating histopathology, molecular genetics, and multimodal therapy.

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CASE REPORT

Diffuse Alveolar Hemorrhage in a Case of Granulomatosis with Polyangiitis: A Case Report

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Received: 26 April 2025; *Accepted:* 17 March 2026

Abstract

Diffuse alveolar hemorrhage (DAH) is a life-threatening pulmonary condition characterized by widespread bleeding into the alveoli, leading to respiratory failure. It can result from various etiologies, including autoimmune disorders, drug reactions, and infections. Here is a rare case of a 37-year-old male who presented with progressive dyspnea, hemoptysis, and hypoxemia. Chest imaging and bronchoscopy confirmed the diagnosis of DAH, while laboratory tests revealed ANCA-associated vasculitis. On diagnosis, the patient with granulomatosis with polyangiitis was initiated on corticosteroids and cyclophosphamide. Early initiation of immunosuppressive therapy and supportive care plays a crucial role in disease management, reducing morbidity in such cases.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1553

Introduction

Diffuse alveolar hemorrhage (DAH) is a rare, life-threatening pulmonary condition characterized by hemorrhage into the alveolar spaces.[1] Patients classically present with hemoptysis, dyspnea, anemia, acute hypoxemic respiratory failure, and new-onset infiltrates on chest imaging.[1] DAH is considered a medical emergency, and to reduce significant morbidity and mortality, immediate and prompt management is required.

Granulomatosis with polyangiitis (GPA) is an ANCA-associated small- to medium-vessel vasculitis that primarily includes the upper respiratory tract, lower respiratory tract, and renal system.[2] Although pulmonary involvement such as interstitial lung disease, nodular lesions, and cavitation are common, DAH is a rare manifestation of GPA. It is associated with a very high risk of respiratory failure.[2] Diagnosing GPA with the primary presentation of alveolar hemorrhage can be difficult, especially when there is no other system involved.

Here is a case of GPA, with an initial presentation of DAH, reported for its rarity.

Case Description

A 37-year-old male laborer by occupation, nonsmoker, presented to the emergency with complaints of dyspnea for four days, cough for 5 days, and hemoptysis for 5 days. Dyspnea was progressive, corresponding to a severity of modified Medical Research Council (mMRC) grade IV, without any history of orthopnea or paroxysmal nocturnal dyspnea. Dry cough was associated with frank hemoptysis characterized by multiple episodes of 15–20 mL each for 4 days. He also reported a history of low-grade fever for 1 day. No history of joint pains, skin rashes, dry mouth or eyes, or fatigue was noted.

On admission, the patient had tachycardia with a pulse rate of 140/min, tachypnea with a respiratory rate of 50/min, room-air saturation of 64%, and a blood pressure of 110/90 mm Hg. Respiratory system examination revealed bilateral diffuse inspiratory crackles. Initial laboratory investigations showed microcytic hypochromic anemia with a hemoglobin level of 6.6 gm/dL, total leucocyte count of 12,300, and elevated ESR and CRP levels (60 mm/h and 42.3.15 mg/L, respectively) (Table 1). An arterial blood gas analysis revealed acute hypoxemic respiratory failure, with a PaO_2/FiO_2 ratio of 95, consistent with severe ARDS. Chest radiograph showed diffuse alveolar opacities in bilateral lung fields (Fig. 1). At the same time, a high-resolution computed tomography (HRCT) of the thorax showed poorly defined ground-glass opacities with early alveolar consolidation, involving central to peripheral lung fields in both lungs (Fig. 2). 2D echocardiography showed an ejection fraction of 60% with mild pulmonary arterial hypertension and mild tricuspid regurgitation. Initial management comprised noninvasive ventilation and IV antibiotics (ceftriaxone 1 gm every 12 hours). With the above findings, an initial differential of viral pneumonia and DAH was considered. Further investigation of the throat swab for H1N1 and COVID-19 returned negative. Autoimmune screening showed a positive cytoplasmic ANCA (cANCA) with proteinase 3 (PR3) specificity, while perinuclear ANCA (pANCA), antinuclear antibodies (ANA), and anticyclic citrullinated peptide (anti-CCP) were negative.

Given the high clinical suspicion of diffuse alveolar hemorrhage associated with ANCA-associated vasculitis, a bronchoscopy with bronchoalveolar lavage (BAL) with transbronchial lung biopsy (TBLB) was performed. This revealed persistently bloody fluid. The cytological analysis of BAL showed abundant hemosiderin-laden macrophages without atypical cells. A TBLB showed alveolar spaces with colored macrophages and hemosiderin deposits, which was confirmed by Prussian blue staining. There was no histological evidence of granuloma formation, capillaritis, or vasculitis (Fig. 3). On confirming the diagnosis of DAH on BAL cytology, a differential of GPA (small-vessel vasculitis) was considered.

The patient was initiated on pulse therapy of IV methylprednisolone (MPS) for 5 days along with IV cyclophosphamide at 15 mg/kg every second week for three doses. An X-ray PNS and nasal examination were done to look for upper respiratory tract involvement, which were normal. The renal evaluation revealed that all routine renal parameters were within the normal range. In the next 2 weeks, the patient demonstrated satisfactory clinical improvement (Fig. 4), with resolving radiological infiltrates and reduced oxygen requirements. He was weaned off noninvasive ventilator support.

During his hospital stay, after 2 weeks, the patient developed multiple erythematous purpuric lesions and ecchymoses over the extensor aspects of both upper and lower limbs (Fig. 5). A skin biopsy from these lesions revealed leukocytoclastic vasculitis involving small vessels, characterized by disruption of vessel walls, red blood cell extravasation, and a prominent inflammatory infiltrate composed of neutrophils, lymphocytes,

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How to cite this article: Shaily KP, Mandadi M, Navothna S, *et al.* Diffuse Alveolar Hemorrhage in a Case of Granulomatosis with Polyangiitis: A Case Report. J Assoc Physicians India 2026;74(6):25–27.

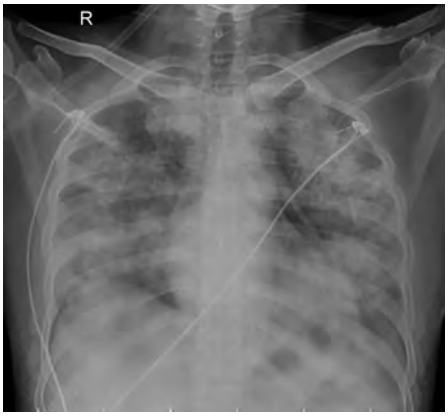

Fig. 1: Chest X-ray (on admission)—showing bilateral diffuse alveolar opacities

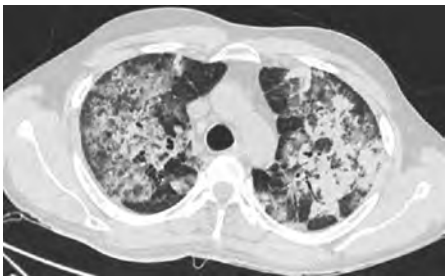

Fig. 2: HRCT thorax—showing bilateral multiple ill-defined diffuse GGOs with early alveolar consolidations, central to peripheral involvement with few areas of sparing

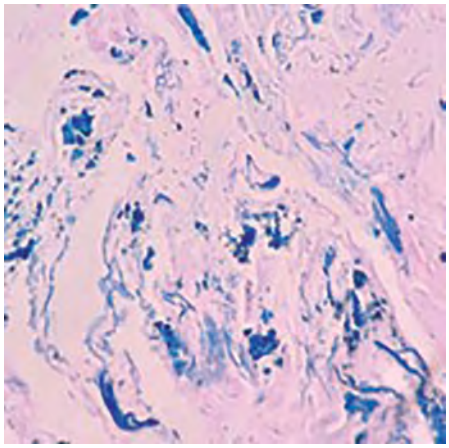

Fig. 3: Histopathological examination of TBLB–showing Prussian blue stain for hemosiderin with blue granules

Fig. 4: Chest X-ray PA view showing radiological resolution as compared to previous chest X-ray (Fig. 1)

Fig. 5: Multiple erythematous purpura and ecchymosis on the extensor aspects of the upper limbs

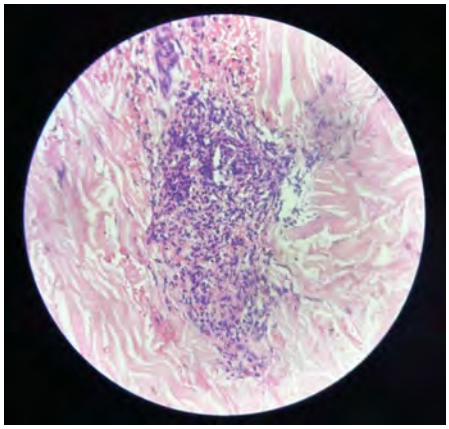

Fig. 6: HPE of skin biopsy showing disruption of small vessel wall lumen with red cell extravasation. Significant infiltration of the vessel with neutrophils, lymphocytes, and plasma cells was seen

Table 1: Laboratory investigations

Test	*Patient value*	*Reference range*
Hemoglobin	6.60 gm/dL	Male: 13.5–17.5 gm/dL
Total leukocyte count (TLC)	12,700/µL	4,000–11,000/µL
Platelets	128,000/µL	150,000–450,000/µL
Peripheral blood smear (PBS)	Microcytic hypochromic (iron deficiency anemia)	Normal RBC morphology
Liver function test (LFT)	Within normal limits (WNL)	Normal
PT/INR	13.4 s/1.13	PT: 11–15 s; INR: 0.8–1.2
Renal function test (RFT)	WNL	Normal
Urine microscopy		
Protein	Trace	Negative
Glucose	Trace	Negative
RBCs	4–5/hpf	0–2/hpf
C-reactive protein (CRP)	16.15 mg/L	< 5 mg/L
Uric acid	4.60 mg/dL	Male: 3.4–7.0 mg/dL
Erythrocyte sedimentation rate (ESR)	30 mm/h	Male: < 15 mm/h
Urine protein-creatinine ratio (UPCR)	0.05	< 0.2

and plasma cells (Fig. 6). This confirmed the diagnosis.

On follow-up, the patient was continued on tapering doses of oral MPS over 2 months with cyclophosphamide at 15 mg/kg every 3 weeks till remission. He remained asymptomatic with complete resolution of pulmonary infiltrates on imaging. Review renal evaluation remained unremarkable throughout the course, with normal renal function tests and no urinary abnormalities.

Discussion

Diffuse alveolar hemorrhage is a clinically life-threatening condition characterized by dyspnea, hemoptysis, and acute hypoxemic respiratory failure.

However, in one-third of the cases, hemoptysis may be absent, making early diagnosis challenging.[3] DAH can be caused by various etiologies, including infections, autoimmune vasculitides, coagulopathies, and drug-induced injuries. Granulomatosis with polyangiitis (GPA) is a well-known but rare contributor to DAH among the autoimmune causes.[4] Among all the causes, pulmonary hemorrhage as a primary presentation is seen in only 5–15% of GPA cases.[4]

Granulomatosis with polyangiitis is an ANCA-associated, small- to medium-vessel vasculitis characterized by necrotizing granulomatous inflammation. Although DAH is an uncommon manifestation, it is associated with increased morbidity and mortality due to severe respiratory compromise.[5] The pathophysiology of DAH in GPA is believed to involve capillaritis, which is characterized by the disruption of the alveolar-capillary basement membrane as a result of neutrophil-mediated injury. This disruption allows red blood cells to infiltrate the alveolar spaces.[6]

In our case, the patient presented with acute hemoptysis, hypoxemic respiratory failure, and bilateral alveolar infiltrates, which prompted a suspicion for DAH. The diagnosis was confirmed through bronchoscopy, which revealed a persistently bloody bronchoalveolar lavage fluid and abundant hemosiderin-laden macrophages—considered the hallmark cytological finding in DAH.[7] Although the transbronchial biopsies may frequently be nondiagnostic in small-vessel vasculitis due to sampling limitations and poor yield of the TBLB when compared to renal biopsies.[8] In this patient, the lung biopsy confirmed alveolar hemorrhage but did not reveal capillaritis or granulomatous inflammation. These findings may sometimes only be evident in more extensive surgical lung biopsies or renal biopsies when systemic involvement is present.[9]

The presence of cANCA with PR3 positivity, along with pulmonary hemorrhage and skin vasculitis confirmed on biopsy, supported the diagnosis of GPA. Although renal and upper airway involvement are common in GPA, the absence of such features does not exclude the disease, particularly in cases where pulmonary manifestations predominate.[10] Interestingly, our patient had no renal involvement throughout the course of his illness, and his renal parameters remained within normal limits on follow-up.

Treatment of DAH in GPA requires prompt and aggressive immunosuppression to halt ongoing vascular inflammation and hemorrhage. High-dose intravenous corticosteroids remain the cornerstone of initial therapy, often supplemented with additional immunosuppressive agents such as cyclophosphamide or rituximab in severe or refractory cases.[11] In our case, the patient demonstrated significant clinical and radiological improvement with the combination of corticosteroids and cyclophosphamide therapy, highlighting the potential for favorable outcomes with timely intervention. The early use of immunosuppression likely contributed to the rapid resolution of his pulmonary infiltrates and stabilized respiratory function.

This case emphasizes the importance of considering vasculitis in the differential diagnosis of DAH, particularly in younger patients without obvious infectious or cardiac etiologies. DAH may occasionally be the sole manifestation of GPA, as observed in this patient, underscoring the need for thorough autoimmune evaluation in such presentations. Early recognition and prompt initiation of immunosuppressive therapy are crucial to reducing morbidity and improving survival in these patients.

To the best of our knowledge, this represents one of the few reported cases from India of GPA presenting initially with DAH, highlighting the rarity of this presentation and the need for heightened clinical suspicion in appropriate settings.

Conclusion

This case highlights the significance of identifying diffuse alveolar hemorrhage (DAH) as a rare but life-threatening initial presentation of granulomatosis with polyangiitis (GPA). Also emphasizing the importance of early diagnosis and aggressive treatment in GPA-associated DAH to prevent severe respiratory compromise and enhance patient outcomes.

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CASE REPORT

Atypical Presentation of Raine Syndrome in a Middle-aged Lady

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Received: 11 June 2025; *Accepted:* 12 August 2025

Abstract

Raine syndrome (OMIM # 259775) is a rare disorder characterized by osteosclerotic bone dysplasia and autosomal recessive inheritance due to mutations in *FAM20C*. Classic clinical features include generalized osteosclerosis, dysmorphic facies, and thoracic hypoplasia. FGF23-mediated hypophosphatemic rickets/osteomalacia, besides osteosclerosis, occurs due to mutations in the *FAM20C* gene that encodes a Golgi-enriched fraction casein kinase involved in the mineralization of bone. Most cases were reported to be fatal during the neonatal period; however, some nonlethal variants have also been identified. Here, we report a middle-aged lady presenting with proximal myopathy. On evaluation, she was found to have hypophosphatemia due to increased renal tubular wasting with low TMP/GFR. Radiological evaluation showed findings suggestive of osteomalacia and osteosclerosis. On molecular analysis, a novel homozygous mutation, the *FAM20C* variant c.1375C>T (p.Arg459Cys) located on chromosome 7p22.3, was identified. The current case expands the phenotypic and genetic spectrum of the adult cases of nonlethal variants of Raine syndrome with hypophosphatemic osteomalacia caused by the *FAM20C* mutation.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1354

Background

Initially, in 1989, Raine et al. reported a condition in an infant with characteristic features like microcephaly, exophthalmos, low-set ears, hypoplastic nose, gingival hyperplasia, and cleft palate who died shortly after birth.[1] Radiologically, generalized osteosclerosis was observed particularly in the long bones, skull, and pelvis. In 1992, Kan and Kozlowski reported a case with a similar phenotype and coined the term "Raine syndrome".[2] The incidence of this syndrome was about 1 in 10,00,000, and most of the patients were severely affected and did not survive even into childhood. Hence, it was initially considered to be lethal.[3,4] However, a couple of decades later, two cases of nonlethal Raine syndrome were reported, contrary to the initial perception, of which one had hypophosphatemia.[5] Several cases with mild and nonlethal phenotypes were reported shortly after surviving into adulthood.[6–14] Simpson et al. identified the gene causative for Raine syndrome as the *FAM20C* gene located on chromosome 7p22.3.[15] *FAM20C* (family with sequence similarity 20 member C gene) encodes an atypical kinase that plays a vital role in the normal development of bone. The *FAM20C* gene mutation hampers the mineralization of teeth and bones and also upregulates the expression of fibroblast growth factor 23 (FGF23) mRNA, thereby leading to elevated FGF23 levels resulting in hypophosphatemia.[6] Here, we report a lady with pemphigus vulgaris who was later diagnosed with Raine syndrome.

Case Description

A lady in her late 30s presented to the dermatologist with a 2-year history of skin lesions that were diagnosed as pemphigus vulgaris. She was initiated on oral prednisolone 10 mg daily, which she took for about 18 months. Due to long-term steroid use, she developed glucocorticoid-induced osteoporosis and was referred to endocrinology for further evaluation. She was the second-born of second-degree consanguineous parents. At the age of 5 years, she had a premature loss of teeth, and at 10 years, she became edentulous, requiring a total dental prosthesis. On further evaluation, she had gradually progressive proximal myopathy for the past few years, causing difficulty in performing daily household chores. She had a nonconsanguineous marriage and has an unaffected child. Her mother also had similar facial features with minimal weakness but was not evaluated and died a few years ago due to a possible cardiac event. Her siblings are normal. Physical examination revealed a dysmorphic face with a prominent forehead, exophthalmos, beaked nose, depressed nasal bridge, edentulous, retrognathia, and short stubby fingers (Fig. 1). Her height is 156 cm, weight is 65 kg, and BMI is 26.7 Kg/m^2. Her biochemical investigations are given in Table 1. She had vitamin D insufficiency and was treated with cholecalciferol for 6 weeks before further evaluation, which showed hypophosphatemia with increased renal tubular wasting.

A dual energy X-ray absorptiometry (DXA) scan was performed with GE-Lunar Prodigy Advance, which showed increased bone mineral density in the lumbar spine with a T-score of +4.1 and a Z-score of +3.8, with normal bone mineral density in the hip, with a T-score of +1.1 and a Z-score of +1.3. Based on the above findings—osteosclerosis with hypophosphatemia and characteristic facial features, a possibility of Raine syndrome was considered. Clinical exome sequencing was performed on the Illumina sequencing platform using next-generation sequencing. A novel homozygous missense mutation in exon 8 of the *FAM20C* gene (*chr7:p.Arg459Cys*) was detected. A different missense variant (*p.Arg459Gly*) affecting the same codon has been previously reported in a patient with nonlethal Raine syndrome.[14] Her siblings and child have been counseled for evaluation and were not willing.

Treatment and Outcome

She was started on phosphorus (20–40 mg/kg/day in divided doses) and calcitriol (20–30 ng/kg/day) supplementation.[16] Proximal myopathy improved gradually over time. Currently, she can perform routine daily activities. As she is being continued on corticosteroids for pemphigus vulgaris, considering the increased risk of fractures and steroid-induced osteoporosis, she was treated with intravenous zoledronate despite high bone mineral density (BMD) in DXA.

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How to cite this article: Gogineni SN, Asirvatham AR, Ranjan A, *et al.* Atypical Presentation of Raine Syndrome in a Middle-aged Lady. J Assoc Physicians India 2026;74(6):28–31.

Figs 1A to G: (A) Dysmorphic face; (B) Edentulousness; (C) Short, stubby fingers; (D) Short 3rd and 4th distal phalanges; (E) X-ray pelvis AP view: Endosteal thickening with looser zones in the shaft of femur, sclerosis in acetabular cavity and pelvic bones; (F) X-ray knee joint lateral view: tibial endosteal thickening, periosteal bone formation, and patellar osteophytes; (G) X-ray dorsolumbar spine AP view: syndesmophytes with scoliosis, ligament calcifications

Table 1: Laboratory results

Parameters	*At initial presentation*	*After 6 weeks (after vitamin D correction)*	*Reference range*
Serum calcium (mg/dL)	9.1	9.2	8.8–10.6
Serum phosphorus (mg/dL)	1.9	2.2	2.5–4.5
25-hydroxyvitamin D (ng/mL)	16	32	>30
Alkaline phosphatase (mIU/L)	97	87	30–120
iParathyroid hormone (pg/mL)	95	60	15–65
FGF23 (RU/mL)	N/A	188.8	0–150
TmP/GFR (mg/dL)	N/A	1.1	2.6–3.80
Serum creatinine (mg/dL)	0.8	0.9	0.5–1.1

FGF23, fibroblast growth factor 23; TmP/GFR, tubular maximum reabsorption of phosphate/glomerular filtration rate

Discussion

Here, we report a case of a mild nonlethal variant of Raine syndrome who survived into her thirties, undiagnosed and untreated. To date, besides the pediatric cases, three adult cases of nonlethal Raine syndrome have been reported.[12–14] Clinical phenotypes and age of presentation varied significantly from individual to individual and have been described in Table 2.

FGF23-mediated hypophosphatemia and hypophosphatemic rickets were reported in variants of Raine syndrome.[5–7,17] There are several genes found to be responsible for the inherited forms of rickets, such as DMP1, FGF23, ENPP1, and PHEX. Initially found to be associated with Raine syndrome, the FAM20C gene was later implicated in FGF23-mediated autosomal recessive hypophosphatemia. It encodes a Golgi apparatus casein kinase,

Table 2: Phenotypic and genetic presentation of adult patients with nonlethal Raine syndrome

	Takeyari et al.,[13]	*Rolvein et al.,*[12]	*Mamedova et al.,*[14]	*Current case*
Gender	Male	Male	Female	Female
Age (years)	61	72	39	38
Presentation	Short stature; loss of teeth at 17 years	Spontaneous osteonecrosis of the right knee	Loss of teeth at 18 years	Loss of teeth by 10 years; proximal myopathy
Characteristic facies	Not mentioned	–	+	+
Dentition abnormalities	+	–	+	+
Height (cm)	153	183	166	156
Skeletal abnormalities	–	–	Shortening of distal phalanges	Shortening of distal phalanges
Intracranial calcifications	+	Not investigated	+	Not investigated
Hypophosphatemia	+	+	+	+
DXA scan				
Lumbar spine	+6.3 (Z score)	+7.5 (T score)	+3.1 (Z score)	+3.8 (Z score)
Hip (Left)	+3.6 (Z score)	+4.7 (T score)	−1.8 (Z score)	+1.3 (Z score)
Molecular Analysis	Homozygous variant: c.1222C>T (Arg408Trp) in exon 6	Two variants: heterozygous c.906C > A (p.Phe302Leu) and homozygous c.952_956+ 30dup	Two heterozygous variants: c.1107_1108insTACTG (p.Tyr369 fs) in exon 6; c.1375C > G (p.Arg459Gly) in exon 8	Homozygous variant: c.1375C>T (p.Arg459Cys) in exon 8

+, indicates presence of the signs/symptoms; –, indicates absence

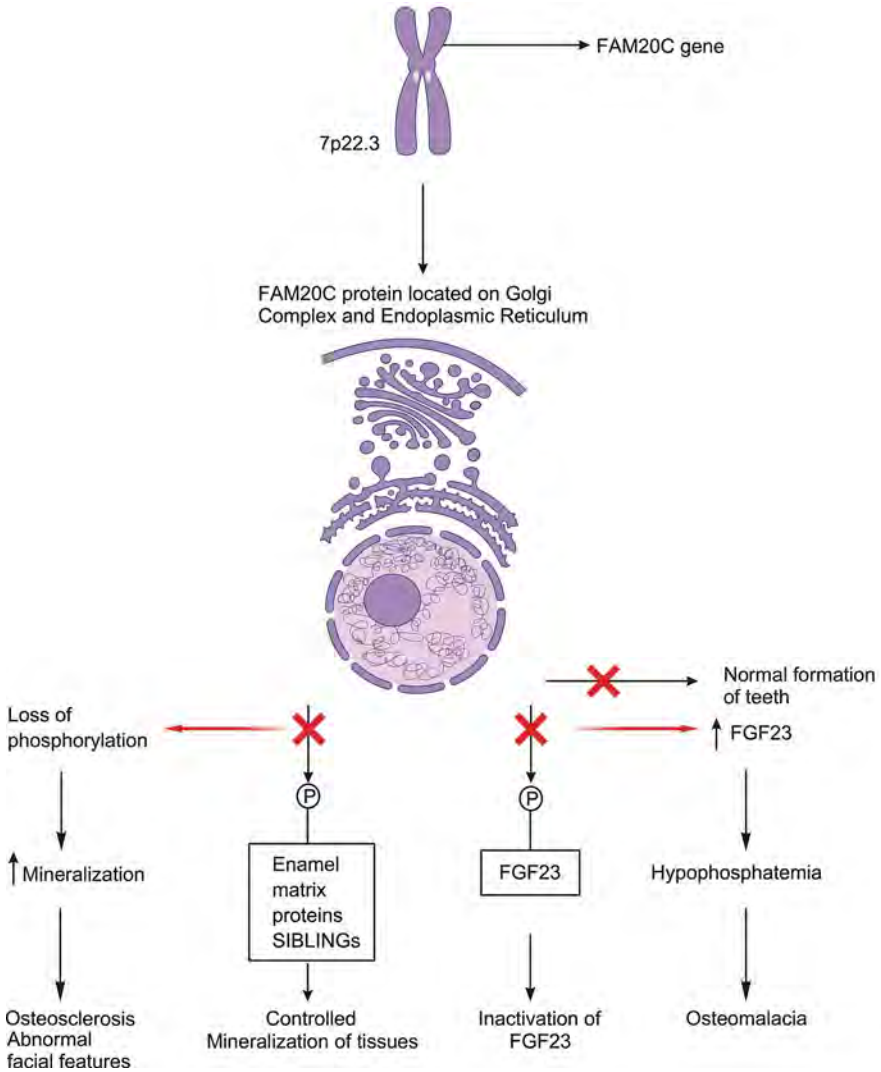

Fig. 2: Overview of the pathogenesis of Raine syndrome. *FAM20C* protein ensures proper and regulated mineralization of tissues and phosphate homeostasis through phosphorylation of SIBLINGs and FGF23, respectively. Hence, alteration of the *FAM20C* protein due to *FAM20C* gene mutations results in altered mineralization and hypophosphatemic osteomalacia (SIBLINGs, small integrin-binding ligand N-linked glycoproteins; FGF23, fibroblast growth factor 23)

which is essential for the phosphorylation of FGF23 and the secretory calcium-binding phosphoprotein family, which includes enamel matrix proteins and small integrin-binding ligand N-linked glycoproteins (SIBLINGs). These proteins are found to play a prominent role in the mineralization of tissues, and their action is regulated by *FAM20C*. In *FAM20C* mutations, the inhibition of the proteins is lost, and increased mineralization and bone formation are seen, resulting in osteosclerosis. By mediating phosphorylation at Ser180 in FGF23, it interferes with O-glycosylation mediated by GALNT3, resulting in increased susceptibility to cleavage by subtilisin-like proprotein convertase three and subsequent FGF23 inactivation. It also phosphorylates DMP1, which inactivates FGF23 and thus contributes to hypophosphatemia in Raine syndrome.[18–20] The osseous features seen in Raine syndrome are attributed to the hypophosphorylation of SIBLINGs. Pathogenesis is illustrated in Figure 2. Our patient has hypophosphatemic osteomalacia associated with increased bone mineral density on DXA scan, which confirms the dual effect of the *FAM20C* gene mutation, causing osteosclerosis as well as FGF23-mediated osteomalacia. Osteoblasts, ameloblasts, and odontoblasts express *FAM20C*. It is thought to be crucial in murine tooth formation, and patients with *FAM20C* compound heterozygous mutations were reported to have dental abnormalities and premature loss of teeth.[6,17,21] Our patient also has worn-down teeth, which strongly favors the diagnosis. These findings are in concordance with *FAM20C*-deficient mice having amelogenesis imperfecta.[22] Clinical clues to diagnose the variants of Raine syndrome due to *FAM20C* gene mutations are the coexistence of osteosclerosis with osteomalacia and premature loss of teeth. Our patient had characteristic facies, short phalanges of the hands, premature loss of teeth, osteosclerosis with increased bone mineral density in DXA, and FGF23-mediated hypophosphatemic osteomalacia with a mutation in the *FAM20C* gene, which are characteristic of Raine syndrome. Based on the data available on genetics in the literature, it was observed that patients who had mutations in the highly conserved C-terminal region had a lethal phenotype. In contrast, most patients who had survived and had a nonlethal phenotype were found to have mutations in the N-terminal part of *FAM20C*, with few exceptions to the above statement.[3,14] In our case, a novel homozygous mutation of the *FAM20C* gene was identified. A similar mutation was previously reported in the ClinVar database as a variant of uncertain significance for a case presenting as Raine syndrome (Variation ID: 930917, Accession: VCV000930917.6). This variant has not been reported in the 1,000 genomes, gnomAD (v3.1), and gnomAD (v2.1) databases. The in-silico predictions of the variant are probably damaging by PolyPhen-2(HumDiv), SIFT, and MutationTaster2. Even though functional studies were not performed in our case, clinical clues strengthen the diagnosis of Raine syndrome. As per our knowledge, there was no association between Raine syndrome and Pemphigus vulgaris in the literature.

Conclusion

Raine syndrome can be nonlethal and present in adulthood. Clinical clues and high BMD despite osteomalacia favor the diagnosis. In our case, we report a novel homozygous mutation in *FAM20C* that extends the clinical and genetic spectrum of patients with *FAM20C* gene mutations causing Raine syndrome.

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CASE REPORT

Index Presentation of Diabetes Mellitus as a Hyperkinetic Movement Disorder: A Thin-veiled Entity Colloquially called Diabetic Striatopathy

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Received: 20 May 2024; *Accepted:* 13 September 2025

Abstract

Often referred to as the diabetes capital of the world, new-wave urbanization and westernization of lifestyle have rendered India vulnerable to the so-called lifestyle diseases, especially diabetes mellitus. Arguably the most characterized of diseases, diabetes somehow still has a few tricks up its sleeve. Diabetic striatopathy (DS), also known as hyperglycemic nonketotic hemichorea/hemiballism, chorea/hemichorea associated with nonketotic hyperglycemia, diabetic hemiballism/hemichorea, or chorea-hyperglycemia-basal ganglia syndrome, is a long-known disease of many names but sparse characterization. With an estimated prevalence of 1 in 100,000 (Ondo, 2011), DS is, in our opinion, greatly underestimated and is often misdiagnosed as intracerebral hemorrhage (ICH), which is a travesty given the excellent prognosis DS carries, even with just the control of blood sugar levels. Here, we describe the case of a 73-year-old male, previously undiagnosed diabetic, who presented with an acute-onset movement disorder, initially thought to have had a stroke, but was later diagnosed as DS. We also discuss in brief the pathophysiology and treatment options.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1392

Case Description

A 73-year-old male presented to the emergency department with complaints of progressively increasing abnormal, violent flinging movements of the left arm for 2 days and abnormal mentation for a few hours. Relatives reported that the movements came on almost abruptly and began with the patient twisting and flinging his left arm violently, about an hour after having his lunch 2 days prior to presentation. The patient complained of an "inability to control his arm," but the seemingly involuntary movements would settle down for some time only to come back on later. The movements had progressively increased in frequency and amplitude, and consequently it became difficult for the patient to carry out his daily chores. The patient, however, had no discomfort in walking or comprehending conversations, and the symptoms were conspicuously absent when he first woke up in the morning. These movements became exaggerated after the patient had his morning tea on the day of presentation, and relatives reported that the patient became increasingly agitated in the hours leading to presentation. The patient had no history of diabetes mellitus or hypertension but was an avid smoker with 60 pack years.

Vitals showed tachycardia (107 beats per minute) with rather normal blood pressure (130/70 mm Hg, right arm supine). The patient had an aggressive, cannula-pulling behavior, and a reliable neurological examination was out of the question on presentation. Involuntary writhing, nonpurposeful, and violent movements of the left upper limb were observed, involving the proximal arm more than the distal, occurring about five times per minute. Twitching of the tongue and face was also observed with slurring of speech. The patient was seen to move all four limbs but was uncooperative and did not follow commands. There was, however, no history of loss of consciousness, incontinence, or hemoptysis. The patient was evaluated for an acute-onset hyperkinetic (left hemichoretic/ballistic) movement disorder with altered mentation, and stroke, infectious, paraneoplastic, and autoimmune etiologies were considered. Blood was drawn for routine investigations, and the patient was given intravenous (IV) haloperidol, after which the movements settled down transiently and the patient was taken for a plain computed tomography (CT) of the head, which showed no gross abnormality. The patient's mentation did not improve after haloperidol, and the movements came back on in about 10 minutes. Random blood sugar was reported to be 709 mg/dL, and the patient was immediately started on IV fluids and human insulin infusion with one-hourly charting. As the blood sugar levels fell below 300 mg/dL, the movements completely ceased, and sensorium became normal over the next few hours. Laboratory reports showed an elevated glycated hemoglobin (HbA1c) (14.4%) with unremarkable liver and kidney function tests. Blood gases showed normal pH, bicarbonate, and lactate levels. The dipstick was negative for urinary ketones.

Postresolution, the patient was fully cooperative, and a detailed neurological examination was carried out and no abnormality was noted. Electroencephalogram (EEG) revealed no epileptiform discharges, while magnetic resonance imaging (MRI) of the brain showed right striatal hyperintensities with negative diffusion-weighted imaging (Fig. 1). The patient was started on treatment for diabetes, and a workup for macro- and microvascular complications was done.

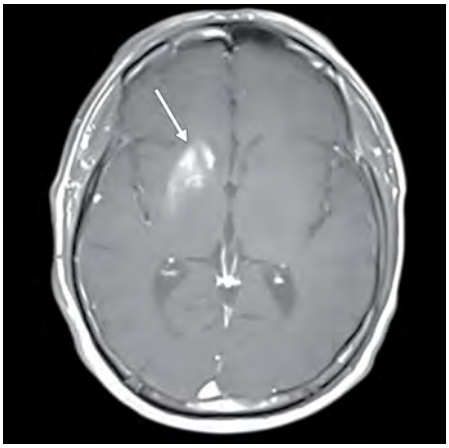

Fig. 1: T1-weighted magnetic resonance image showing hyperintensities in right caudate and putamen nuclei (white arrow). Imaging may be normal in up to 10% cases of diabetic striatopathy

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How to cite this article: Agrawal BK, Singhal K, Sharma NK, *et al.* Index Presentation of Diabetes Mellitus as a Hyperkinetic Movement Disorder: A Thin-veiled Entity Colloquially called Diabetic Striatopathy. J Assoc Physicians India 2026;74(6):32–33.

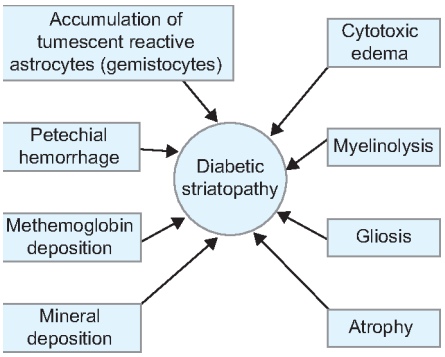

Fig. 2: The ominous octet of diabetic striatopathy

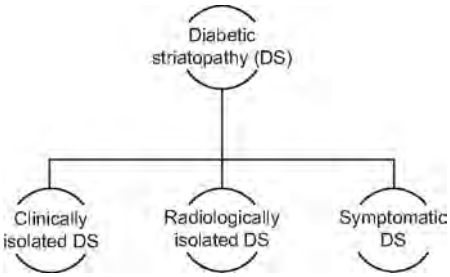

Fig. 3: Classification of diabetic striatopathy according to clinical and imaging presentations

The patient was diagnosed with diabetic striatopathy (DS) and was discharged with full resolution of symptoms. The patient has been compliant with treatment and has not reported any recurrence of symptoms since.

Discussion

Conditional on an appropriate diagnosis, a hemiballistic state secondary to striatopathy (DS) can be considered a disease-defining characteristic of diabetes.[1,2] Though the current nomenclature is largely ambiguous with numerous loose ends, the general usage is to define DS as a hyperglycemic condition associated with chorea/ballism and/or striatal hyperdensity on CT/hyperintensity on T1-weighted MRI.[3]

The exact pathophysiology remains elusive, with many studies suggesting as many hypotheses. A simple yet elegant explanation is that hyperglycemia-induced hyperviscosity leads to decreased perfusion and increased anaerobic respiration in the basal ganglia cells, which results in low levels of gamma-aminobutyric acid (GABA) in striatal nuclei, causing disinhibition.[1–3] Multiple other hypotheses have been put forth, which have been summarized by Dubey et al. as the ominous octet (Fig. 2).[2]

Diabetic striatopathy typically occurs in patients with long-standing, poorly controlled diabetes mellitus but can be seen as a first presentation in up to 17% cases.[1] Most cases present as a nonketotic hemiballistic disease with a slight preponderance for the female sex and Asian race.[4–6] Up to 10% cases may have bilateral involvement, and symptoms might persist even after resolution of the hyperglycemic state. Some patients might experience a prodrome comprised of varied symptoms (chest pain, dizziness, hemiparesis, abdominal distress) and may show progression of chorea/ballismus from upper limb to lower limbs (more common) and vice versa. The symptoms reportedly disappear during sleep.

A low threshold for diagnosis and a high degree of clinical suspicion are needed for diagnosis. CT and MRI are the most frequent modalities for diagnosis, with MRI showing better sensitivity than CT. A contralateral hyperintense striatum on T1-weighted imaging without surrounding edema or mass effect, along with hyperglycemia and hemiballistic/choreiform movements, is pathognomonic of DS. Isolated putaminal involvement is the most frequent finding, followed by combined involvement of the caudate nucleus and putamen and, rarely, the simultaneous involvement of all three striatal components (putamen, caudate, and globus pallidus) can be seen.[1,7]

A clinico-radiological discordance, however, exists. Up to 7% symptomatic patients have no radiological abnormality, and 2% asymptomatic cases have been reported to have pathognomonic MRI.[8] Thus, a classification system[2] has been proposed to streamline the terminology (Fig. 3).

Symptomatic DS is by far the most common presentation, followed by clinically isolated DS. Treatment of the condition is straightforward with adequate hydration and control of hyperglycemia. Most patients respond adequately to glycemic control, with a small subset requiring additional drugs such as haloperidol or tetrabenazine on discharge.[1,7] The disease as such carries an excellent prognosis with appropriate treatment, though other etiologies (stroke, infections, malignancy/paraneoplastic syndrome, autoimmune disorders, metabolic disorders—Wilson's disease, hemochromatosis) must be ruled out first to avoid therapeutic inertia.

Patients almost always show complete reversal with treatment, and the disease carries an excellent prognosis. A misdiagnosis and/or administration of sedatives to control the disorder may result in deep sedation and/or respiratory arrest and mortality. Thus, prompt recognition of the disorder is necessary.

Conclusion

Diabetic striatopathy is a (not so) rare disorder that can complicate diabetes mellitus. Commonly a complication of long-standing diabetes, it may occur as a first presentation in up to 17% cases. Knowledge of the condition is invaluable and pertinent, especially to Indian physicians given the disease burden, excellent reversibility, and favorable prognosis vis-à-vis the most common (mis)diagnosis of ICH. However, keeping in mind the epidemiological parameters, stroke and DS might coexist, given the confounding risk factors, and a de facto diagnosis of DS should never be made without ruling out stroke.

Conflicts of Interest

Nil.

Financial Relationships

All authors declare that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other Relationships

All authors declare that there are no other relationships or activities that could appear to have influenced the submitted work.

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CASE REPORT

An Unusual Case Report of Pseudothalamic Pattern of Sensory Loss in Lateral Medullary Syndrome

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Received: 03 March 2025; *Accepted:* 23 May 2025

Abstract

Lateral medullary syndrome is a collection of different neurological symptoms after ischemic/hemorrhagic insult to either the posterior inferior cerebellar artery/vertebral artery or rarely the anterior inferior cerebellar artery, causing infarction of ipsilateral cerebellum and posterolateral medulla (Tiedt and Weidauer, 2013). Dizziness, nausea, vertigo, vomiting, nystagmus, ataxia, dysphagia, hoarseness of voice, ptosis, and sensory impairment of face and body are typical. Here we report an unusual presentation of a 47-year-old female who was hypertensive and diabetic and who complained of vertigo, nausea, vomiting, slurring of speech, facial deviation toward the left, and loss of pain and temperature over the right side of the face and body without any difficulty in swallowing or nasal regurgitation. The patient was eventually diagnosed with left lateral medullary syndrome, drawing attention to the rare and unusual presentation of the same.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1549

Introduction

Lateral medullary syndrome (Wallenberg syndrome) is caused by ischemia/infarction of vertebral artery or posterior inferior cerebellar artery (PICA) or rarely anterior inferior cerebellar artery (AICA).[1] The syndrome affects inferior cerebellar peduncle, spinal trigeminal nucleus, vagus, glossopharyngeal nerve, sympathetic fibers, spinothalamic tract, and vestibular nucleus. It thus usually causes contralateral loss of pain and temperature in trunk and limbs and ipsilateral loss of sensation on face, Horner syndrome, dysphagia, gait ataxia, absent gag reflex, and hoarseness. However, rarely, sensory loss in contralateral face and body has been described as a pseudothalamic pattern.[2]

Case Description

A 47-year-old woman, P2L2, who was hypertensive and diabetic for the last 2 years and was noncomplaint with medication, presented to us in the emergency department with chief complaints of nausea, vomiting (five to six episodes), and vertigo for the last 12 hours. Within the next 6 hours, the patient noticed slurring of speech along with tingling sensation and reduced sensation on the right side of the face and body. The patient started having ataxia and difficulty walking without support, following which she was brought to the hospital. At presentation, blood pressure (BP) was 190/110 mm Hg, heart rate was 90 beats/minute and regular, respiratory rate was 12/minute, and dextrose was 328 mg/dL.

A detailed neurological examination showed intact higher mental function. On cranial nerve examination, there was normal pupillary reaction and no extraocular muscle involvement with partial ptosis on the left side. There were small saccadic movements toward the right side with relative difficulty in tracking moving objects toward the right. There was loss of pain and temperature sensations on the right side of the face. Jaw jerk was absent. There was right-sided upper motor neuron (UMN) type facial weakness evident by facial deviation to the left and partial loss of nasolabial folds on the right with preserved eye closure and forehead wrinkling. The patient had left-sided sensorineural hearing loss. The patient had a preserved gag reflex, palatal and tongue movements, and shrugging of shoulders. She had left-sided cerebellar signs, scanning speech, a broad-based gait, and swaying mostly toward the left. She was unable to do finger–nose test or heel–shin test with the left-sided limbs.

On motor examination, tone, power, and bulk were grossly normal and symmetrical in bilateral upper and lower limbs. Deep tendon reflexes were not exaggerated, and plantars were bilaterally flexor. On sensory examination, pain and temperature sensations were reduced on the right side. Joint position and vibration sense were grossly preserved. There was no bowel or bladder involvement (Fig. 1).

The above clinical evaluation corresponded to left lateral medullary syndrome. Magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) was suggestive of DWI restriction with reduced ADC in the left lateral pontomedullary junction involving the inferior and middle cerebellar peduncles. Angiography was suggestive of atherosclerotic irregularity in the left AICA. The patient was started on antiplatelets and high-dose statin. Physiotherapy was advised (Fig. 2).

Discussion

Lateral medullary syndrome has various neurological manifestations. It usually

Fig. 1: Right-sided UMN facial palsy in the patient

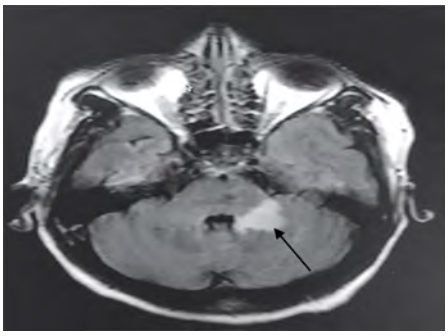

Fig. 2: MRI FLAIR sequence showing left lateral pontomedullary infarct (arrows)

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How to cite this article: Ballabh R, Chakraborty A, Kumar S, *et al.* An Unusual Case Report of Pseudothalamic Pattern of Sensory Loss in Lateral Medullary Syndrome. J Assoc Physicians India 2026;74(6):34–36.

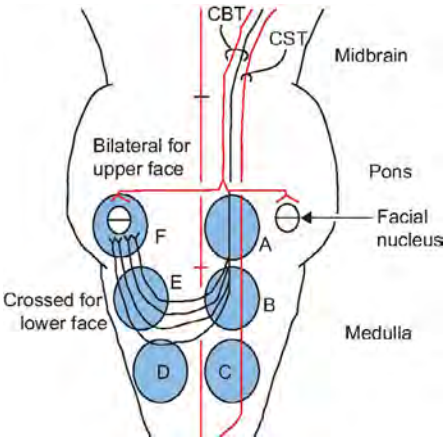

Fig. 3: Hypothetical looping of corticobulbar fibers before reaching the facial nucleus

presents with dysphagia, hoarseness, ataxia, nystagmus, and crossed sensory deficits.[2] What was unusual in our case was that there was contralateral UMN facial palsy along with contralateral facial sensation loss with no involvement of 9th, 10th, and 11th cranial nerves.[3] Although PICA and vertebral arteries are commonly implicated, rarely the cause can be the AICA as seen in our case. Facial involvement is usually rare; ipsilateral facial weakness may occur due to involvement of caudal part of ipsilateral facial nucleus. Contralateral UMN facial palsy may occur due to the hypothetical looping of corticobulbar fibers before reaching facial nucleus (Fig. 3).[1]

Lateral medullary syndrome is characterized by contralateral loss of pain and temperature over the trunk and limbs due to involvement of spinothalamic tract. It can be associated with various patterns of facial sensation loss, including ipsilateral, contralateral, or bilateral facial sensory impairment. This is due to specific somatotopic organization of spinothalamic tract, with cervical afferent fibers arranged medially and lumbosacral fibers arranged laterally. Classical lateral medullary syndrome is characterized by crossed hemianesthesia, i.e., loss of sensation of ipsilateral face and contralateral body (Stopford I).[4] In Stopford II, contralateral face and contralateral upper body are involved by more medial lesions affecting crossed ventral trigeminothalamic tract near the medial part of spinothalamic

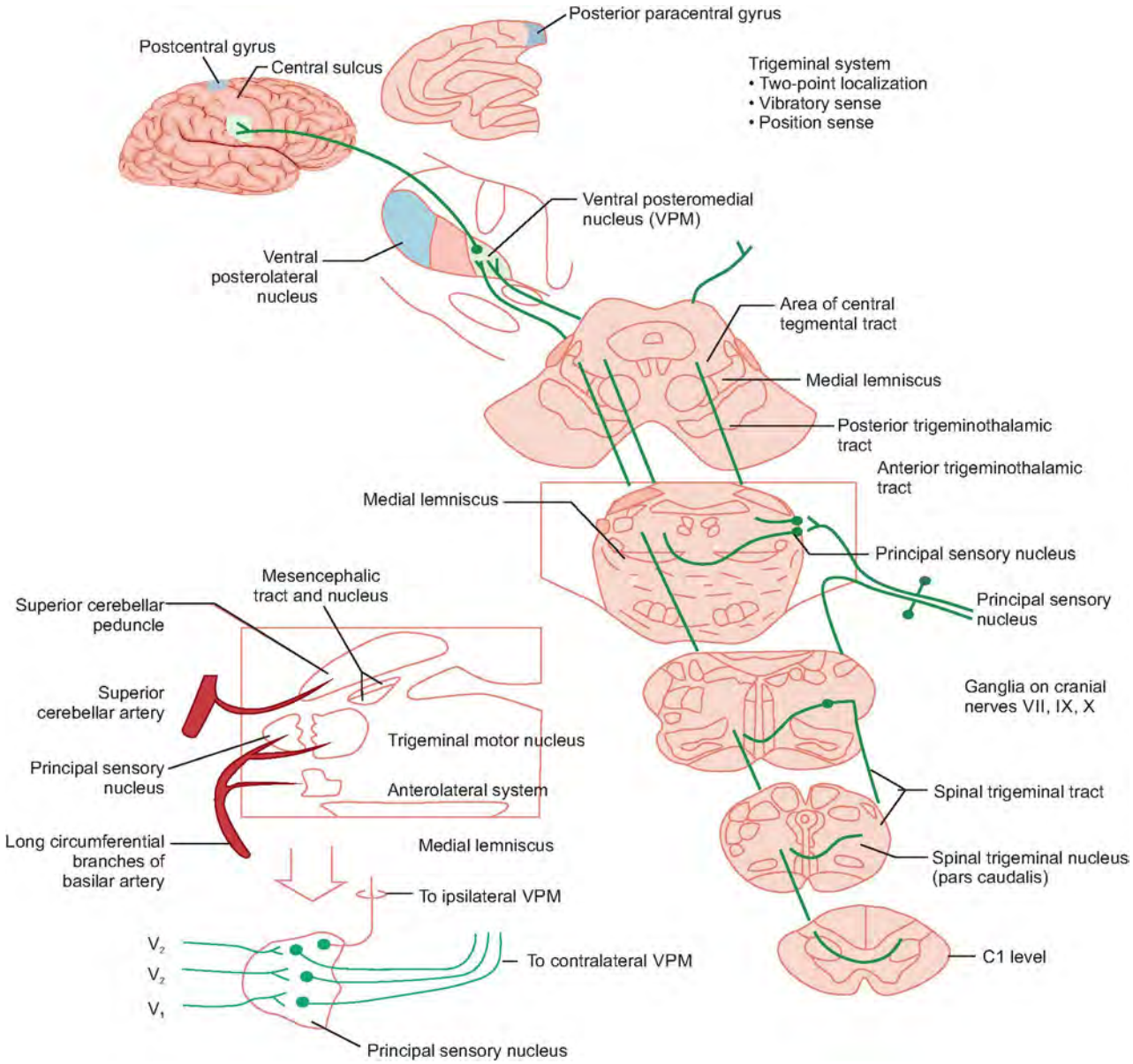

Fig. 4: Pain and temperature sensation of the face is carried by the sensory root of the trigeminal nerve. About half of the fibers divide into ascending and descending fibers, which either cross directly or cross at a lower level

tract, which carries ascending cervical fibers.[5] In type III Stopford sensory loss, large mediolateral lesions affect both descending and ascending trigeminal tract and spinothalamic tract, causing bilateral face and contralateral body sensation loss.[6] In type IV Stopford sensory loss, as seen in our case, there is involvement of only crossed ventral trigeminothalamic tract and spinothalamic tract, causing contralateral body and face sensory loss (pseudothalamic presentation) (Fig. 4).[7]

A diminished gag reflex and palatal paralysis are usually seen in lateral medullary syndrome. However, rarely, due to more medial lesions, the 9th, 10th, and 11th cranial nerves may be spared, causing preserved gag reflex and palatal movements along with preserved shoulder shrugging.[2]

The arteries commonly involved in lateral medullary syndrome are PICA or vertebral artery. It can rarely be caused by AICA involvement, which also supplies lateral part of lower pons, hence causing an infarct of the pontomedullary junction as seen in our case.[8]

Conclusion

Lateral medullary syndrome presenting with contralateral UMN facial palsy and contralateral facial sensation loss is very rare. Hence, we are presenting this case to shed some light on the rare presentations of lateral medullary syndrome. Recognizing these at the earliest and managing them appropriately can ensure a better outcome. Prompt intervention, targeted therapy, and rehabilitation can potentially mitigate the complications of lateral medullary syndrome and ensure better recovery.

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CASE REPORT

Atypical Presentations of Central Nervous System Tuberculosis at a Tertiary Care Center: Case Series

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Received: 12 July 2025; *Accepted:* 25 July 2025

Abstract

This case series highlights three patients with unusual central nervous system (CNS) tuberculosis (TB) manifestations, diagnosed at the Department of Medicine and Neurology, Moti Lal Nehru Medical College, Prayagraj, India, between January and November 2024. The cases underscore the diagnostic challenges of atypical CNS TB and the importance of an integrated diagnostic approach combining clinical, radiological, and laboratory findings. A 35-year-old male presented with sudden-onset right-sided weakness. Imaging revealed intracranial hemorrhage (ICH) in the left parietal region without vascular anomalies. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis, elevated protein, and adenosine deaminase (ADA), while the interferon-gamma release assay was positive. He was diagnosed with CNS TB presenting as ICH secondary to vasculitis. A 49-year-old male developed left-hand weakness. Imaging showed a left parietal infarct. CSF analysis revealed lymphocytic pleocytosis with elevated protein and ADA. Pulmonary TB was suspected based on a chest X-ray. He was diagnosed with stroke secondary to tubercular CNS vasculitis presenting as pseudomedian nerve palsy. A 32-year-old male presented with sudden-onset bilateral lower limb weakness and sensory loss. Magnetic resonance imaging (MRI) spine findings were suggestive of a normal spine but with paraspinal muscle hyperintensity. CSF analysis was normal, and the interferon-gamma release assay was positive. Antitubercular therapy and steroids improved motor function, leading to a diagnosis of MRI-negative paraplegia secondary to tubercular myeloradiculitis. These cases demonstrate the varied and atypical manifestations of CNS TB, including ICH, stroke mimicking nerve palsy, and MRI-negative paraplegia. Prompt recognition and treatment are crucial to improve outcomes in such rare presentations.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1532

Introduction

Tuberculosis (TB) remains a significant global health problem, with an estimated 10.6 million new cases in 2021 and 1.6 million deaths attributed to the disease.[1] While pulmonary TB is the most common form, extrapulmonary manifestations account for 15–20% of cases, with central nervous system (CNS) TB being one of the most severe and debilitating forms.[2,3] CNS TB constitutes approximately 5–10% of all extrapulmonary TB cases and carries a high mortality and morbidity burden when left untreated.[4]

Central nervous system TB typically manifests as tuberculous meningitis (TBM), cerebral or spinal tuberculomas, or spinal arachnoiditis.[5] TBM is the most frequently encountered presentation, characterized by a subacute progression of meningeal symptoms, including headache, fever, and altered mental status.[6] Tuberculomas, which are granulomatous masses, may mimic neoplasms or abscesses and cause focal neurological deficits depending on their location.[7] Spinal arachnoiditis, though less common, can lead to progressive myelopathy and paraplegia.[8] Despite these relatively well-recognized presentations, CNS TB can also exhibit atypical forms that complicate diagnosis and delay appropriate treatment.[9]

Atypical presentations of CNS TB are particularly challenging due to their ability to mimic other neurological conditions, including strokes, intracranial hemorrhages (ICHs), and demyelinating disorders.[10] The pathophysiology underlying these atypical manifestations often involves TB-induced vasculitis, leading to vascular events such as ischemia or hemorrhage.[11] These rare presentations demand a high index of suspicion, particularly in endemic areas or in individuals with known TB risk factors.

Table 1 shows clinical features and investigations of the cases. We report a case series of three patients with unusual manifestations of CNS TB who presented to the Department of Medicine and Neurology, Moti Lal Nehru Medical College, Prayagraj, Uttar Pradesh, India, between January and November 2024: case 1 shows Figs 1A and B normal variation of CT angiography for reference and CNS TB presenting as ICH (Fig. 1C), case 2 Figure 2A shows hypothenar muscle atrophy in hand (Fig. 2B) chest X-ray showing opacities in right lung and (Fig. 2C) shows normal MRI spine and stroke (Fig. 2D) secondary to tubercular vasculitis with pseudomedian nerve palsy (Fig. 2A), and case 3 magnetic resonance imaging (MRI)-negative (Fig. 3A) paraplegia (Fig. 3C) associated with tubercular myelitis (Figs 3A and B). These cases highlight the diagnostic challenges posed by atypical CNS TB presentations and underscore the importance of integrating clinical, radiological, and laboratory findings for timely diagnosis and management.

Case Description

Case 1

A 35-year-old male presented with a complaint of sudden-onset right-sided body weakness for the past 2 days. On examination, the patient was alert and oriented to time, place, and person. Motor examination revealed a power of 2/5 in the right upper and lower limbs, while the power in the left upper and lower limbs was 5/5. The right plantar response was extensor. The patient was evaluated for the cause of young-onset ICH (Fig. 1C). Hematological parameters were within normal limits. However, prothrombin time was elevated at 14.1 (against the reference 11.1–13.8) with an international normalized ratio (INR) of 1.08. Computed tomography (CT) angiography of the cerebral vessels (Figs 1A and B) did not reveal any vascular anomalies. MRI of the brain indicated an ICH in the left parietal region (Fig. 1C). Cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis with elevated protein and adenosine deaminase (ADA) levels (9.6 U/L). CSF testing for cartridge-based nucleic acid amplification test (CBNAAT) was negative, while the interferon-gamma release assay was positive (TB nil 5.38; TB antigen 127.91). A diagnosis of CNS TB

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How to cite this article: Shrivastava A, Dhaneshry D, Sahoo M. Atypical Presentations of Central Nervous System Tuberculosis at a Tertiary Care Center: Case Series. J Assoc Physicians India 2026;74(6):37–40.

Table 1: Clinical features and diagnostic workup of all cases are summarized

Case	*Age*	*Gender*	*Presenting complaints*	*Examination*	*CT angiography*	*MRI*	*CSF*	*IGRA*	*Diagnosis*	*Remarks*
1	35 years	Male	Sudden-onset right-sided body weakness × 2 days	Power of 2/5 in the right upper and lower limbs; Power in the left upper and lower limbs was 5/5 The right plantar response was extensor	No vascular anomaly	Brain: ICH in the left parietal region	Clear appearance, colorless, no clots, trace amounts of blood (16–18 cells/HPF RBCs), 52 mg/dL glucose, 15.04 mg/dL protein, total count of 3, 100% lymphocytes—Lymphocytic pleocytosis with elevated protein and ADA levels CBNAAT negative	Positive	CVA with ICH secondary to vasculitis—CNS tuberculosis	
2	49 years	Male	Sudden-onset weakness, left hand × 1 day	Normal power (5/5) at left shoulder and elbow joints; Weakness at left thumb, index finger, and middle finger; Card test positive; Loss of nasolabial fold on the left lower corner of the mouth		Brain: Infarct in left parietal region Cervical spine: Unremarkable	Total cell count was 100 cells/mm^3, with 80% lymphocytes and mononuclear cells, elevated protein (68 mg/dL), ADA levels (10.2 U/L)—Lymphocytic pleocytosis		Stroke secondary to tubercular CNS vasculitis presenting as pseudomedian nerve palsy	MRI cervical spine and NCS of left upper limb were normal Chest X-ray suggestive of pulmonary Koch's disease
3	32 years	Male	Sudden-onset bilateral lower limb weakness × 10 days Increased urinary frequency × 3 days	Power in both lower limbs was 2/5; Bilateral knee and ankle reflexes were brisk, with sensory loss to touch, pressure, and pain in the left lower limb up to the L1–L2 dermatome		Spine: Hyperintensity was noted in the psoas and paraspinal muscles	Normal	Positive	CNS tuberculosis presenting as MRI-negative paraplegia	Nerve conduction velocity study was normal Following ATT and steroids, bilateral lower limb weakness gradually improved to 4/5 over 8–10 days

CT, computed tomography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; IGRA, interferon-gamma release assay; HPF, high power field; RBC, red blood cells; CVA, cerebrovascular accident; ICH, intracranial hemorrhage; ADA, adenosine deaminase; CBNAAT, cartridge-based nucleic acid amplification test; CNS, central nervous system; NCS, nerve conduction studies; ATT, antitubercular therapy

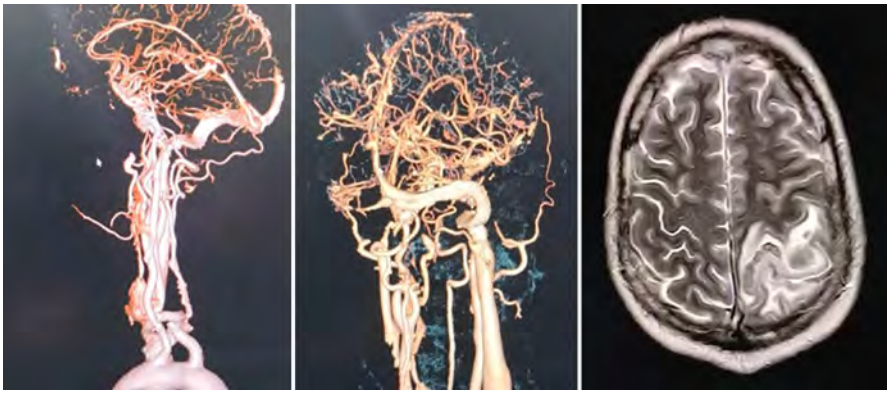
presenting as cerebrovascular accident (CVA) with ICH secondary to vasculitis was made.

Case 2

A 49-year-old male photographer presented with sudden-onset weakness in his left hand, first noticed when he dropped his camera. He was evaluated in the emergency medicine unit. Examination of the left upper limb revealed normal power (5/5) at the shoulder and elbow joints. However, weakness was identified in the left thumb, index finger, and middle finger. The card test was positive, while wrist flexor and extensor were normal. Given the acute onset and upper motor neuron (UMN) findings, an MRI of the brain was performed, revealing an infarct in the left parietal region (Fig. 2D). Further investigations, including MRI of the cervical spine (Fig. 2C) and nerve conduction velocity (NCV) studies (Fig. 3C) of the left upper limb, were unremarkable. To evaluate the cause of young-onset CVA, additional workup was conducted. A chest X-ray (Fig. 2B) was suggestive of pulmonary Koch's disease. CSF analysis demonstrated lymphocytic pleocytosis with elevated protein levels (68 mg/dL) and ADA levels (10.2 U/L). The total cell count was 100 cells/mm^3, with 80% lymphocytes and mononuclear cells. A diagnosis of stroke secondary to tubercular CNS vasculitis presenting as pseudomedian nerve palsy (Fig. 2A) was established.

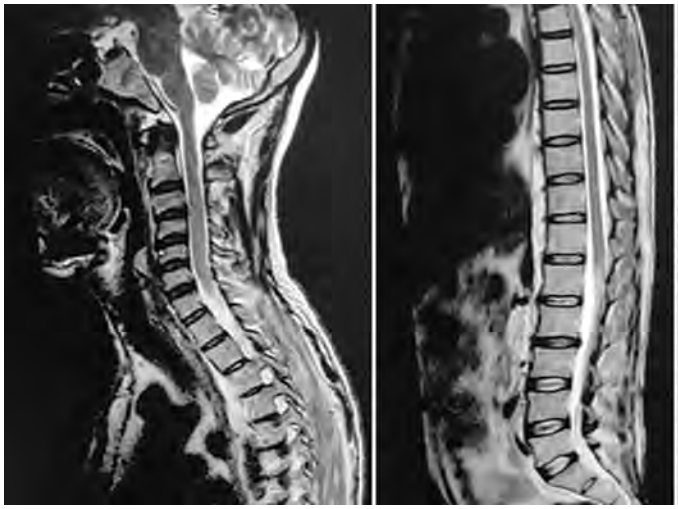
Case 3

A 32-year-old male presented to the emergency medicine unit with a history of sudden-onset bilateral lower limb weakness for 10 days, accompanied by increased urinary frequency for the past 3 days. This was preceded by a prodromal episode of fever lasting 1 month. On examination, the power in both lower limbs was 2/5. Bilateral knee and ankle reflexes were brisk, with sensory loss to touch, pressure, and pain in the left lower limb up to the L1–L2 dermatome. MRI of the spine (Figs 3A and B) was normal; however, hyperintensity (Fig. 3B) was noted in the psoas and paraspinal muscles. Further evaluation included NCV studies and CSF analysis for cell count, glucose, protein, ADA, and CBNAAT, all of which were within normal limits. The interferon-gamma release assay returned a positive result. The patient was



Figs 1A to C: (A) Computed tomography angiography showing normal vessels; (B) CT angiography showing normal vessels; (C) MRI brain (FLAIR) showing hemorrhage in left parietal region

Figs 2A to D: (A) Hypothenar muscle atrophy in hands; (B) Chest X-ray showing opacities in right lung; (C) Normal MRI spine; (D) MRI brain (T1)—infarct in parietal region



Nerve / Sites	Muscle	Latency ms	Amp mV	Segments	Distance mm	Velocity m/s
L Median - APB						
Wrist	APB	3.44	6.0	Wrist - APB		
Elbow	APB	7.08	5.9	Elbow - Wrist	200	55
R Median - APB						
Wrist	APB	3.33	6.0	Wrist - APB		
Elbow	APB	7.00	6.1	Elbow - Wrist	200	55
L Ulnar - ADM						
Wrist	ADM	2.38	6.7	Wrist - ADM		
B.Elbow	ADM	6.90	5.4	B.Elbow - Wrist	250	55
R Ulnar - ADM						
Wrist	ADM	2.10	10.0	Wrist - ADM		
B.Elbow	ADM	7.13	9.3	B.Elbow - Wrist	250	50
L Peroneal - EDB						
Ankle	EDB	4.38	8.3	Ankle - EDB		
Fib head	EDB	13.21	4.5	Fib head - Ankle	410	46
R Peroneal - EDB						
Ankle	EDB	5.21	8.6	Ankle - EDB		
Fib head	EDB	13.40	7.4	Fib head - Ankle	410	50
L Tibial - AH						
Ankle	AH	4.21	1.5	Ankle - AH		
Pop fossa	AH	12.13	0.9	Pop fossa - Ankle	400	51
R Tibial - AH						
Ankle	AH	4.33	8.1	Ankle - AH		
Pop fossa	AH	11.92	8.0	Pop fossa - Ankle	400	53

Figs 3A to C: (A) Normal MRI cervical spine; (B) MRI dorsolumbar shows hyperintensity noted in psoas and paraspinal muscle; (C) Normal NCV

started on antitubercular therapy and steroids, following which the bilateral lower limb weakness gradually improved to a grade of 4/5 over the next 8–10 days. A diagnosis of CNS TB presenting as MRI-negative myeloradiculitis was made. This case highlights the unusual clinical presentation of myeloradiculitis with a normal spinal MRI. Myelitis caused by *Mycobacterium tuberculosis* is a rare entity, and its occurrence with normal MRI findings is exceptionally uncommon.

The comparison of the three cases is shown in Table 1.

Discussion

Tuberculosis is a global health concern, with CNS TB being one of the most severe extrapulmonary manifestations. The cases presented highlight atypical manifestations of CNS TB, emphasizing diagnostic challenges and the role of ancillary investigations in resource-limited settings. CNS TB can involve the vasculature through tuberculous vasculitis, leading to cerebrovascular complications such as stroke or hemorrhage.[12] The first case, characterized by left parietal hemorrhage (Fig. 1C) and vasculitis (Figs 1A and B), underscores the importance of considering TB in young patients with cryptogenic ICH. Lymphocytic pleocytosis and elevated CSF ADA levels supported the diagnosis. Although CBNAAT was negative, the interferon-gamma release assay was pivotal in confirming TB etiology. Similar cases have demonstrated the diagnostic value of interferon-gamma assays in ruling in TB when microbiological confirmation is elusive.[13]

Tuberculous vasculitis can lead to ischemic events in the CNS, often presenting as stroke.[14,15] In the second case, parietal lobe infarction (Fig. 2D) manifested with pseudomedian nerve palsy (Fig. 2A), an unusual clinical finding. A chest X-ray (Fig. 2B) suggestive of pulmonary TB and CSF findings corroborated the diagnosis. This highlights the multifaceted presentation of CNS TB and the need for clinicians to maintain a high index of suspicion, particularly in endemic regions like India. The rapid onset and localized findings necessitated imaging and ancillary tests to establish the connection to TB.

Spinal TB typically manifests with imaging abnormalities, but the third case of MRI-negative myelopathy (Fig. 3A) emphasizes the diagnostic challenges posed by rare presentations.[16] Hyperintensity in the psoas and paraspinal muscles (Fig. 3B) was suggestive of inflammatory involvement, a known but less commonly reported phenomenon in TB-associated myelitis.[17] The absence of MRI abnormalities in the spinal cord itself, despite profound neurological deficits, is exceptionally rare. Positive interferon-gamma release assay findings were crucial in confirming the diagnosis. Such cases demonstrate the heterogeneity of CNS TB and the limitations of standard imaging techniques, underscoring the utility of immunological assays.

Atypical CNS TB presentations often mimic other neurological conditions, leading to delays in diagnosis and treatment. Standard diagnostic tests, including CBNAAT, may yield false negatives due to the paucibacillary nature of CNS TB.[18] In such scenarios, ancillary tests like CSF ADA levels and interferon-gamma release assays are invaluable.[19] However, these tests should be interpreted cautiously, as elevated ADA levels can occur in other infections and inflammatory conditions—bacterial meningitis (*Streptococcus pneumoniae*, *Neisseria meningitidis*), viral infections (herpes simplex virus), fungal infections (cryptococcal meningitis), parasitic infections (neurocysticercosis and toxoplasmosis), nontuberculous mycobacteria (*Mycobacterium avium* complex), autoimmune disorders (neurological involvement in systemic lupus erythematosus, rheumatoid arthritis), neoplastic conditions (CNS malignancies including lymphomas or carcinomatous meningitis), neurosarcoidosis, and other granulomatous diseases (Wegener's granulomatosis).[20]

Antitubercular therapy remains the cornerstone of treatment for CNS TB, often combined with corticosteroids to reduce inflammation and vasculitis. The cases presented demonstrated significant clinical improvement following this approach. However, early diagnosis is critical to prevent irreversible neurological deficits. These cases also emphasize the importance of a multidisciplinary approach, integrating findings from neurology, radiology, and infectious disease specialists to achieve optimal outcomes.

Conclusion

Central nervous system TB can present with atypical features such as ICH, pseudomedian nerve palsy, and MRI-negative myelopathy, as evidenced by the cases discussed. In endemic regions or high-risk populations, TB should remain a differential diagnosis for unusual neurological presentations. Advanced diagnostic methods, alongside clinical acumen, are essential for early recognition and management.

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CASE REPORT

Insulin-secreting Large Cell Neuroendocrine Carcinoma of Pancreas Mimicking Primary Breast Carcinoma

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Received: 15 July 2025; *Accepted:* 08 April 2026

Abstract

Functioning pancreatic neuroendocrine carcinoma (pNEC) is relatively less common. Here, we report a middle-aged lady, initially diagnosed as primary ductal carcinoma of the breast with multiple metastases, who was managed with excision biopsy of the breast tumor and palliative chemotherapy elsewhere. She later developed recurrent episodes of hypoglycemia following chemotherapy and was found to have hyperinsulinemic hypoglycemia, clearly suggestive of insulinoma. Ga-68 DOTANOC PET-CT scan showed DOTA-avid primary lesion in pancreas with intense uptake in several sites, including liver, bilateral adnexa, and intra-abdominal lymph nodes, favoring a probable functioning pancreatic neuroendocrine tumor (pNET) with distant metastases. Histopathology of her breast lesion was then re-examined, which showed features of neuroendocrine carcinoma (NEC) that was confirmed with immunohistochemistry (IHC), thus establishing the diagnosis of functioning pNEC. She was treated conservatively with octreotide and diazoxide for recurrent and refractory level 2 and 3 hypoglycemia. She was later discharged at her request on octreotide in a relatively stable condition, but died a week later. Despite being rare, diagnosing insulin-secreting pNEC is quite challenging. However, the diagnosis can be established based on radiological clues, somatostatin receptor expression based on functional imaging, and careful histopathological examination with appropriate IHC.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1534

Introduction

Insulinomas are the most common secretory neuroendocrine tumors of the pancreas and the major cause of hypoglycemia related to endogenous hyperinsulinism.[1] Recent data show an increasing incidence of insulinomas to about 1–32 cases/10^6 population/year, of which approximately 60–70% of pNET are nonfunctional.[2] However, extrapulmonary neuroendocrine carcinoma (NEC) arising from the pancreas (pNEC) is reported in only 7% of cases and functionality of NEC is observed in not more than 5% cases.[3] Biochemical evaluation with hormone assessment remains to be the initial diagnostic modality, while a prolonged fasting test for a critical sample during the episode of hypoglycemia may be required in certain cases. Noninvasive imaging procedures such as computed tomography and magnetic resonance imaging are commonly used to localize the source of pathological insulin secretion. Invasive modalities, including endoscopic ultrasonography and arterial stimulation venous sampling, are highly accurate for preoperative localization of insulinomas but are seldom performed nowadays, after the advent and availability of functional imaging such as Ga-68 DOTANOC PET/CT and Exendin-4 PET/CT.[1,4] Surgery is still the preferred first-line treatment for insulinoma, which is often benign. However, in patients with malignant insulinoma, an aggressive medical approach is required, which includes extended pancreatic resection, liver resection, liver transplantation, chemoembolization, and radiofrequency ablation. Nevertheless, the initial management for insulinoma is by administering octreotide with continuous glucose monitoring to prevent and reduce the frequency and severity of hypoglycemic episodes.[1] Nonislet cell hypoglycemia (NICH) is another clinical condition that occurs due to overproduction of insulin-like growth factor 2 (IGF-2) and its precursors that activate the insulin receptor and thereby cause hypoglycemia. It is typically observed in large mesenchymal and epithelial tumors.[5] Here, we discuss a case of poorly differentiated yet functioning insulin-secreting pancreatic neuroendocrine carcinoma (pNEC) that mimicked a primary breast malignancy.

Case Description

A 30-year-old lady presented initially with a left breast tumor elsewhere. She was diagnosed with invasive ductal carcinoma based on fine needle aspiration cytology and underwent an excision biopsy of the breast tumor. She was also found to have distant metastases to the liver and lymph nodes (left supraclavicular, mediastinal, right hilar, and retroperitoneal) as well as bilateral adnexal masses. Hence, she was initiated on palliative chemotherapy with doxorubicin and cyclophosphamide and was referred to our institution for episodes of recurrent hypoglycemia while on chemotherapy. On admission, she experienced an episode of severe symptomatic hypoglycemia, with capillary blood glucose of 27 mg/dL (1.5 mmol/L), which was managed with an intravenous bolus of 25% dextrose. She had no family history of malignancy or hereditary syndromes. On clinical exam, her height was 160 cm, weight 58 kg, and BMI 22.7 Kg/m^2. She had no goiter or neurocutaneous markers. Her blood pressure was 110/70 mm Hg, and her system examination was unremarkable.

Diagnostic Assessment

On biochemical evaluation, her renal and liver functions, as well as fasting serum cortisol, were normal. In view of recurrent episodes of level 2 and level 3 hypoglycemia during chemotherapy, a critical sample for plasma glucose, insulin, C-peptide, and cortisol was collected during hypoglycemia (Table 1), which was highly suggestive of hyperinsulinemic hypoglycemia. Poor calorie intake, malabsorption, and other systemic illnesses, including the adverse effects of chemotherapy drugs, were ruled out. The histopathology of the breast lesion was revisited, and immunohistochemistry (IHC) studies were performed, which strongly suggested a poorly differentiated large cell neuroendocrine carcinoma (Table 2).

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How to cite this article: Tara VN, Asirvatham AR, Swaminathan R, *et al.* Insulin-secreting Large Cell Neuroendocrine Carcinoma of Pancreas Mimicking Primary Breast Carcinoma. J Assoc Physicians India 2026;74(6):41–44.

While IHC for vimentin, chromogranin, and synaptophysin were positive, supporting a probable diagnosis of a neuroendocrine tumor (Fig. 1), ER/PR and Her2/neu were negative, ruling out a primary breast malignancy. Ki67 index >20 and presence of poorly differentiated cells clearly favored NEC. IHC for insulin antibodies was negative in this case, which could be due to the monoclonal antibody used or a possible primary proinsulin-secreting tumor. WT1 was also negative, dismissing the possibility of primary ovarian malignancy that had metastasized to the breast. With the existing evidence strongly pointing towards a metastatic NEC, we performed a Ga-68 DOTANOC scan, which showed a DOTA-avid nodular lesion measuring 2.4 × 1.4 cm in the head of the pancreas (larger than that shown by the FDG PET done earlier). This was highly suspicious for a primary somatostatin-receptor-expressing tumor and somatostatin-receptor-expressing metastatic disease involving the liver and the mediastinal, left supraclavicular, and retroperitoneal lymph nodes, as well as bilateral adnexal metastases (Fig. 2). This staged the disease as T2N1M1c, and the diagnosis was revised to functioning poorly differentiated metastatic large cell pNEC grade 3 according to the WHO 2017 classification systems for pancreatic neuroendocrine neoplasms. Meanwhile, the patient developed an acute onset of altered sensorium, with brain imaging revealing multiple brain metastases with no involvement of the pituitary.

Table 1: Laboratory investigations of the patient

Biochemical parameter	*Test values*	*Reference range*
Critical sample serum insulin	64.9	2.6–24.9 µIU/mL
Critical sample C-peptide	3.6	1.1–4.4 ng/mL
Critical sample RBS	47	80–140 mg/dL
Critical sample cortisol	21.45	4.0–22 µg/dL
Serum creatinine	1.2	0.60–1.10 mg/dL
SGOT	112	< 40 U/L
SGPT	20	< 34 U/L
Total bilirubin	0.35	0.1–1.0 mg/dL
Direct bilirubin	0.17	< 0.2 mg/dL
Serum albumin	4.0	3.2–4.8 g/dL
Alkaline phosphatase	83	45–129 U/L
Total counts	8800	4000–11000 cells/mm^3
Platelet count	3.13	1.5–4.5 10 × $10^5/mm^3$
Hemoglobin	10.9	12.0–15.0 g/dL
ESR	27	< 15 mm/h

Treatment

She was initially treated with octreotide and diazoxide for hypoglycemia along with frequent meals containing complex carbohydrates, including corn starch. Besides, she also required continuous intravenous 10% dextrose infusion as well as intermittent intravenous 25% dextrose bolus for refractory hypoglycemia. She also developed hypoglycemia unawareness during the course of the disease. A trial of glucagon was attempted, but it was not beneficial in this case.

Table 2: Histopathological data of the breast tumor

Immunohistochemistry marker	*Result*
Vimentin	Positive
Synaptophysin	Positive
Chromogranin	Positive
Ki67	>20
ER/PR	Negative
HER2/neu	Negative
WT1	Negative
Insulin Monoclonal antibody	Negative

Outcome and Follow-up

As the pNEC was highly aggressive with extensive spread, the multidisciplinary team conducted several discussions with the patient and her husband, and a shared decision compelled us to refrain from surgical options. The patient continued palliative chemotherapy and supportive therapy, and she was discharged at her request. She died at her home a few weeks later.

Discussion

We describe a young lady with functioning metastatic pancreatic neuroendocrine carcinoma who was initially misdiagnosed as having primary breast malignancy, who then developed recurrent episodes of hypoglycemia. At the time of presentation,

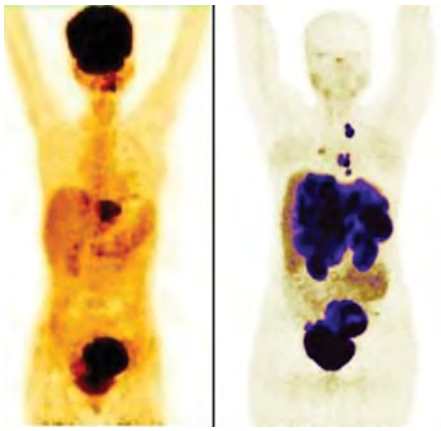

Fig. 2: 68-Gallium DOTANOC PET-CT imaging shows an avid nodular lesion in the head of the pancreas with somatostatin receptor-expressing metastatic disease involving the liver, mediastinal, supraclavicular, and retroperitoneal lymph nodes, and bilateral adnexa

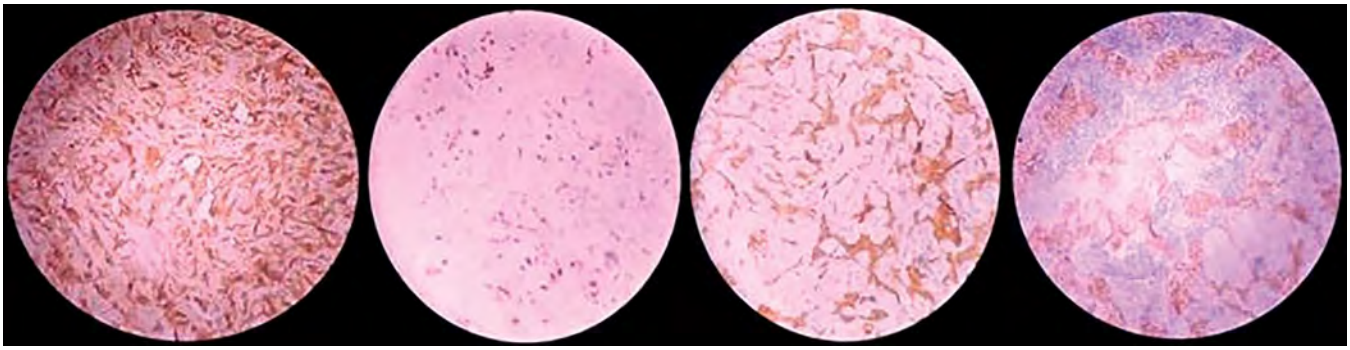

Fig. 1: IHC of the breast tumor showing positive chromogranin, Ki67, synaptophysin, and vimentin staining

she had already started on palliative chemotherapy and underwent re-evaluation when she developed unexplained level 2 and 3 hypoglycemia. Making an accurate diagnosis of the primary malignancy is extremely important for appropriate management, considering aggressiveness and metastases of the tumor, besides mortality. Invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) of the breast are more prevalent than neuroendocrine tumors of the breast that include primary neuroendocrine carcinoma (NEC) of the breast and metastatic neuroendocrine tumors in the breast, of which the latter is more common.[6] Recognizing the less prevalent primary NEC and metastatic NEC of the breast necessitates morphologic clues and prompt immunohistological confirmation. Presence of a well-circumscribed mass with indistinct margins, lack of calcifications, spiculated margins, and posterior shadowing are notable sonographic features of NEC of breast that help to differentiate them from ductal and lobular carcinoma of breast. Furthermore, histological differentiation of NEC could be done with appropriate IHC. However, it is difficult to differentiate metastatic and primary NEC of the breast histologically, and IHC staining remains crucial for diagnosis.[7] Our patient was probably misdiagnosed as IHC was not performed initially despite strong radiological clues.

The primary tumor of an NEC is typically located in the pancreas in about 19% of cases.[2] NEC is largely nonfunctional owing to its poor differentiation.[7–9] However, this case had a poorly differentiated large cell NEC of the pancreas with multiple distant metastases, which was secreting insulin and therefore presented with recurrent episodes of severe hypoglycemia. While most pancreatic neuroendocrine tumors (pNETs) are nonfunctioning, the most common functioning pNET is insulinoma.[8] In the largest series of histologically confirmed cases of poorly differentiated pNEC, only 1 out of 44 cases had demonstrable hyperinsulinism, reiterating the fact that functionality of these tumors is extremely rare.[9] Transformation of nonfunctioning pancreatic neuroendocrine tumors (NF-pNET) into hormonally active functioning subtypes is also reported in 3.4–6.8% of pNET.[10] Several mechanisms have been proposed for the late onset of functioning capability, including functional plasticity of pancreatic stem cells. Nevertheless, the prevalence of liver metastasis in almost all of these reported functional transformation cases suggests a possible potentiating factor in the *milieu* of the liver due to unknown mechanisms.[11] Although insulin secretion from poorly differentiated NEC has not been reported in the literature so far, ectopic insulin secretion by a large cell NEC of cervix has been reported, which was a retrospective diagnosis as in our case.[12] Although it is currently still debatable, neoplastic progression of a well-differentiated pNET into a poorly differentiated pNEC is also being considered as a possible explanation for the persisting functionality of these tumors.[13] Even though metastases of poorly differentiated pNEC to liver and regional lymph nodes are very common at presentation, involvement of the brain, lung, mediastinum, adrenal gland, and kidney was also reported in rare cases.[9] However, metastases to the breast and adnexa have not been reported in the literature so far, as observed in this case, which furthermore contributed to the misdiagnosis earlier.

Conclusion

In conclusion, functioning neuroendocrine tumors are not always benign. Rarely, neuroendocrine carcinomas can also secrete hormones. Early diagnosis of NEC is crucial and mainly depends on radiological imaging and histology. Even though metastasis at presentation is common in these tumors, rarer sites, including breast and adnexa, could be identified during evaluation, especially with the advent of high-quality functional imaging.

Learning Points

- Functioning poorly differentiated metastatic pancreatic neuroendocrine carcinoma secreting insulin is extremely rare.
- Functionality of these tumors, therefore, should not always be considered benign.
- Judicious diagnosis with radiological clues, histological assessment, and immunohistochemistry before planning an appropriate treatment strategy is warranted.
- Uncommon sites of metastasis of these tumors are also recognized, including the breast and adnexa.

Source of Support

None.

Conflict of Interest

None.

Acknowledgments

The authors would like to thank Dr. Suriyakumar, radiologist, for his assistance with Ga-68 DOTANOC PET-CT scan imaging in this patient.

Authors' Contribution Statement

All authors made substantial individual contributions to the authorship of this work. VN, AA, and SM were involved in the diagnosis and management of the patient and manuscript submission. RS and SS were involved in the histopathology section and preparation of histology images. SS was responsible for the palliative care of the patient. All authors reviewed and approved the final draft of the manuscript.

Patient Consent

Signed informed patient consent was obtained directly from the patient's husband.

Disclosures

None declared.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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CASE REPORT

Ask-Upmark Kidney: A Rare Cause of Hypertension in Young Patients

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Received: 21 May 2025; *Accepted:* 08 June 2026

Abstract

Ask-Upmark kidney was originally described as a congenital segmental hypoplasia of the kidney, but recent data suggest it to be a sequela of vesicoureteral reflux or pyelonephritis in early age. This segmental hypoplasia leads to hypertension in young people. This hypertension is treatable with a partial nephrectomy. This reported patient presented with hypertensive urgency in the OPD. On evaluation, he was found to have Ask-Upmark kidney. The patient was managed conservatively. In case of severe and progressive renal damage, surgical resection with or without transplant can be considered. If the disease is nonprogressive with normal kidney function, the patient can be managed with antihypertensive treatment alone. This is one of the rare causes of hypertension in young that should be kept in mind while evaluating such cases.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1535

Introduction

Ask-Upmark kidney is a rare entity, and due to a lack of awareness among clinicians about this disease, its diagnosis is mostly delayed or missed. Here we are reporting this case of a young man in his 20s with secondary hypertension due to a segmental renal scar. After excluding all the other probable causes of secondary hypertension, this diagnosis was made based on relevant investigations. This case is reported to emphasize this diagnosis and to encourage more such cases to be diagnosed and reported.

Case Description

A gentleman in his 20s walked into the medicine OPD with complaints of daily headache, giddiness, and pain in the back of the neck for the last 6 months. He is a student who stays with his family. He does not have any comorbidities. There is no significant addiction history. No history of hypertension in any first-degree relatives. No significant past medical or surgical history. On examination, he was found to have good general health with a BMI of 21 kg/m^2. No significant findings on general physical examination and systemic examinations. His blood pressure was recorded by his family physician at home as well as in the clinic, and was always found to be high on multiple occasions. His blood pressure was found to be 180/126 mm Hg in the right arm and 182/120 mm Hg in the left arm in our OPD. His pulse rate was within normal range without any radio-radial or radio-femoral delay. The patient was started on antihypertensive therapy. On the next visit after 1 week, his blood pressure was again found to be 190/134 mm Hg in the left arm and 188/130 in the right arm.

There was no history of fever, burning micturition, frothy urine, episodes of flushing, or increased frequency of micturition. Routine laboratory workup revealed creatinine 0.77 mg/dL, urea 18.9 mg/dL, uric acid 8 mg/dL, and electrolytes within normal range. His liver function, complete hemogram, and thyroid function were also found to be within normal limits. His ANA screening and profile were negative. His lipid profile revealed total cholesterol 208 mg/dL and LDL 115 mg/dL. His HbA1c level was 4.5%. Urine routine examination revealed proteinuria 2+ (100 mg/dL) without cast or RBCs, and a microalbumin creatinine ratio of 100 mg/gm. His 24-hour urinary protein was 246.5 mg/day and was persistently high. His plasma renin activity and aldosterone were found to be normal. His electrocardiogram and echocardiogram were found to be normal. Ultrasound of the whole abdomen and renal Doppler was found to be normal. Contrast-enhanced CT of abdomen and pelvis revealed: left kidney having irregular outline with smooth cortical indentations on delayed phases with normal contrast excretion, suggestive of segmental renal hypoplasia, probably pyelonephritic scar (Fig. 1).

Dimercapto succinic acid (DMSA) scan obtained by radionuclide static cortical scan was acquired after IV injection of 5 mCi 99mTc, revealing evidence of focal segmental scar at lower pole of left kidney (Fig. 2). There was no past history suggestive of pyelonephritis, even on repeated history taking from the patient as well as family members.

Patient's blood pressure was managed adequately with dual antihypertensive therapy (telmisartan 40 mg and cilnidipine 10 mg once daily).

The patient was followed closely over a period of 12 months. There was adequate BP control without any worsening in renal function. Proteinuria gradually reduced to trace.

Discussion

Ask-Upmark kidney, also known as renal segmental hypoplasia, was first described in 1929 by Erik Ask-Upmark. It was identified as a rare cause of hypertension in the young population. It is an abnormality of nephrogenesis in a localized area, which creates a deep transverse groove (scar) on the cortical surface and dilatation of the corresponding calyces.[1]

Previously, a diagnosis of Ask-Upmark kidney was considered confirmed only after a histological finding after nephrectomy or autopsy because surgery was the only

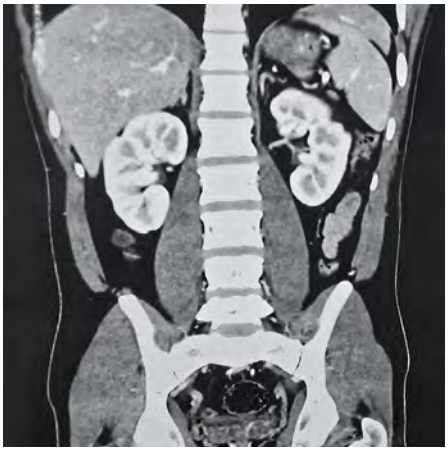

Fig. 1: CT abdomen: Left kidney showing irregular outlines with smooth cortical indentations, suggestive of segmental renal hypoplasia

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How to cite this article: Prakash J, Kumari P. Ask-Upmark Kidney: A Rare Cause of Hypertension in Young Patients. J Assoc Physicians India 2026;74(6):45–46.

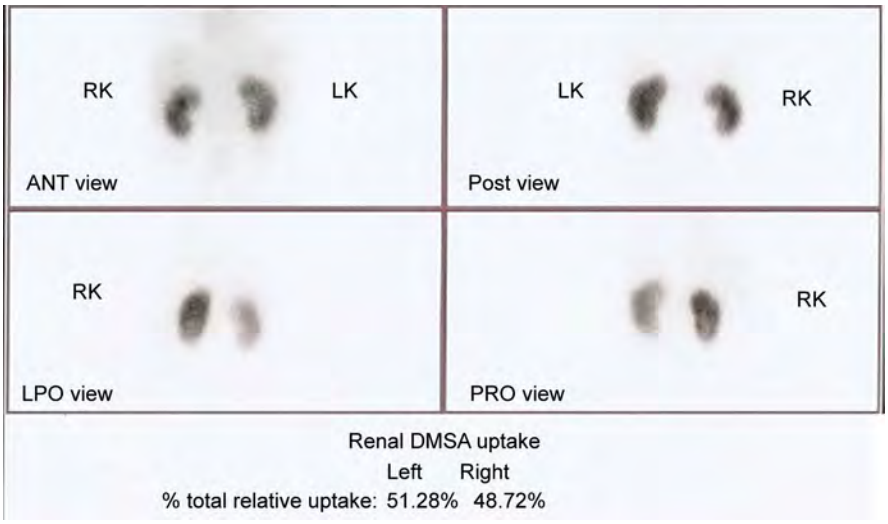

Fig. 2: DMSA scan: Left kidney showing normal cortical uptake with evidence of focal segmental scar (marked by red arrow)

definitive management. With the improved medical management of hypertension, the surgical procedure became unnecessary. Now the diagnosis can be confirmed based on radiological and clinical findings.[1]

Initially considered to be a congenital anomaly, it is now considered likely to be an acquired entity. Chronic pressure over renal parenchyma caused by recurrent urinary reflux and associated infection, which in the long-term leads to segmental atrophy and a scarred kidney, characteristic of Ask-Upmark kidney.[2]

These hypoplastic segments lack glomeruli. Return of blood pressure to normal following nephrectomy suggests that the hypertension is renin-mediated.[2]

Ask-Upmark kidney has been regarded as a result of vesicoureteral reflux rather than a true congenital malformation. Even if we fail to demonstrate the evidence of vesicoureteral reflux in adulthood, the possibility of intrarenal reflux in utero or in infancy cannot be excluded.[3] Previously, nephrectomy has been used for treatment and shown to normalize blood pressure regardless of plasma renin level; hence, the role of renin in the pathogenesis of hypertension is not very clear.[3]

Severe hypertension is the most common presentation in 50% cases; other symptoms include recurrent urinary tract infections, proteinuria, and rarely, end-stage renal disease. The mechanism of hypertension can be attributed to increased renin levels. Some authors believe that hypoplastic areas are not able to release renin due to the lack of glomeruli and juxtaglomerular cells; hence, renin is secreted from adjacent tissue. That explains why renin level is normal in some patients.[4]

In most of the cases, the lesion is discovered during childhood or adolescence and with a female preponderance. Ask-Upmark kidneys are mostly unilateral, although bilateral cases have been described.[5]

It is very challenging to distinguish between chronic pyelonephritis and segmental hypoplasia clinically and radiologically, since pelvicalyceal abnormalities and a history of urinary tract infections may be present in both. However, histologic differences between segmental hypoplasia and chronic pyelonephritis are marked.[6]

The etiology of a unilateral small kidney with hypertension has almost always been attributed to pyelonephritis or primary hypoplasia, and the early descriptions of ask-Upmark have been consistently overlooked.[7]

Ask-Upmark is rare but a probable differential diagnosis in cases of young hypertension with unknown etiology. Even in cases with normal plasma renin activity, as in our case, Ask-Upmark should be considered and investigated in patients with secondary hypertension with unknown etiology. The cases of Ask-Upmark are rarely diagnosed and even more seldomly reported. Hence, the purpose of this case report is to make our clinicians more aware of the disease entity and to encourage more such diagnoses and case reports. This will attract the attention of researchers to consider the Ask-Upmark kidney for more studies.

Learning Points

- While evaluating a case of hypertension in young, we should look for any scarring of segmental hypoplasia of the kidney to diagnose Ask-Upmark kidney.
- We established the diagnosis for our patient based on clinical history and investigations with the help of some reported cases of this disease entity.
- Patients with Ask-Upmark kidney need closer follow-up with kidney function tests and repeated DMSA scans to look for progression of scar. Hence, establishing a definite diagnosis is crucial.

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CASE REPORT

Osmotic Demyelination Syndrome Secondary to Hypernatremia and Hypokalemia: A Case Report of Complete Recovery

Keerthana Manoharan[1], Geetha T[2*], Sivakumar K[3]

Received: 10 December 2024; *Accepted:* 17 March 2026

Abstract

Background: Osmotic demyelination syndrome (ODS) presents as quadriplegia with pseudobulbar palsy, and most cases occur with rapid correction of hyponatremia. It is due to demyelination of the pons without any inflammation. Other causes include chronic malnutrition, alcoholism, and underlying medical illnesses such as post-liver transplant. Here, we present a case report of a patient with hypernatremia and hypokalemia leading to ODS, whose early diagnosis and effective treatment resulted in complete recovery of the patient.

Case description: A 33-year-old female patient presented with vomiting followed by confusion and weakness of all four limbs. On admission, the patient was drowsy, obeying oral commands, mildly dyspneic, dehydrated, weakness of all four limbs. Deep tendon reflexes were present, and the bilateral plantar reflex showed no response. Her vitals were stable. On evaluation, arterial blood gas (ABG) showed hyperchloremic normal anion gap metabolic acidosis. Serum potassium level was very low, and serum sodium level was significantly high. MRI brain T2-FLAIR image showed hyperintensity in the central pons with peripheral sparing. Pons appeared swollen and edematous, suggestive of ODS. On further evaluation, she was found to have distal renal tubular acidosis. With this presentation and in the background of renal tubular acidosis, autoimmune disease was considered. It was negative in our case. In view of hypernatremia, after calculating the water deficit, she was given IV 5% dextrose and free water through the nasogastric tube, along with potassium supplements. She was also given steroids and other supportive measures. The patient recovered completely.

Conclusion: There was no evidence of hyponatremia during admission. Here, we consider that the osmotic demyelination could have occurred due to hypernatremia. The cause for hypernatremia in this case would have been hypokalemia. Moreover, hypokalemia leads to hypernatremia through a combination of increased sodium reabsorption in the kidneys, aldosterone-mediated effects, impaired renal concentrating ability, cellular electrolyte shifts, and associated volume depletion and dehydration. These mechanisms explain the complex relationship between sodium and potassium. Early diagnosis with MRI brain imaging and treatment allowed our patient to recover completely.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1552

Introduction

Osmotic demyelination syndrome (ODS) occurs in cases rapidly corrected for hyponatremia and also in hyperosmolar states.[1,2] It rarely occurs in hypernatremia, and the mechanism is not fully understood.[3–5] It occurs in other conditions such as chronic malnutrition, alcoholism, and underlying medical illness, such as post-liver transplant.[6] The symptoms of hypernatremia are mostly neurological and could be fatal.[6] Some nonfatal presentations have also been reported. ODS presents with confusion, quadriplegia, and dysarthria. The symptoms are primarily neurological, can be severe, and potentially fatal. Diagnosis relies mainly on neuroimaging, with demyelination often localized as central pontine myelinolysis (CPM) or extrapontine myelinolysis (EPM).[7] Treatment involves lowering the sodium level slowly to normal in order to avoid cerebral edema. The plasma sodium concentration should be corrected at a rate of <10 mM/day (in severe hypernatremia, it may take more than 48 hours). In patients with acute hypernatremia, correction can be done rapidly at a rate of 1 mM/hour. Underlying causes for hypernatremia include hypokalemia, hyperglycemia, hypercalcemia, volume status, and drugs. They need to be identified and corrected.

Case Description

A 33-year-old female patient with no known comorbidities presented to our medicine department with complaints of vomiting followed by weakness of both upper and lower limbs and altered mental status. She developed pain in both upper and lower limbs 1 week prior to admission. No history of seizures. There was no fever. There was no history suggestive of previous treatment for hyponatremia. On admission, the patient was drowsy, confused, but obeying oral commands. She was severely dehydrated. Examination revealed motor power of 1/5 in both lower limbs and 2/5 in both upper limbs. Deep tendon reflexes were present. Bilateral plantar reflex showed no response. There were no signs of meningitis. Cranial nerve examination was unremarkable. Pulse rate was 88/minute, regular rhythm, normal volume, no specific character, no radioradial or radiofemoral delay, and felt equally in all palpable peripheral vessels. Blood pressure was 110/70 mm Hg. Respiratory rate was 20/minute with 96% saturation in room air. The other physical examination was normal. Her random blood sugar value was 104 mg/dL; coagulation profile, liver parameters, renal parameters, and lipid profile were normal. Initially, the total leukocyte count was high, 17,000 mm^3. Erythrocyte sedimentation rate 44 mm/hour. Lactate dehydrogenase was 1200 U/L, serum uric acid 3 mg/dL, C-reactive protein value of 5.2 mg/L. Arterial blood gas (ABG) analysis showed hyperchloremic anion gap metabolic acidosis of pH 7.03, PCO_2 = 41.7, HCO_3^- = 11.2, Cl^- = 128, Na^+ = 152, and K^+ = 1.5. ECG showed normal axis with sinus tachycardia. There was ST-segment depression in the inferior leads suggestive of hypokalemic changes with serum potassium of 2.6 mEq/L. The echocardiogram was normal. MRI brain T2-FLAIR image showed hyperintensity in the central pons with peripheral sparing, suggesting ODS (Figs 1 and 2). The patient was negative for human immunodeficiency virus, hepatitis B, and C

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How to cite this article: Manoharan K, Geetha T, Sivakumar K. Osmotic Demyelination Syndrome Secondary to Hypernatremia and Hypokalemia: A Case Report of Complete Recovery. J Assoc Physicians India 2026;74(6):47–48.

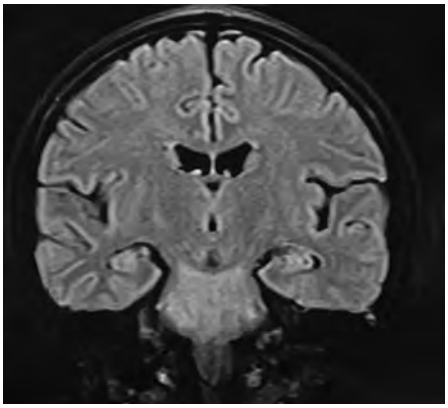

Fig. 1: Sagittal MRI brain image showing pontine edema and central pontine hyperintensity

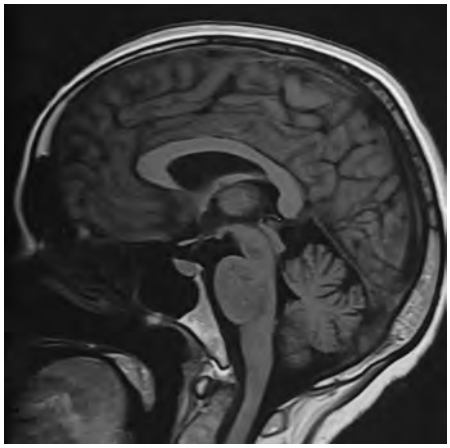

Fig. 2: Coronal FLAIR MRI brain image showing central pontine hyperintensity with peripheral sparing suggestive of osmotic demyelination syndrome

viruses. The rheumatoid factor was negative. The thyroid profile was normal. On further workup for hypokalemia, we identified distal renal tubular acidosis. Antinuclear antibody profile tested negative. Patient was treated with IV methylprednisolone for 5 days and tapered to oral steroids 1 mg/kg/day,[8,9] IV fluids, and free water correction given for hypernatremia. IV potassium (not exceeding 10 mEq/h) was administered via peripheral line and later changed to oral potassium supplements. Patient's sensorium improved, and she became fully conscious after 10 days of treatment, but was found to have dysarthria. Motor weakness improved completely in 1 month with supportive care. The patient was advised to continue oral potassium supplements and was discharged. The patient was, however, lost to follow-up.

Discussion

Most cases of ODS have been reported in patients who were rapidly corrected for hyponatremia. It is also reported in cases presenting without hyponatremia. Hypernatremia causes cellular dehydration, including brain cells, which can impair neurological function. Here, we have discussed a rare case of ODS presenting with hypernatremia and hypokalemia, which contrasts with the more common association with hyponatremia. The patient's clinical presentation of quadriplegia, dysarthria, altered mental status, and dehydration typically aligns with ODS symptoms. The patient had preserved deep tendon reflexes and thus, we ruled out Guillain-Barré syndrome (acute motor axonal neuropathy) variant. MRI brain findings showed central pontine hyperintensity with peripheral sparing support the diagnosis. Demyelination of white matter tracts in the basilar pons causes quadriplegia and pseudobulbar symptoms, sometimes leading to coma and death. On further evaluation of hypokalemia, our patient had normal magnesium levels, normal phosphate levels, no glycosuria, and urinary pH was alkaline with a value of 8. Urine osmolality was 629.3 mOsm/kg H_2O. The transtubular potassium gradient was 16. Urine anion gap was 12. There was no evidence of renal calculi or liver pathology. Hyperchloremic normal anion gap metabolic acidosis leads to distal renal tubular acidosis and confirms renal potassium wasting. Some cases of Sjögren's syndrome are reported in ODS with hypokalemia and hypernatremia.[10,11] In our patient, the antinuclear antibody profile was negative. Buccal mucosa biopsy was also negative. A cause for distal renal tubular acidosis could not be identified. But we managed the patient with early diagnosis and intervention. Correcting the hypokalemia resulted in complete recovery of motor weakness. Her sensorium improved completely after normalizing her serum sodium levels. The patient was discharged and advised to take oral potassium supplements. However, our patient lost follow-up.

Conclusion

This case highlights a rare presentation of ODS associated with hypernatremia and refractory hypokalemia. Despite the absence of common comorbidities or a history of rapid correction of hyponatremia, the patient exhibited classic ODS symptoms such as quadriplegia, dysarthria, and altered mental status. Detailed evaluation revealed distal renal tubular acidosis as the underlying cause of hypokalemia, and neuroimaging supported the diagnosis of central pontine myelinolysis. Early intervention and appropriate management of electrolyte imbalances led to significant recovery. This case indicates the importance of considering ODS in differential diagnosis for patients presenting with quadriplegia, even in the absence of hyponatremia, and the need for appropriate intervention for favorable outcomes. Regular follow-up, continued potassium supplementation, and monitoring are essential to prevent recurrence.

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CASE REPORT

Serial Imaging and Burnout Transition of Extramedullary Hematopoiesis in Sickle Beta-thalassemia: A Two-year Case Study

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Received: 12 June 2024; *Accepted:* 17 March 2026

Abstract

The synthesis of blood cells, initiated during fetal development, transitions from the yolk sac to the liver and spleen, and finally to the bone marrow by 18 weeks of gestation, continuing throughout adulthood. Postnatally, hematopoiesis occurs exclusively in the bone marrow, but can be taken over by other organs in various hematological disorders. Extramedullary hematopoiesis (EMH) can involve numerous organs and lead to conditions such as hepatomegaly, splenomegaly, and paraspinal masses. Rarely, EMH occurs in atypical sites such as the gastrointestinal tract, lungs, or central nervous system, especially in patients with conditions such as thalassemias, myelofibrosis, hemolytic anemias, and hematological malignancies.

This report describes a 26-year-old man with sickle beta-thalassemia and EMH, observed through serial imaging over 2 years. Initial imaging showed paravertebral masses and diffuse skeletal sclerosis on radiography and CT, with MRI revealing lobulated lesions without spinal canal extension. Treatment included radiotherapy and hydroxyurea, leading to fatty replacement in EMH masses, evidenced by changes in MRI characteristics over time.

The case provides a longitudinal perspective on EMH. The observed transition from active EMH to fatty replacement underscores the dynamic response to treatment and highlights the importance of serial imaging in managing EMH. This case emphasizes the need for further studies to optimize treatment strategies and improve understanding of EMH progression in hematological disorders.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1555

Introduction

The synthesis of blood cells is a complex and meticulously regulated process that begins during fetal life. It starts with the yolk sac at three weeks, followed by the liver and spleen, and transitions to the bone marrow around 18 weeks, continuing into adulthood.[1] After birth, hematopoiesis is exclusively carried out by the bone marrow, which remains in adulthood. However, in various hematological disorders, this function can be taken over by other organs.[2]

Typically, microscopic foci of extramedullary hematopoietic tissue are present in various organs, but this can progress to conditions such as hepatomegaly, splenomegaly, lymphadenopathy (due to infiltration by extramedullary hematopoietic tissue), or paraspinal masses (formation of pseudotumors) when the demand for blood cells increases and bone marrow activity is impaired. Extramedullary hematopoiesis (EMH) can occur in virtually any organ of mesenchymal origin as a physiological response to the need for blood cells. Moreover, in rare instances of hematological pathologies—including but not limited to thalassemias, myelofibrosis, hemolytic anemias, hematological malignancies, and myelodysplastic syndromes—extramedullary hematopoiesis can be observed in uncommon locations such as the gastrointestinal tract, lungs, or even the central nervous system.[3–5]

Extramedullary hematopoiesis presents variably on imaging, which can be attributed to the differing proportions of hematopoietic cells, fat, and fibrotic elements in various EMH masses. In this report, we describe the case of a 26-year-old man diagnosed with sickle beta-thalassemia and EMH, who underwent imaging in our department over a period of 2 years. The imaging demonstrated the evolution of EMH in response to treatment (radiotherapy and hydroxyurea), culminating in the characteristic appearance of inactive/burnout EMH on magnetic resonance imaging (MRI). To date, we have not encountered any published literature that details the serial imaging appearance of EMH. Most existing studies and reports tend to focus on single imaging snapshots or case studies, without tracking the progression or regression of EMH over time. This gap in the literature underscores the significance of our case report, as it provides a unique longitudinal perspective on the imaging characteristics of EMH. By documenting the changes observed in EMH through serial imaging, we offer valuable insights into its evolution and response to treatment, which could enhance understanding and management of this condition in clinical practice.

Case Description

A 26-year-old man with a known history of sickle beta-thalassemia and EMH presented with a headache in 2024. The patient first came to our department for imaging in 2022. Imaging from both instances is shown in Figures 1 to 4. 2 years ago, conventional radiography revealed paravertebral masses on a chest radiograph and areas of diffuse sclerosis scattered throughout the skeletal system. However, typical calvarial and phalangeal findings commonly associated with thalassemia were absent (Fig. 1). Computed tomography (CT) showed large, lobulated paravertebral masses of EMH with soft-tissue density and enhancement. Diffuse sclerotic areas were confirmed on CT, along with additional findings of a calcified spleen and gallbladder calculi (Fig. 2). MRI revealed lobulated lesions that were T1-isointense and T2-isointense to hyperintense, with heterogeneous enhancement. There was no extension into the spinal canal. Additionally, multiple areas of altered signal intensity in the vertebral bodies suggested marrow conversion (Fig. 3). The patient underwent two cycles of radiotherapy (20 Gy in 10 fractions), 1 year apart, along with hydroxyurea. He is not on regular blood transfusions, and his current hemoglobin level is 9.5 gm/dL.

The MRI was repeated recently, revealing lobulated, T1/T2-hyperintense paraspinal

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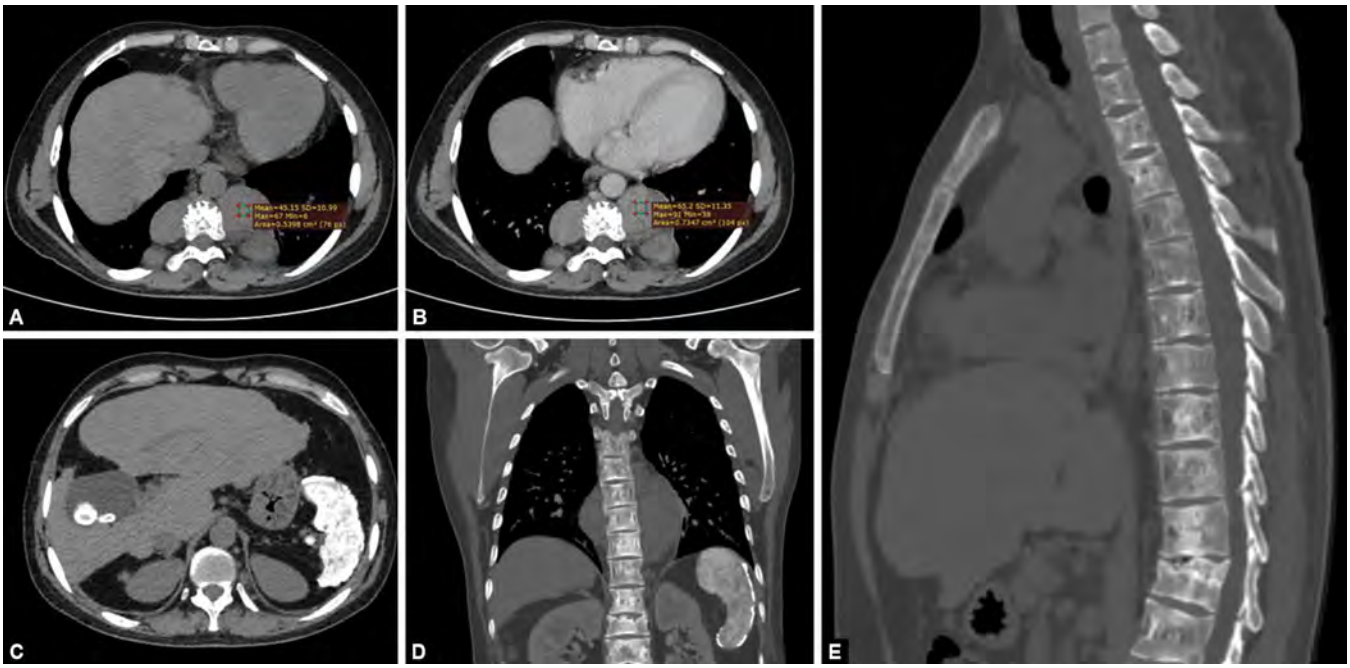
How to cite this article: Sharma N, Handa S, Gupta A, *et al.* Serial Imaging and Burnout Transition of Extramedullary Hematopoiesis in Sickle Beta-thalassemia: A Two-year Case Study. J Assoc Physicians India 2026;74(6):49–52.

Figs 1A to G: Conventional radiography revealed paravertebral masses on a chest radiograph (arrow in A), with a calcified spleen in the left hypochondrium, and areas of diffuse sclerosis scattered throughout the skeletal system (arrows in B to E), with absence of typical calvarial and phalangeal findings commonly associated with hemolytic anemia (D, F, and G)

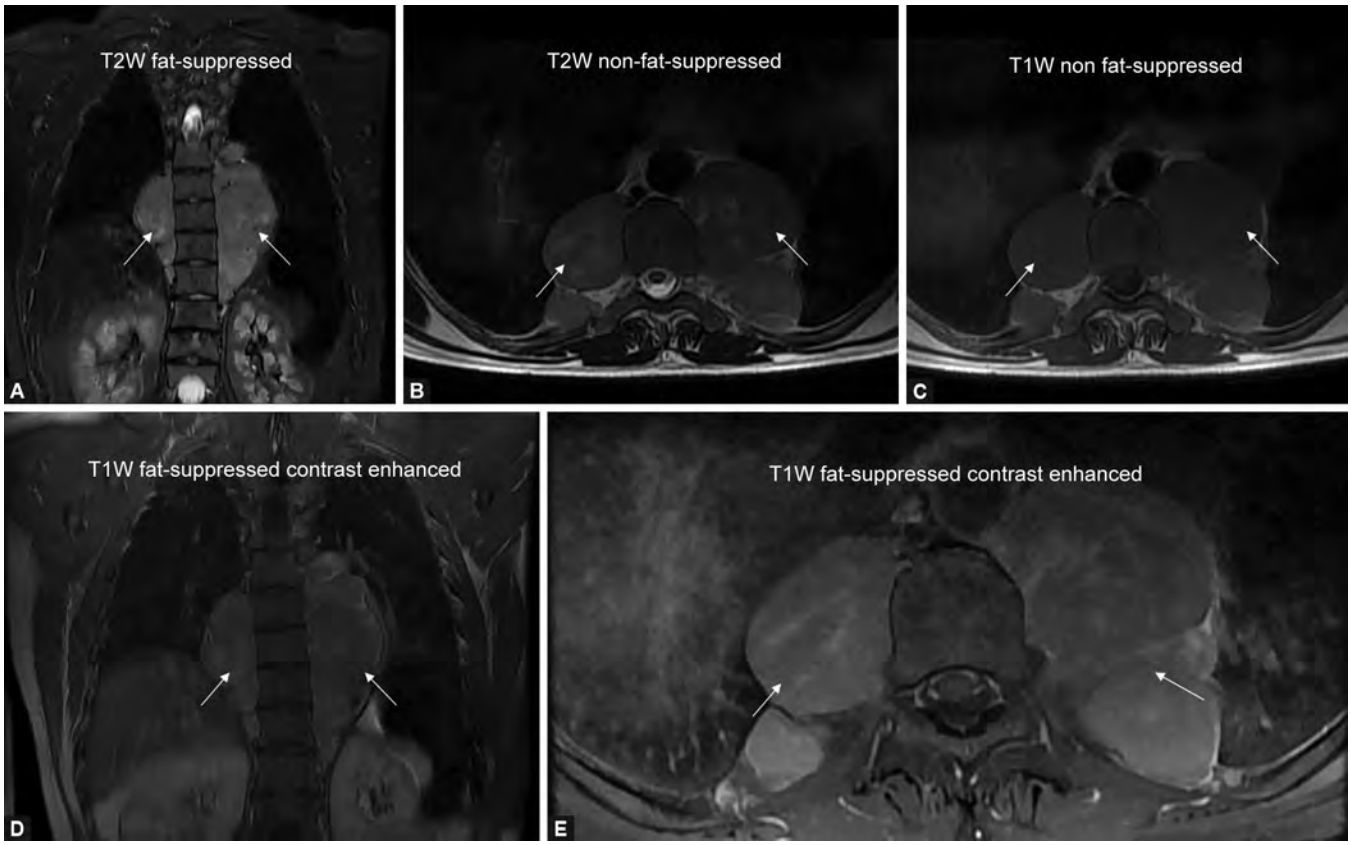


Figs 2A to E: Computed tomography (CT) showing large, lobulated paravertebral masses of extramedullary hematopoiesis (EMH) with soft-tissue density and enhancement (A and B); calcified spleen and gallbladder calculi can be seen in C; and diffuse skeletal sclerotic areas can be seen in the vertebral bodies (D and E)

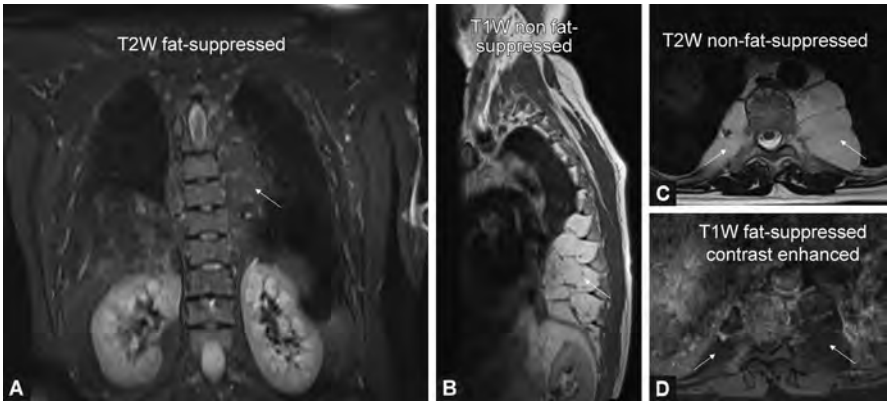
masses that showed suppression on fat-suppressed imaging with subtle minimal enhancement of internal septa. This was indicative of fatty replacement in these masses (Fig. 4).

Discussion

Sickle beta-thalassemia is marked by the coexistence of a sickle cell anemia gene and a beta thalassemia gene (either β^0 or β^+), resulting in both qualitative and quantitative abnormalities in hemoglobin biosynthesis. This condition is relatively common in regions with a higher prevalence of beta thalassemia alleles, such as the Middle East, the Mediterranean, and



Figs 3A to E: Pretreatment magnetic resonance imaging (MRI) in 2022 showing large, lobulated paravertebral masses of extramedullary hematopoiesis (EMH) (arrows), with T1-isointense and T2-isointense to hyperintense signals. Heterogeneous enhancement is noted within the lesions, with no extension into the spinal canal



Figs 4A to D: Posttreatment magnetic resonance imaging (MRI) in 2024 showing lobulated, T1- and T2-hyperintense paraspinal masses that showed suppression on fat-suppressed imaging, with subtle minimal enhancement of the internal septa. This was indicative of fatty replacement in these masses

the Indian subcontinent.[6] The case presented illustrates the dynamic nature of EMH in a patient with sickle beta-thalassemia, showcasing both the initial presentation and the subsequent response to treatment over a period of 2 years. This longitudinal perspective is particularly valuable given the paucity of literature following the evolution of EMH through serial imaging. EMH is a compensatory mechanism that occurs when the bone marrow is unable to meet the body's hematopoietic demands, often due to underlying hematological disorders. In this case, the patient's sickle beta-thalassemia—a condition characterized by ineffective erythropoiesis and chronic hemolysis—prompted the development of EMH. The presence of paravertebral masses and diffuse skeletal sclerosis observed initially highlights the extent of hematopoietic activity outside the bone marrow.

The initial imaging findings are consistent with typical presentations of EMH. Conventional radiography and CT scans revealed paravertebral masses with soft-tissue density and enhancement, alongside areas of diffuse sclerosis. The absence of typical thalassemia-related calvarial and phalangeal findings underscores the variability in skeletal manifestations among patients. MRI provided further insights, showing T1-isointense and T2-isointense to hyperintense lobulated lesions with heterogeneous enhancement. These imaging characteristics reflect the mixed cellular composition of EMH masses, which include hematopoietic cells, fat, and fibrotic elements. Notably, there was no extension into the spinal canal, an important consideration in avoiding potential neurological complications.

The patient's treatment regimen included two cycles of radiotherapy and hydroxyurea. Radiotherapy is known to be effective in reducing the size of EMH masses by inducing fibrosis and fatty replacement.[7,8] Hydroxyurea, on the other hand, promotes the production of fetal hemoglobin, thereby reducing sickling and hemolysis.[9] The follow-up MRI demonstrated significant changes in

the EMH masses, with T1/T2 hyperintense paraspinal masses showing suppression on fat-suppressed imaging and minimal enhancement of internal septa. These findings are indicative of fatty replacement, suggesting a transition to an inactive, or "burnout," EMH. This transformation is a favorable response, indicating reduced hematopoietic activity and stabilization of the condition.

The progression from active EMH to fatty replacement has significant clinical implications. It suggests effective management of the underlying hematological disorder and a potential decrease in the patient's hematopoietic demands. This transition also reduces the risk of complications associated with active EMH, such as mass effect and organ infiltration. The longitudinal imaging data provided in this case report offer a unique perspective on the natural history and treatment response of EMH. Clinicians can utilize these insights to better predict the course of EMH in similar patients and tailor treatment strategies accordingly.

Conclusion

This case report underscores the importance of serial imaging in understanding the evolution of EMH. The documented transition from active EMH to the burnout phase following radiotherapy and hydroxyurea treatment highlights the dynamic nature of this condition and provides valuable insights for clinical practice. Future studies with larger cohorts are needed to further elucidate the long-term outcomes and optimal management strategies for patients with EMH secondary to hematological disorders such as sickle beta-thalassemia.

Acknowledgment

None.

Source of Support

Nil.

Conflict of Interest

None.

Patient Consent Statement

Written informed patient consent for publication has been obtained.

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CASE REPORT

"The Eye of the Storm"—A Rare Case of Nontyphoidal *Salmonella*-related Splenic Abscess and Functional Asplenia in Lupus Nephritis

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Received: 28 June 2025; *Accepted:* 20 August 2025

Abstract

Splenic abscess is a rare entity, with a reported incidence of 0.1–0.7%, often necessitating source control of infection with percutaneous drainage or even partial or complete splenectomy in refractory cases. It carries a high morbidity and mortality risk despite treatment, with immunocompromised states such as malignancy, immunosuppressive medications, acquired immunodeficiency syndrome (AIDS), end-stage kidney disease, cirrhosis, and contiguous sites of infection acting as predisposing factors. We report the case of a 19-year-old lady with lupus nephritis who presented with persistent high-grade fever and sepsis-associated acute kidney injury. After extensive evaluation for potential sources of infection, imaging revealed an abscess in the spleen measuring 6 × 4 × 3 cm. Percutaneous pigtail catheter drainage of the collection under ultrasonography guidance was done. Cultures from pus revealed nontyphoidal *Salmonella*. She also developed progressively worsening thrombocytosis, which was attributed to functional asplenia and was managed with prophylactic antiplatelet to alleviate thrombotic risk, in addition to hydroxyurea therapy. This is the first reported case of nontyphoidal *Salmonella*-associated splenic abscess and further complications in a case of lupus nephritis.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1357

Introduction

Splenic abscess is an uncommon entity, with nearly 100% mortality reported in untreated cases and 16.6% in the first 3 months even in treated cases.[1] Causative pathogens implicated comprise *Escherichia coli*, streptococcal spp., *Proteus mirabilis*, *Staphylococcus* spp., *Candida* spp., *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, and *Clostridium difficile* among the most frequently reported, with geographic variations. Rarer pathogens include fungi, parasites (Plasmodia), Mycobacteria, *Burkholderia pseudomallei*, *Brucella*, *Bartonella*, Actinomycetes, and *Morganella morganii*.[2] Historically, splenectomy was considered the gold standard of therapy. Less invasive modalities like percutaneous drainage have become the cornerstone of current management, in addition to tackling the causative pathogen with appropriate antimicrobials.[1] Prolonged antibiotic cover is often necessary, guided by culture-sensitivity patterns and clinical and radiological resolution. Multilocular collections, abscesses with thicker consistency, and fungal abscesses may not be amenable to percutaneous drainage and potentially warrant splenectomy if refractory to therapy.[3]

Case Description

We report the case of a 19-year-old lady with biopsy-proven lupus nephritis (class IV/V with activity index 3/24 and nil chronicity). She had initially been on steroids and mycophenolate mofetil, switched to tacrolimus 2 years later in view of worsening proteinuria on the existing regimen. She remained in complete clinical remission over the next 5 years. Subsequently, owing to relapse on therapy, she received a single dose of low-dose rituximab (100 mg) followed by 3 more doses of 200 mg each. Cluster of differentiation 19 (CD19) levels showed suppression to 0.14%. Serum creatinine touched a peak of 2.9 mg/dL from a baseline of 0.5 mg/dL, with worsening albeit subnephrotic proteinuria. A rebiopsy of the kidney revealed class III/V lupus nephritis, with activity index 2/24, chronicity index 1/12, and thrombotic microangiopathy. Antiphospholipid antibody (APLA) workup was negative. Plasmic score stratification (score 4) was consistent with low risk, and she was treated with pulse steroids sans anticoagulation or plasma exchange.

Shortly afterward, she developed a right upper lobe consolidation yielding *Acinetobacter baumannii* and *Candida* on bronchoalveolar lavage and, a month later, a right middle lobe lung abscess with features of atypical pneumonia. Serum galactomannan tested positive. She received intravenous antibiotics and *Aspergillus* coverage. She was also initiated on empiric antituberculous therapy from an outside center with a modified regimen with dose adjustment for renal failure, comprising isoniazid, low-dose ethambutol, and pyrazinamide, owing to a clinical suspicion revolving around cavitating pneumonia.

She presented to our center with persistent high-grade fever sans chills and repeated emesis. She was hemodynamically stable with pallor and features of volume overload. Systemic examination was noncontributory. Pertinent labs upon admission were: TC 30,300 cells/mm^3, 90% N, 10% L; Hb 6.3 gm/dL; platelet count 3.1 lakh/mm^3; serum creatinine 2.4 mg/dL; blood urea 48 mg/dL; serum albumin 2 gm/dL; CRP 104 mg/L; urine routine: albumin trace, 2–4 RBC/hpf, no casts or crystals; 24 hours urine protein 400 mg/day.

She was empirically started on intravenous antibiotics to offer broad coverage (meropenem and teicoplanin), along with continuation of antifungals (voriconazole) in view of positive galactomannan assay despite unyielding cultures. Antituberculous therapy was withheld since sputum studies were noncontributory. A comprehensive evaluation for potential foci of infection was undertaken, including echocardiography, which ruled out infective endocarditis. Blood and urine cultures were sterile. Noncontrast computed tomography (CT) abdomen identified a well-defined subcapsular cystic

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How to cite this article: Yoonus F, KS SK, Haridas S, *et al.* "The Eye of the Storm"—A Rare Case of Nontyphoidal *Salmonella*-related Splenic Abscess and Functional Asplenia in Lupus Nephritis. J Assoc Physicians India 2026;74(6):53–55.

hypodense lesion with thin internal septations involving the inferior pole of the spleen, suggestive of a splenic abscess (Fig. 1).

She underwent percutaneous aspiration and drainage of the collection with a pigtail catheter until residual collection was negligible and not amenable to further aspiration. Following the procedure, she improved clinically. Serum creatinine touched a nadir of 1.2 mg/dL. Pus cultures yielded nontyphoidal *Salmonella* (Fig. 2), sensitive to carbapenems and cotrimoxazole. She was continued on meropenem for 4 weeks and switched over to cotrimoxazole, with 6 weeks of antibiotic therapy in toto. Voriconazole was given for a total of 12 weeks, since repeat galactomannan assay remained positive albeit down-trending.

Despite the resolution of infection, a novel challenge in the form of progressively worsening thrombocytosis reared its head, with no clinical history suggestive of a genetic predisposition for essential thrombocytosis. The most likely etiology was considered to be functional asplenia secondary to abscess and some degree of splenic infarction. However, since platelet counts crept up to threatening levels of 10 lakh cells/mm^3, raising the risk for thromboembolic events, she was started on single antiplatelet therapy along with hydroxyurea, following which platelet counts developed a downward trend.

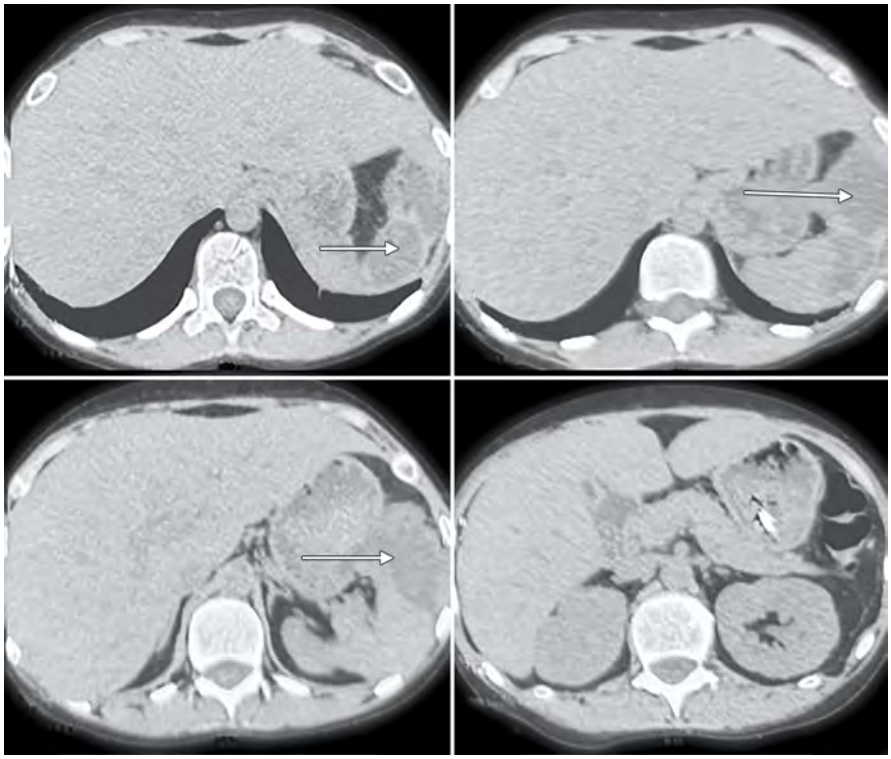
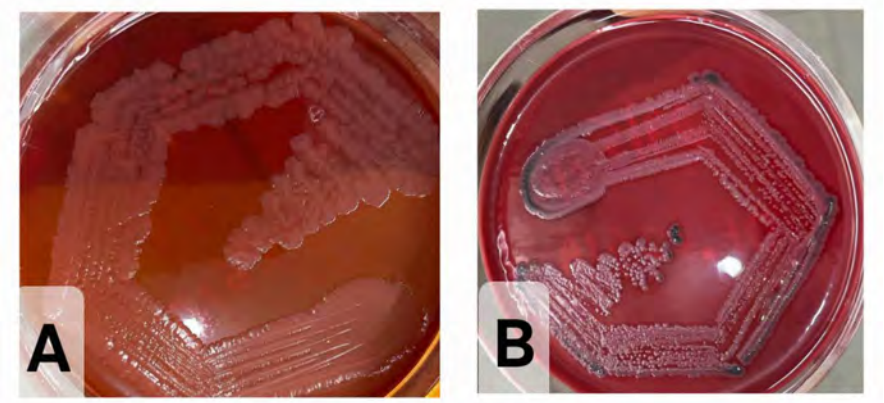


Fig. 1: Noncontrast CT scan of the abdomen showing a well-defined subcapsular cystic hypodense lesion with thin internal septations involving the inferior pole of the spleen, measuring 6.7 × 3.6 × 4.6 cm (AP/transverse/CC), suggestive of splenic abscess



Figs 2A and B: (A) Nonlactose-fermenting colorless colonies of nontyphoidal *Salmonella* on MacConkey agar culture; (B) Nontyphoidal *Salmonella* colonies on XLD agar with a reddish translucent zone and black areas depicting H2S production

Discussion

Lupus nephritis has been associated with a plethora of infectious complications by virtue of its immune dysregulated state and secondary to chronic immunosuppression. Urinary (30.7%), gastrointestinal (22.0%), and pleuropulmonary (16.3%) sources are the leading sites of infection.[4] Splenic abscess in itself is a rare entity, and its association with lupus nephritis has been hardly reported. Apart from 1 other case of multiple aseptic splenic abscesses in a case of SLE, our literature search with "splenic abscess" and "lupus nephritis" as keywords did not yield any other report of a similar presentation. To the best of our knowledge, this case remains the first reported case of splenic abscess due to nontyphoidal *Salmonella* in a case of lupus nephritis.

The patient had been heavily immunocompromised. States of immunosuppression are a major harbinger for occult infections such as splenic abscess, which may be masked in presentation. Just like a subphrenic abscess is often a diagnostic black hole, identifying a splenic abscess remains challenging and may be missed if not for an index of suspicion in persistent infection, particularly if cultures remain sterile and extensive imaging is not undertaken in resource-limited settings. Though the patient may respond transiently to intravenous antibiotics, the occult infection could prove life-threatening without source control and prompt drainage and may even spiral toward a splenectomy but for timely intervention.

Percutaneous needle aspiration is recommended in abscesses of size <5 cm and percutaneous catheter drainage in bilocular abscesses and those exceeding 5 cm.[3] Since our patient had the largest dimension of collection exceeding 6 cm, percutaneous pigtail catheter drainage was undertaken. Antimicrobial cover needs to be tailored to the offending pathogen owing to wide geographical variations, with fungal splenic abscesses being a hallmark of immunosuppressed patients in particular. A broad coverage for gram-positive, gram-negative, and anaerobes with prophylactic antifungals in heavily immunosuppressed individuals could be an initial empiric regimen until cultures can isolate the pathogen. Other potential seeding sources, like hematogenous spread from infective endocarditis lesions or contiguous septic foci, need to be ruled out.[1]

Splenic infarction evolving into an abscess is of concern in potential cases, especially with a background of thrombotic microangiopathy (TMA) as in our case.

Among the myriad complications of splenic abscesses, 1 with potentially grave consequences if untreated is thrombocytosis owing to functional asplenia and reduced splenic sequestration. Thrombotic events such as acute myocardial infarction, pulmonary embolism, and mesenteric vein thrombosis have been reported in extreme thrombocytosis. Treatment with acetylsalicylic acid, hydroxyurea, anagrelide, interferon alpha, ticlopidine, and enoxaparin has been described, with resorting to thrombocytapheresis in hyperthrombocytosis should cytoreductive therapies fail.[5] Our patient was started on hydroxyurea and prophylactic antiplatelet therapy with a stable response to treatment.

Persistent B cell depletion following rituximab has been reported in the literature as a rare complication in 2% of patients treated with rituximab for glomerular and autoimmune diseases, with the underlying disease remaining in remission at the cost of infection risk and late-onset neutropenia. It has been described as <5 CD19+CD20+ cells/μL persisting for >2 years following the last dose of rituximab. Hypogammaglobulinemia with high risk of infections, which can be partially addressed with intravenous immunoglobulin therapy, is also characteristic. Other risk factors like concomitant use of cytotoxic agents in addition to rituximab have been implicated in its pathophysiology since rituximab by itself causes total depletion of the peripheral B cell pool while only partially suppressing the B cell population in secondary lymphoid organs and other tissues. This eventually leads to B cell repopulation in the normal setting, unlike in the select set of patients with persistent B cell depletion. It remains to be seen whether our patient attains B cell repopulation in the coming years or remains a potential case of persistent B cell depletion. Owing to the benefit of doubt in the background of recurrent infections in the wake of sequential rituximab therapy, she was subjected to intravenous immunoglobulin therapy (single dose of 200 mg/kg) despite absence of hypogammaglobulinemia.[6]

A causal association between lupus and nontyphoidal salmonellosis has also been described, whereby the same underlying immune dysregulation could be a potential trigger for both lupus and nontyphoidal salmonellosis, lupus in itself could predispose to nontyphoidal salmonellosis (NTS) infections, or NTS act as a flare trigger in lupus. Extraintestinal manifestations are the classic presentation in lupus patients suffering from NTS infections, encompassing osteomyelitis, septic arthritis, or even asymptomatic bacteriuria. Splenic abscess owing to NTS in lupus nephritis is being reported here as the first of its kind, but this potential association requires further study in light of the implications of NTS infection on the immune milieu of lupus, particularly in the wake of periods of intensified immunosuppression.[7]

This case report is meant to serve as an eye opener that underscores the significance of identifying occult sites of infection such as splenic abscesses in heavily immunosuppressed individuals who may not present typically and employing stringent and prompt source control to avert undue catastrophic consequences. It also highlights the need for streamlining immunosuppressive protocols during lupus flares, avoiding overimmunosuppression owing to the delicate balance between infection and immunosuppression in lupus nephritis.

Declaration of Patient Consent

The authors state that they have obtained appropriate patient consent.

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CASE REPORT

Bidirectional Ventricular Tachycardia Culminating in Cardiac Arrest: A Diagnostic and Management Conundrum

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

Abstract

Bidirectional ventricular tachycardia (BDVT) is a rare arrhythmia marked by beat-to-beat QRS axis alteration. We report a 36-year-old female with recurrent palpitations who presented with BDVT degenerating into polymorphic ventricular tachycardia and ventricular fibrillation. An extensive evaluation, including cardiac magnetic resonance imaging (MRI), stress and adrenaline provocation testing, and a comprehensive genetic arrhythmia panel, revealed no definitive etiology. Given the concern for proarrhythmic implantable cardioverter-defibrillator (ICD) shocks in a potential channelopathy and after shared decision-making, the patient was managed with high-dose beta blocker therapy. This case underscores the diagnostic and management challenges of BDVT in a structurally normal heart, particularly when balancing guideline recommendations against individualized patient factors.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1356

Introduction

Bidirectional ventricular tachycardia (BVT) is a rare form of ventricular tachycardia with QRS morphologies alternating from beat to beat in frontal plane leads. Originally described in the 1920s in association with digitalis,[1] many etiologies have since been reported, which include fulminant myocarditis, sarcoidosis, catecholaminergic polymorphic ventricular tachycardia (CPVT), cardiac tumors, Andersen–Tawil syndrome, and aconite poisoning.[1,2] We present the case of a young woman who experienced bidirectional VT progressing to cardiac arrest. Despite an extensive investigation, a definitive underlying etiology could not be identified, leading to a working diagnosis of idiopathic bidirectional VT and posing a significant management dilemma.

Case Description

A 36-year-old woman without any comorbidities presented with a 4-year history of recurrent palpitations, each lasting 15–20 minutes, which were paroxysmal, without syncope. She presented with recent palpitations associated with giddiness and vomiting, followed by syncope. The electrocardiogram (ECG) on attachment of the limb leads revealed (Fig. 1) regular, wide QRS tachycardia at approximately 200 beats per minute with a beat-to-beat alternating QRS axis in the limb leads, characteristic of BVT. This rhythm rapidly degenerated into polymorphic ventricular tachycardia (Fig. 2) and subsequently ventricular fibrillation, requiring immediate direct current defibrillation with 200 J. She was promptly defibrillated with 200 J and started on lidocaine infusion. The postresuscitation 12-lead ECG, recorded approximately 30 minutes after the event (Fig. 3), showed sinus rhythm at 75 bpm with deep, asymmetric T-wave inversions in leads V1–V4 and biphasic T waves in the inferior leads. These T-wave abnormalities completely resolved on a follow-up ECG performed 72 hours later, suggesting they were likely a transient phenomenon related to postcardiac arrest myocardial stunning or T-wave memory (Fig. 3). Routine laboratory reports, quantitative troponin I, and serum electrolytes were within normal limits. She did not have a history of digitalis intake or use of alternative medicines. There was no family history of sudden death.

Echocardiography and cardiac magnetic resonance imaging (MRI) were normal. Treadmill stress test (TMT) did not bring out any premature ventricular complexes or VT. Adrenaline provocation test was similarly unremarkable. A genetic panel, which included testing for RyR2, CASQ2, CALM1–4, and KCNJ2, was negative for channelopathies.

The patient's presentation with resuscitated cardiac arrest met the Class I guideline indication for a secondary prevention implantable cardioverter-defibrillator (ICD). However, this was carefully weighed against several factors. The underlying mechanism, while unproven, was highly suspicious for a calcium-handling channelopathy (e.g., CPVT), where painful ICD shocks can trigger an adrenergic surge, potentially leading to electrical storm. This risk is highlighted in observational studies.[3] After extensive shared decision-making with the patient and her family, discussing the risks of both sudden death and ICD-related complications, the patient opted for a trial of aggressive medical therapy and close monitoring. Therefore, an ICD was not implanted at the time of discharge. She was started on high-dose propranolol (40 mg twice daily).

Discussion and Review of the Literature

This case of resuscitated cardiac arrest secondary to bidirectional VT highlights a significant diagnostic and therapeutic challenge. The absence of structural heart disease and a negative comprehensive workup led to a diagnosis of exclusion, idiopathic BVT. This ambiguity forced a difficult management decision, balancing guideline-based ICD implantation against the potential for harm in a suspected but unproven channelopathy.

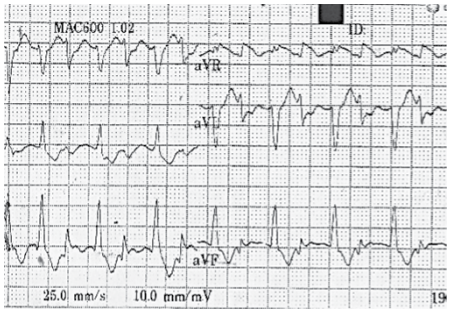

Fig. 1: ECG showing wide complex tachycardia with 2 different QRS morphologies suggestive of BDVT (only limb leads available)

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How to cite this article: Limaye SV, Anand AB, Nathani PJ, *et al.* Bidirectional Ventricular Tachycardia Culminating in Cardiac Arrest: A Diagnostic and Management Conundrum. J Assoc Physicians India 2026;74(6):56–58.

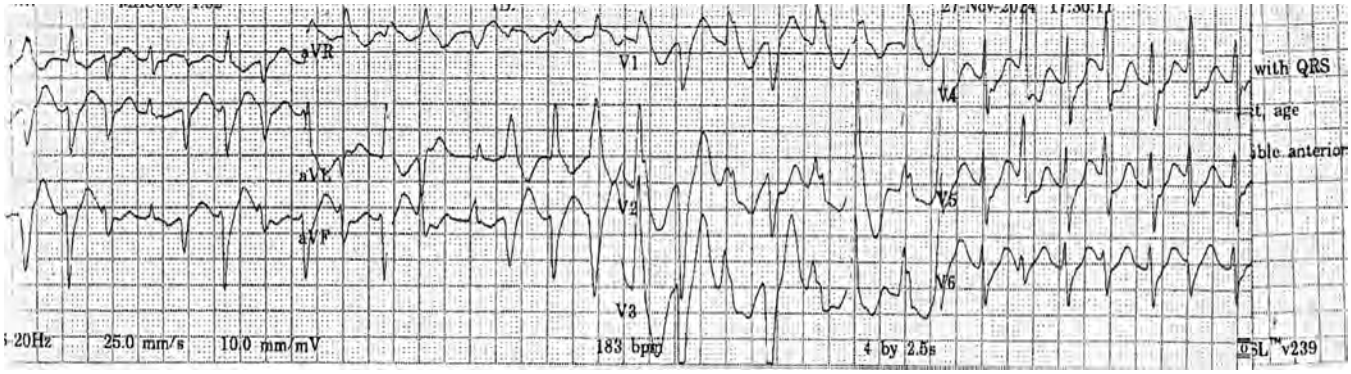

Fig. 2: ECG showing polymorphic ventricular tachycardia, precordial leads with alternating QRS morphologies and axis suggestive of BDVT

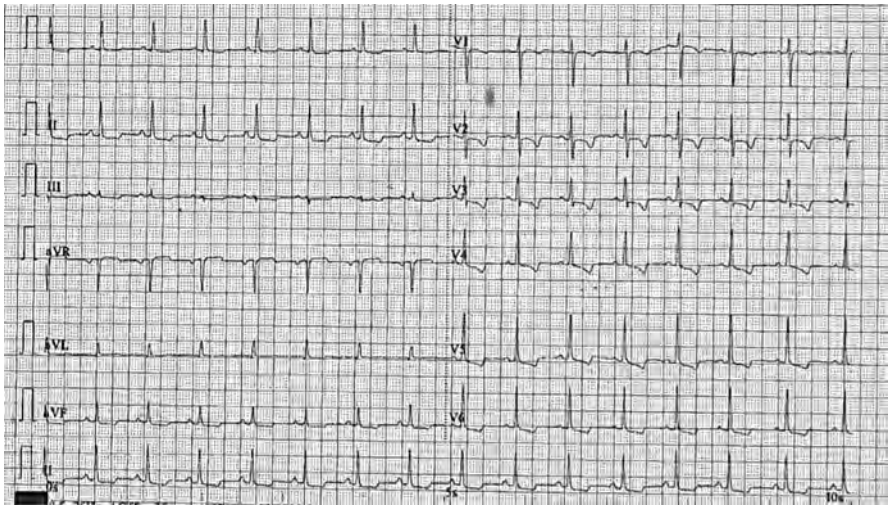

Fig. 3: ECG post-DC cardioversion suggestive of sinus rhythm with 1:1 conduction and precordial T wave inversions suggestive of memory T wave signs

Bidirectional ventricular tachycardia is a rare arrhythmia defined as every other beat alternating in cycle length and direction, typically resulting from triggered activity due to delayed afterdepolarizations. Delayed afterdepolarizations result from calcium overload causing spontaneous SR release, activating the sodium-calcium Na^{+}/Ca^{2+} exchanger and triggering a transient inward current.[4] While originally described in association with digitalis toxicity, various etiologies, including catecholaminergic polymorphic ventricular tachycardia (CPVT), have been recognized. The ping-pong theory suggests that bidirectional VT arises from alternating bigeminy between 2 His-Purkinje sites. If 3 or more sites are involved, it can lead to polymorphic VT.[2]

Catecholaminergic polymorphic VT is an inherited arrhythmogenic disorder caused by mutations in the ryanodine (*RYR2*) or calsequestrin (*CASQ2*) genes, leading to calcium-handling abnormalities that predispose to ventricular arrhythmias. The diagnosis is often supported by clinical features such as adrenergic-induced polymorphic or BDVT and a positive family history, though genetic testing provides definitive confirmation.[5] Provocation tests can be carried out, including exercise provocation testing with sensitivity of 63% and adrenaline provocation testing, which has sensitivity of 80%.[6] Adrenaline provocation testing is carried out after rest of 10 minutes followed by adrenaline infusion at 0.0225 µg/kg/minute and sequential increment every 5 minutes to 0.2 µg/kg/minute. The test is considered positive when ≥3 beats of VPCs or bidirectional VT are induced.[7] Both were negative in our patient. Beta blockers are the first line of management. While guidelines strongly recommend an ICD for secondary prevention of sudden cardiac arrest,[7] our management strategy was nuanced by the potential diagnosis. In CPVT, for example, the adrenergic surge caused by a painful shock can be proarrhythmic, a concern supported by data showing worse outcomes in some CPVT cohorts with an ICD.[3] This potential for iatrogenic harm was the primary driver of our shared decision-making process with the patient, leading to the decision to defer ICD implantation in favor of high-dose beta blockade and vigilant surveillance with an ILR.

Upper thoracic sympathectomy is also a viable option, in addition to beta blockers. Another etiology of bidirectional VT is Andersen–Tawil syndrome, which is an autosomal dominant condition caused by mutation in the *KCNJ2* gene, which encodes the inward rectifier potassium channel. It has a classic triad of periodic paralysis, cardiac arrhythmias, and facial dysmorphism. The baseline ECG may show a prolonged QT-U interval.[8] Other described etiologies include aconite poisoning.[9] Aconite is used in herbal and Chinese medicines and has been reported to result in bidirectional VT,[10] as has fulminant myocarditis.

In our case, the patient presented with recurrent palpitations over 4 years, with an episode of bidirectional VT and ventricular fibrillation. The absence of structural heart disease, normal electrolyte levels, normal troponin I, lack of exposure to digitalis or aconite poisoning, negative genetic panel, and negative provocative testing suggest an idiopathic variant in our current state of knowledge. The yield of genetic testing in catecholaminergic polymorphic VT remains modest; the yield is highest for the *RYR2* gene, around 60–70%, and <10% for other genes.

Conclusion

Bidirectional VT is a rare arrhythmia with varied causes. This case, with no identifiable etiology despite extensive workup, suggests an idiopathic variant. The patient remains stable on propranolol, with careful long-term follow-up advised.

Acknowledgments

All authors had access to the data and a role in writing the manuscript.

Orcid

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CASE REPORT

Artesunate-resistant *Plasmodium falciparum* at a Tertiary Care Hospital in North India

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Received: 08 November 2024; *Accepted:* 23 May 2025

Abstract

The emergence of artemisinin resistance poses a serious global challenge to malaria elimination programs. Artemisinin and its derivatives, especially artesunate, are highly effective against *Plasmodium falciparum*, particularly in severe and uncomplicated cases. However, increasing reports of treatment failure, particularly with artesunate monotherapy, raise concerns regarding emerging resistance. We present a clinically significant case of suspected artesunate-resistant *P. falciparum* in an Indian male residing in Nigeria. Despite standard therapy, parasite clearance was delayed, necessitating therapeutic modification. While this case report demonstrates clinical resistance, the lack of confirmatory genetic testing (such as Pfkelch13 mutation screening) remains a limitation.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1121

Case Description

A 51-year-old Indian male, residing in Nigeria, known case of type 2 diabetes mellitus, presented with complaints of high-grade fever with chills since 5 days, dry cough since 3 days, and shortness of breath on exertion since 5 days. He gave a recent travel history to Andhra Pradesh 10 days back. On examination, the patient was conscious and oriented. He had pallor and was febrile with a temperature of 100°F. He had hypotension with a blood pressure of 90/60 mm Hg, tachycardia with a pulse rate of 111/minute, and a saturation of 93% on room air.

On systemic examination, he had bilateral basal crepitations on auscultation and hepatosplenomegaly on palpation. His cardiac examination was within normal limits.

He was admitted and routine investigations were done. Complete blood count revealed hemoglobin 9.0 gm/dL, total leukocyte count 4.22 thousand/µL, and platelets 159 thousand/µL. Liver function tests and renal function tests were within normal limits.

Peripheral blood smear for malarial parasites showed trophozoites and gametocytes of *Plasmodium falciparum*. Urine routine and microscopy showed occasional pus cells, and cultures were sterile. Blood cultures were sterile. Glucose-6-phosphate dehydrogenase deficiency screening was negative.

Patient was started on monotherapy of injection artesunate 120 mg twice daily. On the 1st day of therapy, a parasitic index was done, which was 85.4 parasites/µL of blood. Treatment response was checked on the 4th day of therapy by parasitic index, which came out to be 111.2 parasites/µL of blood. Patient started to develop a fall in hemoglobin to 7 gm/dL and thrombocytopenia to 103 thousand/µL and was transfused one unit of packed red blood cells. The treatment of artesunate was continued for 2 more days with an addition of oral tablets of quinine 600 mg thrice daily on the 4th day of artesunate therapy. Parasite index was done on the 7th day, that is, after 2 days of quinine, and it reduced to 20.6 parasites/µL of blood. Another parasitic index that was done on day 9 revealed no parasites and complete clearance of parasite from bloodstream. The patient was afebrile and discharged on oral tablets of quinine and was recommended a total course of 7 days. Patient is doing well on follow-up with normal hemogram and liver function test.

Discussion

Artemisinin and various formulations, including artesunate, artemether, and dihydroartemisinin, have potent killing tendencies against various stages of falciparum parasites, including symptomatic stages of malaria like trophozoites and schizonts, and also the transmitting sexual stages, that is, the gametocyte stages. These formulations are sesquiterpene lactones that comprise the endoperoxide bonds, which get cleaved by the heme-associated iron release formed from the parasitic infestation of red blood cells. This, in turn, leads to the release of various reactive oxygen species that kill and attack parasitic structures.[1] *P. falciparum* malarial ring forms are present in the bloodstream for several hours before converting into trophozoite forms. When artemisinin therapy is introduced, these ring forms undergo precipitation into inclusions resembling Howell–Jolly bodies; these condensed parasites are then sequestered in the spleen and killed.[2,3] Due to such promising results of rapid destruction of parasitic forms, it has reduced malarial mortality in Asian countries by a significant amount and is thereby regarded as a first-line therapy for uncomplicated malaria.[4]

In 2009, a randomized trial conducted in Cambodia was the first reported study on resistance of the drug; there was a slow clinical and parasitic response when compared *in vitro*.[5] On defining artemisinin resistance, it can be stated as parasite clearance half-life of >5 hours following treatment with artesunate alone or a combination therapy.[5] The parasite clearance half-life is calculated by plotting the parasite density against time in a graph, and the slope is used to calculate half-life.[6] A term, partial resistance, has also been documented in studies and is considered as a time delay in the clearance of malarial ring forms solely after 48 hours of therapy. Complete artemisinin resistance has not been seen so far.[7] The gene primarily implicated as a marker of artemisinin resistance is *P. falciparum* Kelch 13 (*Pfk13*). Research has pointed out that early forms of rings, typically seen up to 3 hours of the life cycle, express resistance, whereas later forms do not.[8] A surrogate measure of artemisinin resistance is slow parasite clearance, which can be seen as high parasite index even after 3 days of therapy, as in our case. Although parasitic clearance and response are based on several factors like initial parasitic load, renal functioning, prior spleen removal, or presence of sickle cell disease.[9] *In vitro* tests for detecting resistance

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How to cite this article: Taneja V, Khosla P, Narula S, *et al.* Artesunate-resistant *Plasmodium falciparum* at a Tertiary Care Hospital in North India. J Assoc Physicians India 2026;74(6):59–60.

include the trophozoite inhibition maturation assay (TMI) and the ring survival assay (RSA) with a parasite survival rate ≥1%.[10]

There is a reduced susceptibility of the malaria parasite's initial ring stage to the effects of artesunate, primarily due to mutations in the *Pfk13* gene, notably the C580Y mutation.[11] Artemisinins, like artesunate, induce oxidative damage within the parasite. Mutations in *Pfk13* may lead to adaptations that diminish the impact of this oxidative stress, contributing to drug resistance.[12] Lower levels of ubiquitinated proteins within the parasite suggest a compromised ability to eliminate damaged or misfolded proteins, potentially aiding the parasite in coping with stress and evading the effects of artesunate.[13,14] Mutations in *Pfk13* may result in elevated levels of phosphatidylinositol-3-phosphate (PI3P) due to changes in its association with phosphatidylinositol-3-kinase (PfpI3K), the enzyme responsible for its synthesis. This altered lipid metabolism could influence various cellular functions, possibly contributing to drug resistance.[15] Changes to the infected red blood cell membrane caused by *Pfk13* mutations may reduce the spleen's capacity to recognize and clear the parasite, allowing it to persist in the bloodstream. Mutations in *Pfk13* could lead to increased vesicle activity in the parasitic endoplasmic reticulum, impacting the parasite's ability to respond to stress and maintain cellular balance, thus aiding in drug resistance.[16,17]

Due to the risk of severe malarial complications, multiple modified regimens have been tested, which include a prolonged course of artesunate combination therapy.[18] The prolonged treatment course includes usage of combination therapies for 5–6 days, which has proved to be efficacious in dealing with resistance cases.[18] On evaluating the usage of dihydroartemisinin-piperaquine in cases of artemisinin resistance, improvement was seen when treatment duration was extended from 3 to 5 days.[19] Prolonging the treatment also raises concerns about dosage-related side effects, but a 5-day treatment course of artemether-lumefantrine was found to be safe in cases of treatment of uncomplicated malaria in trials done in Africa.[20,21] Several modifications of antimalarials had been tried in multiple cases reported in South India. In a case series comprising four pediatric cases from Andhra Pradesh and Odisha, artesunate treatment with a combination of sulfamethoxazole-pyrimethamine was unable to clear the parasite from blood after a 3-day course. Administering intravenous quinine and clindamycin in these patients along with primaquine cleared the parasite from blood within 2–3 days of initiation.[22] A similar scenario was reported in Cambodia with artesunate-mefloquine usage for the treatment of drug-resistant falciparum malaria, and promising results were obtained.[23] Unfortunately, we were unable to perform artemisinin resistance gene testing. The PfATPase6, which is the product of the *pfserca* gene, has been suggested to be a specific target of the artemisinin drugs.[24] The increasing parasite load, as in our case, even after administration of artesunate monotherapy indirectly identified resistance patterns in our patient. Despite the efficacy of artemisinins, clinical resistance has been increasingly documented in Southeast Asia and parts of Africa, particularly Nigeria. Studies from Nigeria have reported delayed parasite clearance and recurrence, often associated with genetic mutations in the *Pfk13* gene (notably C580Y and R561H).[25] In our case, parasite index increased despite three days of artesunate monotherapy, which was used as a surrogate marker for resistance. However, without genetic confirmation (such as *Pfk13* sequencing or RSA assay), definitive diagnosis remains incomplete in our case.

Conclusion

This case highlights the potential emergence of artesunate resistance in *P. falciparum* among Indian expatriates in malaria-endemic regions like Nigeria. The delayed parasitic clearance despite artesunate therapy and rapid response upon addition of quinine support probable resistance. However, absence of molecular diagnostic confirmation limits the strength of evidence. Such cases point out the significance of developing global screening tools like *PfK13* gene mutation tests and identifying such cases at the earliest in order to prevent treatment-failure–related mortality.

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CASE REPORT

Coexistence of Neuromyelitis Optica Spectrum Disorder and Proliferative Lupus Nephritis: A Rare Case Report

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Received: 10 May 2025; *Accepted:* 04 August 2025

Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune demyelinating disease manifesting with transverse myelitis and optic neuritis. Systemic lupus erythematosus (SLE) also commonly affects kidneys and central nervous system. Here, we describe a case of proven NMOSD for almost 16 years with multiple relapses over a period of time, presented to us with acute nephritic syndrome. Her kidney biopsy revealed class 4 lupus nephritis. She responded to steroid, rituximab, and mycophenolate mofetil and achieved complete remission at 3 months. Subsequent relapse at 6 months was initially treated with addition of tacrolimus without success. Later, she dramatically responded to a single dose again. This is one of few cases of coexistence of both diseases from India. Rituximab, MMF, and steroids should be considered as an initial treatment even for proliferative lupus nephritis when NMOSD and SLE coexist.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1346

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disorder characterized by inflammatory lesions in the optic nerves and spinal cord, mediated by pathogenic aquaporin-4 (AQP4) antibodies.[1] Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease with a wide range of clinical manifestations, including neurological and renal involvement. Although these two conditions are distinct entities, their coexistence has been reported in several case studies, highlighting the potential overlap in autoimmune pathways.[2] Here we report a case of proliferative lupus nephritis coexisting with NMOSD who was managed successfully with rituximab, which is actually not recommended for lupus nephritis.

Case Description

A 35-year-old woman with a 16-year history of NMOSD, confirmed by positive anti-AQP4 antibodies and relevant MRI findings, presented with acute nephritic syndrome. She was diagnosed with NMO after experiencing a complete loss of vision, which responded to corticosteroid treatment. Subsequently, she experienced multiple relapses involving transverse myelitis and optic neuritis, treated with immunosuppressive agents, including azathioprine, mycophenolate mofetil, and rituximab.

During her current presentation, the patient reported facial puffiness, pedal edema, anorexia, and dyspnea on exertion for the past 2 weeks. Physical examination revealed bilateral pedal edema and hypertension.

Results

Laboratory investigations showed hematuria, subnephrotic proteinuria (urine protein-to-creatinine ratio of 2.93 gm/gm), and elevated serum creatinine (2.3 mg/dL) (Tables 1 and 2). Serological tests revealed positive antinuclear antibodies (ANA) by indirect immunofluorescence, low complement levels (C3: 0.6 gm/L; C4: 0.06 gm/L), and negative antidouble-stranded DNA (dsDNA) antibodies. This renal involvement and ANA positivity occurred for the first time, 16 years after her NMO had set in. Previous testing of ANA and ANA profiles by immunofluorescent and ELISA methods on six occasions were negative, until the time of the current episode of lupus nephritis, when it turned positive.

A renal biopsy was performed, which revealed diffuse endomesengial proliferation, lobular accentuation, obliteration of capillary lumina, mild neutrophilic exudation, thickening and reduplication of the basement membrane, and a full-house pattern on immunofluorescence staining. (Figs 1 and 2). These findings were consistent with class IV proliferative lupus nephritis according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification.[3]

The patient was treated with high-dose intravenous corticosteroids (methylprednisolone 1 gm/day for 3 days), followed by oral prednisolone, a single dose of rituximab (1 gm), hydroxychloroquine (200 mg), and mycophenolate mofetil (MMF) (initially low dose, gradually increased to a maximum tolerated dose of 2 gm/day). After 3 months of treatment, the patient achieved complete remission, with normalization of renal function and resolution of proteinuria. She developed a relapse at 6 months which was treated by the addition of tacrolimus to MMF and steroids. Unfortunately, she did not respond to it. She was again treated with a single dose of 1 gm rituximab. After 12 weeks she again got complete remission.

Discussion

The association of NMOSD and SLE is a rare phenomenon, with an estimated prevalence of less than 1%.[4] Very few cases of simultaneous or subsequent occurrence of both diseases have been reported from India.[5] Several mechanisms have been proposed to explain this association, including shared genetic and environmental factors contributing to autoimmunity, disruption of the blood–brain barrier in SLE facilitating access of AQP4 antibodies to the central nervous system, and potential common immunopathological pathways such as vasculopathy.[6] It is not certain which disorder will precede or follow other while simultaneous coexistence is also reported.

Distinguishing between the manifestations of NMOSD and SLE can be challenging, as both conditions can involve the central nervous system and present with overlapping neurological symptoms.

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How to cite this article: Shah MK, Makwana M, Desai S, *et al.* Coexistence of Neuromyelitis Optica Spectrum Disorder and Proliferative Lupus Nephritis: A Rare Case Report. J Assoc Physicians India 2026;74(6):61–64.

Table 1: Laboratory and radiological investigations

On admission	*Day 1*	*Day 5*	*Day 8*	*Day 12*	*3 months*	*6 months*	*9 months*	*1 year*
Hb (gm/dL)	8.9	8	7.9	7.8	9.2	7.7	7.5	9.4
TLC (/mm^3)	5400	7800	9000	6000	7400	4500	4800	5200
Platelet count (/mm^3)	1,85,000	2,03,000	2,15,000	1,65,000	1,75,000	1,25,000	1,40,000	1,35,000
Serum creatinine (mg/dL)	1.85	2.3	2.1	1.2	0.8	1.5	2.1	1.2
Na^+, K^+, Cl^- (mmol/L)	136/5.1/94	135/4.8/98	138/4.5/96	139/4.2/98	141/4.9/98			
Total protein with albumin (gm/dL)	6.5/2.7				7.2/3.8/3.4			
SGPT/SGOT(U/L)	11/13							
Urine R/M	$Protein^{++}$, $Blood^{++}$, pus cells 20–22/hpf				$Protein^{+}$, Blood nil, pus cells occ/hpf	$Protein^{+++}$, $Blood^{++}$, pus cells: 20–25/hpf	$Protein^{++++}$, $blood^{++}$, pus cells 15–20/hpf	$Protein^{+}$, Blood–nil Pus cells—occasional
Urine protein creatinine ratio (gm/gm)	2.93				0.325	1.5 Tacrolimus added	3.54 Rituximab 1 gm given, tacrolimus stopped	0.450
PT with INR	12.4/1.05							
APTT	27.5							
Blood C/S	No growth							
Urine C/S	No growth							
X-ray chest	B/L pleural effusion							
USG KUB	RK—9.5 × 4.5 cm LK—9.8 × 5 cm, CMD preserved							

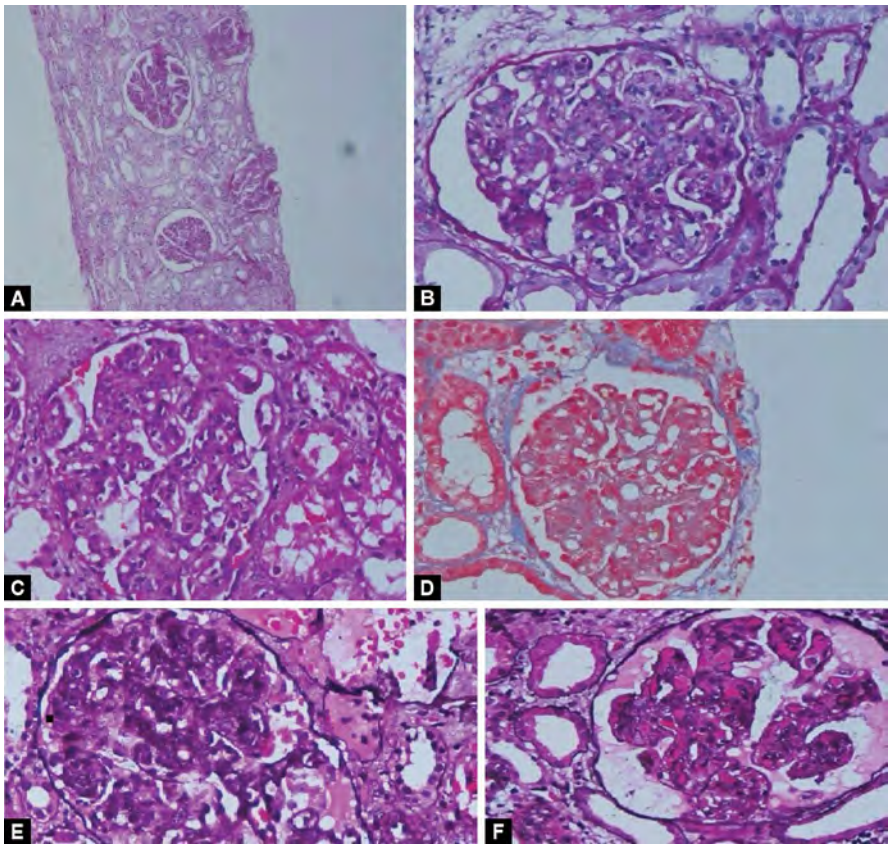
Table 2: Immunological investigations

	Previous admissions	*This admission*
ANA by IF	Negative	1+ by IF
DsDNA by ELISA	Negative	6.37 IU/mL—negative
Complement protein C3	Normal	0.6 gm/L—low
Complement protein C4	Normal	0.06 gm/L—very low
ANCA-C and P by ELISA	Negative	Negative
Anti-NMO	Positive	Not done
Lupus anticoagulant	Absent	Absent
Anticardiolipin antibody IgG, IgM	Not done	Negative
Beta2 glycoprotein antibody IgG, IgM	Not done	Negative

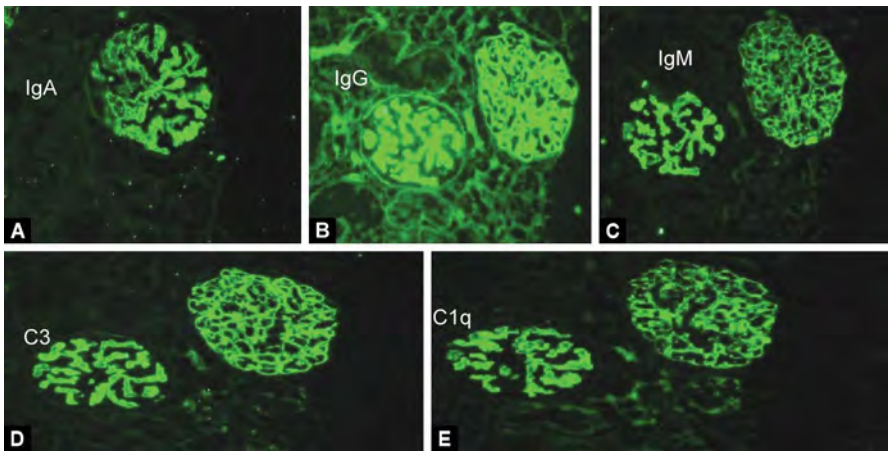
Presence of AQP4-IgG antibodies in patients with SLE without any symptoms and presence of ANA in patients with NMOSD without connective disease (CTD) are also described. However, the presence of ANA and clinical symptoms suggestive of SLE strengthens diagnosis of NMOSD even in the absence of AQP4-IgG provided seronegative criteria are fulfilled. In this case, the presence of anti-AQP4 antibodies and the characteristic relapsing episodes of optic neuritis and transverse myelitis confirmed the diagnosis of NMO. The subsequent development of acute glomerulonephritis, positive ANA, and low complement levels, in the absence of anti-dsDNA antibodies, suggested an overlap with SLE and the presence of proliferative lupus nephritis.

As per recent consensus, the treatment approach in cases of coexisting NMOSD and SLE should focus on which condition is predominantly flared up. Acute treatment of NMOSD includes intravenous methylprednisolone alone or with plasmapheresis. MMF, azathioprine, and methotrexate are common drugs used for maintenance treatment for NMOSD. Rituximab, eculizumab, satralizumab, and inebilizumab are most effective in preventing relapse of seropositive NMOSD as per recent data. Treatment-resistant cases, especially with simultaneous CTD should be offered IV cyclophosphamide.[6] Acute lupus nephritis should be treated with cyclophosphamide or MMF and glucocorticoids with or without a calcineurin inhibitor. Use of rituximab in proliferative lupus nephritis is still not recommended.[7] Complement inhibitors are FDA-approved for NMOSD, but data in SLE are limited.[5]

Here we were compelled to use cyclophosphamide based on KDIGO guidelines for management of lupus nephritis.[8] However, the patient was not ready to give consent for it, considering its adverse effects profile, and previous relapses of NMOSD were also treated with rituximab successfully. Hence, we used rituximab for active lupus nephritis and its subsequent flare. The patient responded to it dramatically. We suggest its use whenever these two diseases coexist along with MMF and low-dose steroids.



Figs 1A to F: (A) Scanner view shows lobular accentuation (PAS x100); (B) Diffuse endomesengial proliferation with obliteration of capillary lumina (PAS x400); (C) Mild neutrophilic exudation (H&E x400); (D) Few hyaline thrombi (trichrome x400); (E and F) Thickened and focal reduplication of basement membrane



Figs 2A to E: By immunofluorescence, there is intense, global staining for (A) IgA, (B) IgG, (C) IgM, (D) C3, and (E) C1q in the mesangium and glomerular capillary walls

Limitations of this case report include the lack of long-term follow-up data. Future research should focus on elucidating the underlying mechanisms and identifying biomarkers that can aid in the early recognition. Clinical trials comparing rituximab with cyclophosphamide in proliferative lupus nephritis with NMOSD are required to figure out the appropriate management of these rare cases.

Conclusion

This case report highlights the coexistence of NMO and proliferative lupus nephritis, a rare and challenging clinical scenario. Early recognition and prompt initiation of appropriate immunosuppressive therapy can lead to favorable outcomes in such cases. Multidisciplinary collaboration among neurologists, rheumatologists, and nephrologists is essential for effective management and personalized treatment approaches.

Acknowledgment

The authors would like to express their gratitude to the nephropathologist Dr Shailesh Soni and Dr Amit Jojera.

This manuscript has been read and approved by all the authors, that the requirements for authorship have been met, and that each author

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CASE REPORT

Burkholderia pseudomallei—An Underrecognized Cause of Community-acquired Pneumonia: A Case Series from Central Kerala, India

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Received: 12 June 2025; *Accepted:* 09 August 2025

Abstract

Melioidosis, caused by *Burkholderia pseudomallei*, is an emerging infectious disease endemic in several regions of the world, including India. It presents with a wide spectrum of clinical manifestations, among which pneumonia is the most common. Due to its clinical resemblance to bacterial pneumonia and pulmonary tuberculosis, coupled with limited access to advanced microbiological diagnostics, pulmonary melioidosis is frequently underdiagnosed. We report 3 culture-confirmed cases of pulmonary melioidosis from a tertiary care hospital in central Kerala. All patients were diabetic males, with additional comorbidities such as chronic obstructive pulmonary disease (COPD), chronic liver disease, anemia, smoking, and alcoholism. Notably, 2 had a prior history of pulmonary tuberculosis. Imaging revealed multifocal lung involvement, including consolidations, opacities, and cavitary lesions. Following microbiological confirmation, empirical therapy for community-acquired pneumonia (CAP) was modified to ceftazidime with or without cotrimoxazole. Despite intervention, 2 patients succumbed to the illness. This case series underscores the need for heightened clinical suspicion and robust microbiological support in diagnosing melioidosis. In high-risk patients presenting with multifocal pulmonary lesions, early modification of empirical antibiotic therapy may improve clinical outcomes and reduce mortality.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1322

Introduction

Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*, a gram-negative, facultative intracellular bacterium characterized by its distinctive bipolar staining, which resembles a safety-pin under the microscope.[1,2] It is endemic to tropical and subtropical regions such as Southeast Asia and northern Australia.[2,3] However, cases have also been reported in regions beyond the Asia-Pacific, including India, Mauritius, the Americas, and Africa.[4] The primary routes of transmission are percutaneous inoculation and inhalation.

While most exposed individuals remain asymptomatic, symptomatic cases exhibit a wide spectrum of clinical manifestations, with pneumonia being the most common clinical presentation.[2,5,6] Other presentations include skin infections, septic arthritis or osteomyelitis, abscesses in internal organs, genitourinary infections, and neurological melioidosis.[1,6] Individuals with comorbidities such as diabetes mellitus (T2DM), chronic obstructive pulmonary disease (COPD), rheumatic heart disease (RHD), or behavioral risk factors like smoking and alcoholism are more vulnerable to severe disease.[1,3,7,8] *B. pseudomallei* exhibits intrinsic resistance to many commonly used antibiotics,[4] and risk of relapse is reported in approximately 10% of cases.[3]

Here, we describe 3 culture-confirmed cases of melioidosis pneumonia from a tertiary care teaching hospital in central Kerala (2020–2024).

Case Description

Table 1 presents the clinical profiles and investigation findings of cases diagnosed with pulmonary melioidosis.

Discussion

We report a series of 3 cases of community-acquired pneumonia (CAP) caused by *B. pseudomallei*, documented between 2020 and 2024. All 3 cases involved either middle-aged or elderly male patients. All 3 had common comorbidities, including diabetes. Additionally, 2 had a history of pulmonary tuberculosis (TB), while 1 had a history of COPD and chronic liver disease (CLD). One patient was also a known smoker and alcohol consumer. In agreement with our findings, case reports by Almarhabi et al., Sheet et al., and Thorve et al. also reported a history of type 2 diabetes mellitus in patients with melioidosis pneumonia.[7,9,10] A review on melioidosis pneumonia by Meumann et al. also noted the association of primary pneumonia with various comorbid conditions like rheumatic heart disease or congestive cardiac failure (RHD/CCF), COPD, current smoking, and diabetes mellitus.[5]

Melioidosis pneumonia presents in acute, subacute, and chronic forms, with the acute variant being the most common and often resembling acute bacterial pneumonia. The chronic form can mimic pulmonary tuberculosis both clinically and radiologically,[2,6] leading to frequent misdiagnosis.[7,8] In our reports, 2 cases had a history of pulmonary tuberculosis; however, documented confirmation was unavailable. Radiological features vary with disease chronicity and infection mechanism. In acute pulmonary melioidosis, the predominant radiological manifestation is lung nodules, whereas the chronic form is characterized by cavitary lesions.[11] Other findings such as opacities, consolidation, and alveolar infiltrations have also been observed.[2,4] Similar radiological features with bilateral multifocal lung involvement were observed in the first 2 cases, whereas unilateral involvement was noted in the third case.

In this study, 2 out of 3 cases resulted in mortality during the course of treatment. A study by Meumann et al. found that patients with melioidosis pneumonia had a significantly higher incidence of septic shock (33 vs 10%) and mortality (20 vs 8%) compared to those with other primary manifestations of melioidosis.[5] Similarly, a retrospective study by Reechaipichitkul in southern Thailand observed that acute pulmonary melioidosis was associated with a higher mortality rate compared to subacute or chronic forms. Septic shock and acute respiratory failure were major complications contributing to morbidity and mortality in these cases.[2]

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How to cite this article: George A, Jose R, Valsan C, *et al. Burkholderia pseudomallei*—An Underrecognized Cause of Community-acquired Pneumonia: A Case Series from Central Kerala, India. J Assoc Physicians India 2026;74(6):65–67.

Table 1: Clinical characteristics and diagnostic findings in pulmonary melioidosis

Parameter	*Case I*	*Case II*	*Case III*
Age (years)/gender	75/male	52/male	45/male
Location	Thrissur, Kerala	Palakkad, Kerala	Palakkad, Kerala
Presenting complaints	Fever and cough for 4 days Breathing difficulty for 2 days	Loose stools and generalized weakness for 10 days Fever, cough, and right-sided chest pain for 7 days	Fever and cough for 10 days Exertional dyspnea for 4 days
Risk factors	T2DM, chronic liver disease, hypertension, COPD, old pulmonary tuberculosis	T2DM (uncontrolled), hypertension, old pulmonary tuberculosis, anemia	Newly detected T2DM (HbA1C 7.5%), chronic smoker and alcoholic, ketosis present
Physical examination	Febrile, with bilateral lung crepitations with rhonchi		
Empirical treatment	Injection ceftriaxone Tab. clarithromycin	Injection ceftriaxone	Injection ceftriaxone
Radiological findings	Chest X-ray: Cystic opacities noted in right and left upper and middle zones of both lungs	CT chest: Multifocal consolidation with cavitary lesions in right and left lobes of lung with atelectasis of few segments in left lobe	Chest X-ray: Consolidation noted in left lobe of lung. CT chest: Heterogeneously enhancing hyperdense lesion in left upper lobe with left mild pleural effusion and left hilar lymphadenopathy
Blood investigations			
TC	4330/µL	9490/µL	13.61 10^3/µL
DC	N—85%	N—89%	N—93.5%
Culture and sensitivity report			
B. pseudomallei grown in	Sputum	Sputum	Bronchoalveolar lavage
AST report	Susceptible to: Ceftazidime, cotrimoxazole, meropenem, levofloxacin		
Targeted therapy	Inj. ceftazidime (started on D5)	Inj. ceftazidime (started on D4)—2 weeks followed by tab. Cotrimoxazole—2 weeks	Inj. ceftazidime and tab. cotrimoxazole (started on D9)
ICU support during hospital stay	Yes		
Outcome/follow-up	Expired on D5	Discharged on D20; no recurrence noted at 1 year follow-up period	Expired on D9

Culture-based isolation of the organism remains the gold standard for confirming a diagnosis of melioidosis.[2,4,7] However, the sensitivity of this method may be compromised, particularly in cases with low bacterial loads or in specimens where the organism is challenging to culture. Chances of misidentification by automated systems are also common. Rapid diagnostic methods, such as direct immunofluorescence microscopy, offer the advantage of providing results within 30 minutes, facilitating timely initiation of treatment. Serological tests like indirect hemagglutination assay (IHA) are considered the most sensitive tests for diagnosing melioidosis.[7] Additionally, molecular techniques like polymerase chain reaction (PCR) targeting the *T3SS1* gene and matrix-assisted laser desorption or ionization time-of-flight (MALDI-TOF) mass spectrometry have been developed for the detection and identification of *B. pseudomallei*, although their sensitivity can vary based on the specimen type and bacterial load.[1] All 3 cases presented here were culture-confirmed melioidosis, showing susceptibility to ceftazidime, cotrimoxazole, meropenem, and levofloxacin.

Culture isolation and confirmation of *B. pseudomallei* typically take longer compared to other common pathogens.[4] Additionally, *B. pseudomallei* shows intrinsic resistance to many commonly used empiric antibiotics.[7,9] Hence, prolonged treatment in a staged manner is required to prevent recurrences. For initial intensive therapy, ceftazidime, meropenem, or imipenem is preferred for 10–14 days, with additional cotrimoxazole in cases of extrapulmonary melioidosis, followed by oral eradication therapy preferably with cotrimoxazole or other second-line antibiotics like doxycycline and amoxicillin-clavulanic acid for 3–6 months.[12]

Melioidosis is a preventable but increasingly recognized infectious disease in India, often described as the tip of the iceberg due to significant underdiagnosis. Tourists to endemic areas should avoid barefoot walking and water activities, while at-risk individuals must use protective gear like footwear and masks, especially during the rainy season and in agricultural settings. Laboratory personnel should adhere to strict biosafety practices, including working in BSC class II cabinets and avoiding sniffing culture plates. Although no human vaccine is currently available, various candidates, such as live attenuated, subunit, DNA-based, and killed whole-cell vaccines, are under investigation in animal models, making early clinical suspicion by both clinicians and microbiologists crucial.[13]

Conclusion

Our report highlights the importance of timely diagnosis and prompt initiation of treatment to improve patient outcomes, emphasizing the need to consider melioidosis in high-risk individuals with multifocal lung involvement. It also underscores the necessity of adjusting empiric treatment for CAP in these high-risk groups.

Authorship

Conception and design, or analysis and interpretation of data: Rosmi Jose, Chithra Valsan, and Anuja George.

Drafting the article or revising it critically for important intellectual content: Rosmi Jose, Chithra Valsan, and Anuja George.

Final approval of the version to be published: Chithra Valsan, Rosmi Jose, and Anuja George.

Consent

This research constitutes a retrospective case series focusing on patients who have passed away. Given that all 3 individuals had died prior to data collection, verbal informed consent was obtained from their next of kin.

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CASE REPORT

A Complex Case of Systemic Sclerosis with Concurrent Breast Malignancy and Treatment-related Complications

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Received: 14 March 2025; *Accepted:* 11 August 2025

Abstract

Systemic sclerosis (SSc) is a complex autoimmune disease marked by vasculopathy, fibrosis, and multisystem involvement. Interstitial lung disease (ILD) and pulmonary hypertension (PH) are major mortality contributors. Importantly, SSc is associated with an increased risk of malignancy.

This report presents a challenging case of SSc with severe Raynaud's phenomenon (RP), digital gangrene, calcinosis cutis, extensive ILD, severe PH, and right heart failure. The patient underwent mesenchymal stem cell therapy (MST), following which she developed breast cancer and chemotherapy-related complications, ultimately leading to death. This case highlights the need for timely intervention, screening for malignancy, and awareness of potential therapy-related risks in SSc.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1350

Introduction

Systemic sclerosis is a rare systemic autoimmune disorder affecting the skin and internal organs. Interstitial lung disease (ILD) occurs in approximately 50% of SSc patients. Pulmonary fibrosis and pulmonary hypertension (PH) are leading causes of mortality. Raynaud's phenomenon (RP), often the initial symptom, may progress to digital ischemia and gangrene in secondary forms like SSc.

The association between SSc and malignancies, especially lung and breast cancers, is increasingly recognized. Risk is influenced by immunosuppressive therapy, genetic predispositions, and certain autoantibodies. The relationship with breast cancer remains controversial, necessitating more focused research and surveillance strategies.

Case Description

A 46-year-old woman presented with heartburn, generalized skin darkening, and small joint pain in her hands and legs since 2007. She also reported RP. Over time, she developed dry cough and breathlessness [grade 2 modified Medical Research Council (mMRC)] but no chest pain. She was managed symptomatically.

Four years later, her breathlessness worsened to mMRC grade 4. She developed salt-and-pepper pigmentation on her upper chest and trunk, restricted mouth opening, and tightening of the skin over her arms and fingers, which led to limitation of joint movement. Examination revealed a pulse rate of 110/minute, blood pressure of 90/70 mm Hg, and respiratory assessment showed bilateral end-inspiratory Velcro crackles. Other systems were unremarkable.

Further evaluation revealed a speckled antinuclear antibody (ANA) pattern at 1:100 titers with an intensity of 4+, strongly positive anti-Scl-70 antibodies, and mild PH on 2D echocardiography. High-resolution computed tomography (HRCT) of the chest showed a usual interstitial pneumonia (UIP) pattern of ILD. She was diagnosed with diffuse cutaneous systemic sclerosis (dcSSc) complicated by UIP pattern ILD, mild PH, and RP. She received cyclophosphamide pulse therapy followed by maintenance therapy with azathioprine but was lost to follow-up for 4 years.

She returned with digital gangrene, calcinosis cutis, and worsening breathlessness (mMRC grade 4). Clinical examination revealed pitting pedal edema, flexion contractures of the fingers, elevated jugular venous pressure (JVP), tachycardia (118/minute), tachypnea (20/minute), loud P2, and bilateral mid and infrascapular crepitations with room air saturation of 88%. Echocardiography revealed severe PH [right ventricular systolic pressure (RVSP) 92 mm Hg], right heart enlargement, and restrictive lung disease on pulmonary function tests (PFTs) [forced vital capacity (FVC) 28%]. She was treated with rituximab, mycophenolate, nintedanib, tadalafil, ambrisentan, and diuretics.

Following the second rituximab dose, she developed herpes zoster and required multiple admissions for severe RP. Oxygen dependence increased and her functional status deteriorated. She underwent three cycles of mesenchymal stem cell therapy (MST) using adipose-derived cells from a teenage donor. Post-MST, her functional class improved, and oxygen requirement reduced.

A year later, she developed a right breast lump. Mammography and biopsy confirmed Her2/neu-positive invasive ductal carcinoma (T4N1M0). Surgery was deferred due to her comorbidities, and she was started on chemotherapy. The breast lesion regressed, but she developed recurrent chemotherapy-induced hydropneumothorax (Figs 1 and 2), and infections, including candidiasis and gastroenteritis.

She was maintained on sildenafil, bosentan, diuretics, calcium channel blockers, and capecitabine. Her breathlessness improved to MRC grade 2. However, her family later informed that she had passed away at her hometown.

Discussion

Patients with SSc have a 1.5-fold higher cancer risk, particularly for lung, hematologic, and breast cancers.[1,2] Various studies suggest that immune dysregulation, chronic inflammation, hormonal influences, and therapy exposures play roles in this association.

Breast cancer risk is elevated in female SSc patients [standardized incidence ratio (SIR) 1.62]. Scope et al. reported that 75% of SSc-associated breast cancer cases occurred within 3 years of SSc diagnosis.[3] Derk et al. found a higher prevalence of pulmonary fibrosis in SSc patients with breast cancer.[4]

Certain subgroups of SSc patients are at a higher risk of malignancy, particularly those with anti-RNA polymerase III antibodies, diffuse cutaneous SSc, and late-onset disease. These factors are crucial in determining the timing and frequency of cancer screening in high-risk

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How to cite this article: Parimi VP, Tejaswini RN. A Complex Case of Systemic Sclerosis with Concurrent Breast Malignancy and Treatment-related Complications. J Assoc Physicians India 2026;74(6):68–69.

Fig. 1: Axial sections of computed tomography of the chest: UIP ILD with left pneumothorax

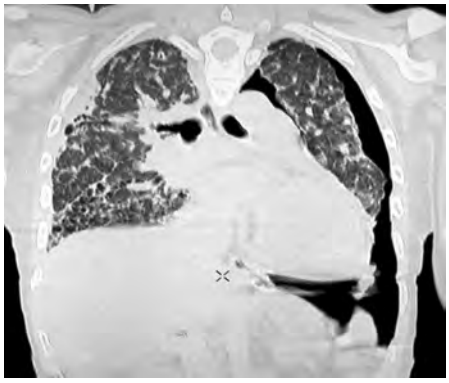

Fig. 2: Coronal section of computed tomography of the chest with interstitial irregular honeycombing and left pneumothorax

patients. The close association between SSc onset and cancer in specific antibody subsets raises the question of whether more intensive screening strategies should be implemented. Notably, SSc patients diagnosed with cancer shortly after their SSc onset often test positive for anti-polymerase III antibodies, reinforcing a molecular link between autoimmunity and malignancy.

Several factors may contribute to the shared pathogenesis of these diseases.[5] The female predominance in SSc suggests a role for hormonal influences, similar to those seen in breast cancer.[6] Additionally, calcium channel blockers, commonly used to treat SSc vasculopathy, have been associated with an increased breast cancer risk in the general population. Immunosuppressive therapies for SSc may further elevate cancer risk, while chemotherapy agents (e.g., taxanes) and ionizing radiation, known for their fibrotic effects, could exacerbate preexisting SSc.[7–9]

The use of mesenchymal stem cells, though promising for fibrotic conditions like SSc, raises safety concerns. Mesenchymal stem cells (MSCs) can contribute to tumor stroma and have been implicated in tumor progression. Ning et al. noted a higher recurrence of hematologic malignancy with MSC cotransplantation. Although rare, the oncogenic potential of MSCs remains a concern.[10] In this case, MST preceded the development of breast cancer, though causality cannot be established.

This case underscores the aggressive nature of SSc and highlights the challenges in its management, especially in the setting of treatment-related complications and malignancy. Despite significant morbidity and limited treatment adherence, the patient initially improved. However, after 1 year, the patient's relative conveyed that she had expired at her hometown, emphasizing the need for vigilant care.

Conclusion

Early diagnosis and prompt therapeutic intervention to control inflammation are essential in reducing the long-term complications of SSc. Given the increased malignancy risk in SSc patients, identifying high-risk individuals for early screening and intervention is crucial. Detecting cancer at an early stage and initiating timely treatment can significantly improve outcomes and enhance survival rates in this vulnerable population.

Conflict of Interest

None of the authors have any conflicts of interest.

Funding

This research received no external funding.

Informed Written Consent

An informed written consent has been obtained from the patient's daughter.

Institutional Ethics Committee for Stem Cell

Stem cell therapy referenced in this study was administered at an external facility. Hence, IEC approval for the procedure was not obtained at our center.

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CASE REPORT

Acute Transverse Myelitis and Pulmonary Thromboembolism Following Scorpion Envenomation: A Rare Case Report

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Received: 02 August 2025; *Accepted:* 20 December 2025

Abstract

Scorpion envenomation is common in India but rarely leads to neurovascular complications. We present a rare case of a 72-year-old male who developed acute transverse myelitis, subarachnoid hemorrhage, and pulmonary thromboembolism following a scorpion sting. The patient presented with sudden-onset paraparesis. Magnetic resonance imaging (MRI) of the spine revealed longitudinal hyperintensity from T5 to T12, suggestive of transverse myelitis, along with evidence of spinal subarachnoid hemorrhage. Computed tomography (CT) pulmonary angiography confirmed bilateral pulmonary thromboembolism. Cerebrospinal fluid analysis showed a hemorrhagic tap with elevated protein and lactate dehydrogenase (LDH), but no infectious or malignant cells. Neuromyelitis optica (NMO) and myelin oligodendrocyte glycoprotein (MOG) antibodies were negative. Nerve conduction studies showed bilateral sensorimotor axonal polyneuropathy. The patient was treated with corticosteroids and anticoagulants and showed gradual improvement. This case underscores the systemic toxicity of scorpion venom and highlights the importance of early recognition and multidisciplinary management of rare neurovascular complications.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1340

Introduction

Scorpion stings are frequent medical emergencies in rural India and are known to cause severe autonomic disturbances, myocarditis, and pulmonary edema.[1,2] However, central nervous system (CNS) involvement is rare. Even more unusual is the development of transverse myelitis[3] or thromboembolic events following envenomation.[4–7] We present a case of acute transverse myelitis, spinal subarachnoid hemorrhage, and pulmonary thromboembolism in a patient following a scorpion sting. This report highlights the potential for immune-mediated or toxic neurovascular injury following systemic envenomation.

Case Description

A 72-year-old male with no known comorbidities presented with acute onset bilateral lower limb weakness following a scorpion sting to the right index finger. He initially developed local pain that resolved within 30 minutes. Four hours later, he experienced headache, restlessness, and chills, for which he was treated at a local hospital and referred for further care.[1,8] On the third day, he underwent coronary angiography for evaluation of chest discomfort, which revealed double vessel disease. Approximately 12 hours postprocedure, he developed bilateral lower limb weakness and paresthesia.[7]

Neurological examination revealed complete motor paralysis (power 0/5) in both lower limbs, absent deep tendon reflexes in the lower limbs, and a sensory level below T6. Cranial nerves were intact, and bladder/bowel involvement was initially absent.[5,6]

Investigations

- Neuroimaging: Magnetic resonance imaging (MRI) of the thoracic spine revealed T2-weighted hyperintensity extending from D5 to D12, consistent with acute transverse myelitis. There was T2 hypointensity in the thecal sac suggestive of subarachnoid hemorrhage.[5,9,10] MRI of the lumbar spine showed anterolisthesis of L5 over S1, a fluid level in the thecal sac, and hyperintensity in the conus medullaris (Fig. 1).
- Computed tomography (CT) spine angiography: Prominent radicular arteries at C7–D1 and D5–D6, with no aneurysm or vascular nidus.
- CT pulmonary angiography: Partial filling defects in the right pulmonary artery and bilateral lower lobar arteries, consistent with pulmonary thromboembolism.[7]
- Cardiac evaluation: Coronary angiography showed 90% lesion in the diagonal branch of the left anterior descending (LAD) and 99% lesion in the mid-right coronary artery (RCA) (TIMI 1 flow), suggesting double vessel disease. Troponin I was mildly elevated (0.03 ng/mL).
- Cerebrospinal fluid (CSF): Hemorrhagic tap, protein 2.91 gm/L, sugar 23 mg/dL, lactate dehydrogenase (LDH) 1165 U/L. Cartridge-based nucleic acid amplification test (CBNAAT) negative. Cytology: Hemorrhagic background with few lymphocytes, no malignant cells. Antinuclear antibody (ANA) negative; neuromyelitis optica (NMO) and myelin oligodendrocyte glycoprotein (MOG) antibodies negative.[6]
- Coagulation: D-dimer 5172 ng/mL; fibrinogen >20 µg/mL (hypercoagulable).
- Nerve conduction study: Bilateral sensorimotor axonal polyneuropathy.

Treatment and Outcome

The patient was started on intravenous methylprednisolone 1 gm/day for 5 days.[5,6] After CT confirmation of pulmonary embolism, subcutaneous enoxaparin 0.6 mL BD was initiated.[7] Dual antiplatelet therapy was withheld due to the hemorrhagic CSF. The patient received supportive intensive care unit (ICU) care including bladder training and physiotherapy. Gradual motor improvement was observed over the following weeks, and he was discharged with rehabilitation advice.

Discussion

Scorpion venom contains potent neurotoxins that provoke autonomic, inflammatory, and vascular reactions.[1,2,8] While cardiovascular effects such as myocarditis and arrhythmia are well documented, CNS complications like transverse myelitis are exceedingly rare.[4–6] The pathogenesis may involve direct neurotoxicity, immune-mediated demyelination, or ischemic injury due to

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How to cite this article: Rijhwani P, Jain S, Gupta D, *et al.* Acute Transverse Myelitis and Pulmonary Thromboembolism Following Scorpion Envenomation: A Rare Case Report. J Assoc Physicians India 2026;74(6):70–71.

Fig. 1: Sagittal T2-weighted MRI of the lumbosacral spine showing hyperintense signal in the conus medullaris with a fluid level within the thecal sac, suggestive of spinal subarachnoid hemorrhage. Mild anterolisthesis of L5 over S1 is also noted

vasospasm. Subarachnoid hemorrhage in this case may result from vascular fragility or venous infarction.[9,10]

Pulmonary embolism has occasionally been reported following scorpion envenomation and may be related to endothelial injury, venom-induced procoagulant state, or postprocedural immobility.[7] Elevated D-dimer and fibrinogen supported the diagnosis. Negative NMO and MOG antibodies, absence of infection, and noncontributory malignancy screen suggest a para-toxic or immune-mediated cause of transverse myelitis.

This case demonstrates a rare but serious systemic complication of scorpion envenomation and underscores the importance of early diagnosis, supportive care, and multidisciplinary management.[1,2,4–10]

Conclusion

We report a rare case of acute transverse myelitis, subarachnoid hemorrhage, and pulmonary thromboembolism following scorpion envenomation. This highlights the potential for multisystem involvement and the importance of early imaging, CSF analysis, and close monitoring. A multidisciplinary team approach is essential for optimal outcomes.

Patient Consent

Obtained.

Funding

None.

Conflict of Interest

None declared.

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CASE REPORT

Gastric Antral Vascular Ectasia in a Patient with Chronic Myeloid Leukemia on Imatinib Treatment: A Rare Case Report

Kanhaiya Lal Sharma[1*], Ranjana Veerwal[2], Gurdeep Kaur[3], Sakshi Otwani[4]

Received: 02 April 2024; *Accepted:* 17 March 2026

Abstract

Imatinib is the standard first-line therapy for chronic myeloid leukemia (CML) and is generally well tolerated. Gastrointestinal adverse effects are common; however, gastric antral vascular ectasia (GAVE) is an extremely rare complication. We report a 77-year-old woman with chronic-phase CML who developed severe upper gastrointestinal bleeding 1 month after the initiation of imatinib therapy. Endoscopy revealed classic features of GAVE, and no alternative etiology was identified. Discontinuation of imatinib resulted in complete clinical and endoscopic resolution. Clinicians should consider this rare complication in patients receiving imatinib who present with unexplained anemia or gastrointestinal bleeding.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1577

Introduction

Imatinib mesylate is an oral tyrosine kinase inhibitor targeting BCR-ABL and related signaling pathways.[1] It has significantly improved survival in patients with chronic-phase chronic myeloid leukemia (CML) and remains the standard first-line therapy.[2] The drug is generally well tolerated, with most adverse effects being mild to moderate in severity.

Gastric antral vascular ectasia (GAVE) is an uncommon but recognized cause of upper gastrointestinal bleeding.[3] It is most frequently associated with liver cirrhosis and autoimmune disorders.[4] Drug-induced GAVE is rare, and only isolated cases associated with imatinib therapy have been described.[5,6] We report a case of imatinib-associated GAVE in a patient with chronic-phase CML.

Case Description

A 77-year-old woman was diagnosed with chronic-phase CML in November 2023 based on marked leukocytosis (322,900/mm^3) with 2% blasts on peripheral smear examination. BCR-ABL testing was positive. She was started on imatinib 400 mg daily.

One month after the initiation of therapy, she presented with hematemesis, melena, generalized weakness, and dyspnea on mild exertion [New York Heart Association (NYHA) class III] for 3 days. On examination, she was markedly pale but hemodynamically stable. Hemoglobin was 3.9 gm/dL. Total leukocyte count was 6,930/mm^3 without circulating blasts. Peripheral smear findings were consistent with hematological remission.

Liver and renal function tests were within normal limits. Antinuclear antibody testing was negative. Ultrasonography of the abdomen showed no hepatosplenomegaly. Bone marrow examination confirmed chronic-phase disease without progression.

Upper gastrointestinal endoscopy revealed longitudinal erythematous vascular streaks in the gastric antrum consistent with GAVE (Fig. 1).[3] Endoscopic cauterization was performed.

She received packed red cell transfusions, intravenous iron supplementation, vitamin B12, and proton pump inhibitors. As no other cause of bleeding was identified, imatinib was discontinued.

On follow-up, hemoglobin improved to 11 gm/dL without further transfusion requirement. Repeat endoscopy demonstrated complete resolution of the vascular lesions. No recurrent bleeding episodes were observed.

Discussion

Gastric antral vascular ectasia is an uncommon but clinically significant cause of upper gastrointestinal bleeding.[3] Patients may present with chronic iron-deficiency anemia or acute hemorrhage. The characteristic endoscopic appearance consists of longitudinal erythematous streaks radiating from the pylorus.

Most cases are associated with cirrhosis or autoimmune disorders.[4] Only isolated reports have documented GAVE in patients receiving imatinib therapy.[5,6] The mechanism remains unclear but may involve drug-induced vascular endothelial injury.

In the present case, no evidence of liver disease or autoimmune disorder was found. The close temporal relationship between the initiation of imatinib and the onset of bleeding, along with complete resolution following drug withdrawal, strongly suggests a probable drug-related adverse event.

Conclusion

Gastric antral vascular ectasia is a rare but potentially serious adverse effect of imatinib therapy. Early endoscopic evaluation should be considered in patients presenting with anemia or gastrointestinal bleeding after the initiation of treatment. Withdrawal of the offending drug may lead to complete recovery.

Declaration

Written informed consent was obtained from the patient for publication of this case

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How to cite this article: Sharma KL, Veerwal R, Kaur G, *et al.* Gastric Antral Vascular Ectasia in a Patient with Chronic Myeloid Leukemia on Imatinib Treatment: A Rare Case Report. J Assoc Physicians India 2026;74(6):72–73.

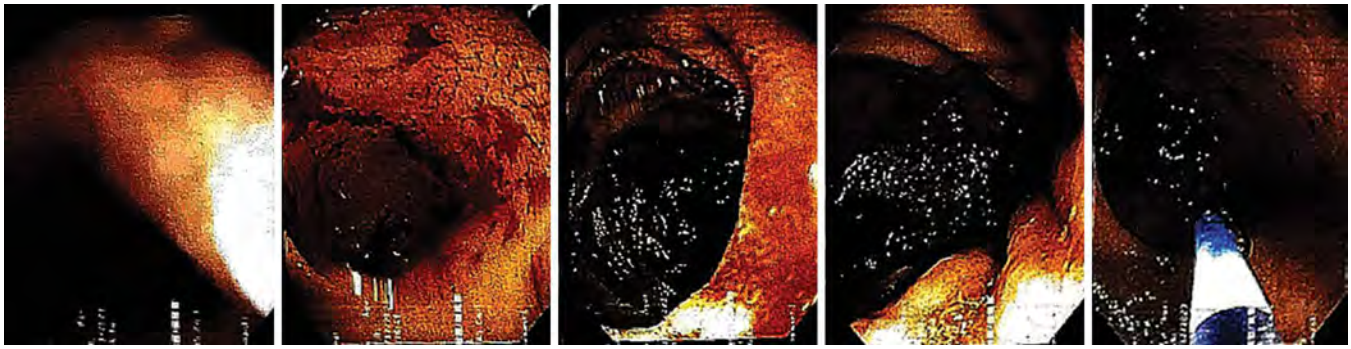

Fig. 1: Upper gastrointestinal endoscopy showing longitudinal erythematous vascular streaks in the gastric antrum consistent with GAVE

report and the accompanying endoscopic image.

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CASE REPORT

Triple Central Nervous System Pathogen Infections and Vascular Events in Advanced Human Immunodeficiency Virus—Implications for Early Diagnosis and Multidisciplinary Management: A Case Series from Two Tertiary Centers

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Received: 02 July 2025; *Accepted:* 31 December 2025

Abstract

Background: Central nervous system (CNS) infections remain a major cause of morbidity and mortality in people living with HIV (PLHIV), particularly in the setting of advanced immunosuppression and recent initiation of antiretroviral therapy (ART). While individual opportunistic CNS infections are well-documented, simultaneous infections with multiple pathogens are rare and diagnostically challenging.

Methods: We report a case series of 11 HIV-positive individuals aged 25–50 years, presenting within 3 months of ART initiation to two tertiary centers over a 2-year period. All patients exhibited clinical features of meningitis and underwent cerebrospinal fluid (CSF) analysis, PCR testing, neuroimaging, and comprehensive microbiological workup.

Results: All 11 patients were diagnosed with triple-pathogen CNS infections. The most common combination was *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, and herpes simplex virus type 1 (HSV-1). Additional pathogens included *Toxoplasma gondii*, *Treponema pallidum*, and CMV. Median CD4 count was <70 cells/μL. Coinfections were frequently unmasked shortly after ART initiation, suggestive of immune reconstitution inflammatory syndrome (IRIS). Despite aggressive treatment, mortality was 45%. One complex case included CNS vasculitis, ischemic stroke, pulmonary embolism, and multiple systemic infections.

Conclusion: This series underscores the diagnostic and therapeutic complexities of managing CNS coinfections in PLHIV, especially in the context of IRIS. A high index of suspicion, early multiplex diagnostic testing, and multidisciplinary management are crucial. Furthermore, the presence of noninfectious complications such as stroke and thromboembolism highlights the broader spectrum of HIV-related neurological disease. Early recognition and targeted treatment can improve outcomes in this high-risk population.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1595

Introduction

People living with HIV (PLHIV) continue to face significant health challenges due to both opportunistic infections and noninfectious clinical complications. Central nervous system (CNS) infections, particularly meningitis, are common in individuals with acquired immunodeficiency syndrome (AIDS). The immunodeficient state, primarily due to defective T-cell-mediated immunity, predisposes these individuals to a variety of opportunistic infections of viral, fungal, and parasitic origin.

Tuberculous meningitis (TBM) remains a prevalent CNS manifestation, with an estimated prevalence of 13.6% among HIV-positive individuals and an incidence rate of 1.5 cases per 1,000 person-years.[1] Additionally, cryptococcal meningitis continues to be a major cause of morbidity and mortality, accounting for approximately 152,000 cases annually among PLHIV, predominantly in sub-Saharan Africa.[2]

Although rare, coinfection with multiple CNS pathogens has been documented. A multicountry cohort study conducted across Cameroon, Malawi, and Tanzania found that 6% of participants with cryptococcal meningitis harbored a second CNS infection. These included TBM, bacterial meningitis, cerebral toxoplasmosis, and neurosyphilis. Similarly, 13% of patients with TBM were diagnosed with an additional CNS infection.[3] These findings underscore the complexity of diagnosing and managing CNS infections in PLHIV, where the coexistence of multiple pathogens can hinder timely treatment and worsen prognosis.

Apart from infectious etiologies, PLHIV are increasingly experiencing noninfectious neurological complications, particularly cerebrovascular accidents (stroke). A study published showed that the prevalence of stroke among PLHIV aged at least 15 years was 1.30% (95% CI: 1.01%, 1.59%), and for those aged at least 50 years, the prevalence was higher at 3.98% (95% CI: 2.45%, 5.51%). The pooled incidence of stroke was 17.86 per 10,000 person-years (95% CI: 15.96, 19.76), of which the incidence of ischemic stroke was 31.50 per 10,000 person-years (95% CI: 11.11, 51.89), while hemorrhagic stroke had an incidence of 4.43 per 10,000 person-years (95% CI: 1.95, 6.91).[4] Risk factors include traditional cardiovascular risk determinants such as hypertension, diabetes mellitus, smoking, and hyperlipidemia, as well as HIV-related factors including chronic inflammation, immune activation, and antiretroviral therapy (ART)-associated metabolic abnormalities. Coinfections like hepatitis C virus (HCV) and syphilis also appear to contribute to increased stroke risk in PLHIV.

We report a case series of 11 PLHIV who were diagnosed concurrently with triple-organism CNS infections. These cases were diagnostically and therapeutically challenging, necessitating the initiation of multiple antimicrobial regimens. Management was further complicated by drug interactions, potential adverse effects, and altered immune responses.

Our primary objective in presenting these cases is to highlight the importance of maintaining a broad differential diagnosis and a high index of suspicion for coinfections in PLHIV presenting with neurological symptoms. In many instances, inadequate

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How to cite this article: Puri S, Chatterjee R, Aleena I, *et al.* Triple Central Nervous System Pathogen Infections and Vascular Events in Advanced Human Immunodeficiency Virus—Implications for Early Diagnosis and Multidisciplinary Management: A Case Series from Two Tertiary Centers. J Assoc Physicians India 2026;74(6):74–78.

clinical response may be attributed to an undetected secondary or tertiary pathogen. Early identification of these coinfections, although not always associated with favorable outcomes, can significantly influence therapeutic strategies and clinical trajectories. In our series, targeted treatment led to successful recovery in a subset of patients.

One case, in particular, merits special mention—a PLHIV with triple-pathogen CNS infection complicated by ischemic stroke and pulmonary embolism. Despite the severity and complexity of the clinical picture, the patient was successfully treated through timely diagnosis, comprehensive antimicrobial therapy, anticoagulation, and supportive care.

Case Description

We report a case series of 11 HIV-positive individuals who presented to two tertiary care centers over a span of 2 years. All patients were aged between 25 and 50 years and were diagnosed with HIV infection within 3 months prior to presentation. ART had been initiated in each case, with an average initiation time of 3 months postdiagnosis. The predominant clinical presentation included headache, fever, neck rigidity, and altered mental status—symptoms strongly suggestive of central nervous system (CNS) involvement.

All patients underwent urgent stabilization and lumbar puncture for cerebrospinal fluid (CSF) analysis. Notably, multiple pathogens were detected in the CSF of each patient, with the majority showing evidence of triple CNS infections. A comprehensive diagnostic workup was performed, including:

- PCR panel for common neurotropic viruses.
- CSF CBNAAT and GeneXpert MTB/RIF assays for *Mycobacterium tuberculosis*.
- BACTEC MGIT culture for tubercular meningitis.
- India ink staining and cryptococcal antigen testing for cryptococcal meningitis (Fig. 1).
- HSV-1/HSV-2 PCR assays for viral etiology.
- Of the 11 cases, 9 patients demonstrated coinfection with *M. tuberculosis*, *Cryptococcus neoformans*, and herpes simplex virus type 1 (HSV-1). The remaining cases involved additional rare coinfections, including *Treponema pallidum* (syphilitic meningitis) and *Toxoplasma gondii*.

Management and Outcomes

All patients were managed with disease-specific treatment regimens, including:

- Antitubercular therapy (ATT) for tubercular meningitis.
- Amphotericin B and fluconazole for cryptococcal meningitis.
- Acyclovir or valganciclovir for HSV infections.
- Intravenous penicillin for syphilitic meningitis.
- ART continuation and comprehensive supportive care.

Despite aggressive and timely management, the overall mortality was significant. Only 5 out of the 11 patients survived and continue to do well on follow-up. The remaining 6 succumbed to their illness. Among the deceased:

- One patient had coinfection with tuberculosis, cryptococcosis, and neurosyphilis.
- Another had tuberculosis, HSV-1, and cerebral toxoplasmosis.
- One particularly challenging case is described in detail below due to its complexity and atypical course.

Immunological Profile and Observations

CD4 counts ranged from 14 to 82 cells/mm^3. All patients presented within 3–4 months of initiating ART, suggesting a possible immune reconstitution inflammatory syndrome (IRIS) phenomenon that may have unmasked latent infections. Additionally, concurrent opportunistic infections were identified in all cases, as summarized in Tables 1 and 2.

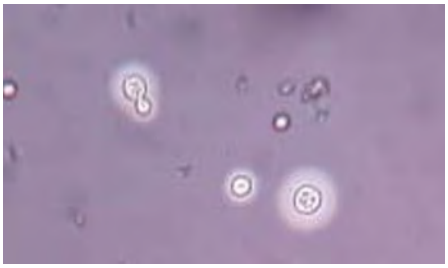

Fig. 1: India ink staining of cerebrospinal fluid showing encapsulated budding yeast cells of *Cryptococcus* species

Table 1: Clinico-microbiological and laboratory profile of the cases (Cases 1 to 5)

Characteristics	*Case 1*	*Case 2*	*Case 3*	*Case 4*	*Case 5*
Age (years)	27	25	33	38	26
Duration of starting ART	2 months	3 months	15 days	28 days	2.5 months
Symptoms at presentation	Headache, fever, altered mental sensorium	Fever, neck rigidity, convulsions	Headache, altered mental sensorium, neck rigidity	Fever, convulsions, neck rigidity	Altered mental sensorium, neck rigidity
Baseline CD4 count	56	24	21	32	22
CSF opening pressure	High	Normal	High	High	Normal
CSF cell count	2300 (60% lymphocytes)	3600 (70% lymphocytes)	4500 (55% lymphocytes)	2880 (67% lymphocytes)	4890 (70% lymphocytes)
Organism detected	Tubercular + cryptococcal + HSV type 1	Tubercular + cryptococcal + HSV type 1	Tubercular + cryptococcal + HSV type 1	Tubercular + cryptococcal + HSV type 1	Tubercular + cryptococcal + HSV type 1
Other associated opportunistic infections	Oral candidiasis, PCP pneumonia	CMV retinitis, oral candidiasis, *Cryptosporidium* in stool	CMV retinitis, oral candidiasis, and *Cryptosporidium*	CMV retinitis, oral candidiasis, extrapulmonary tubercular lymphadenopathy	CMV retinitis, oral candidiasis, herpes simplex genital ulcer
Outcome	Death	Discharged after successful treatment	Death	Death	Discharged after successful treatment

Table 2: Clinico-microbiological and laboratory profile of the cases (Cases 6 to 10)

Characteristics	*Case 6*	*Case 7*	*Case 8*	*Case 9*	*Case 10*
Age (years)	38	42	27	50	33
Duration of starting ART	18 days	1.5 months	20 days	50 days	10 days
Symptoms at presentation	Fever, altered mental sensorium, convulsions	Headache, neck rigidity	Fever, altered mental sensorium	Fever, convulsions, neck rigidity	Headache, neck rigidity, fever, altered mental sensorium
Baseline CD4 count	62	48	37	82	14
CSF opening pressure	High	Normal	High	High	High
CSF cell count	2500	4667	3400	1980	1725
Organism detected	Tubercular + cryptococcal + HSV type 1	Tubercular + cryptococcal + HSV type 1	Tubercular + cryptococcal + HSV type 1	Tubercular + cryptococcal + syphilitic meningitis	Tubercular + HSV type 1 + *Toxoplasma* meningoencephalitis
Other associated opportunistic infections	Oral candidiasis, herpes zoster	Oral candidiasis, PCP pneumonia	CMV retinitis, *Cystoisospora* in stool	Oral candidiasis, herpes zoster	CMV retinitis, oral candidiasis, *Cryptosporidium* in stool
Outcome	Discharged after successful treatment	Discharged after successful treatment	Death	Death	Death

Case 11

A 46-year-old male presented with a 2-day history of headache, neck pain, and altered mental status, preceded by 7 days of fever. He had a known history of hypertension and dyslipidemia, and was recently diagnosed with HIV infection. ART had been initiated 2 weeks prior to presentation, with a baseline CD4 count of 68 cells/µL.

On admission, the patient was febrile and disoriented, with a Glasgow Coma Scale (GCS) score of 10/15. Neurological examination revealed neck rigidity and a positive Kernig's sign. Vitals were stable: heart rate 100 bpm, blood pressure 100/80 mm Hg, and oxygen saturation 100% on 2 L/min oxygen.

Lumbar puncture revealed a markedly elevated cerebrospinal fluid (CSF) white cell count of 2560 cells/µL (60% neutrophils), protein 533 mg/dL, and glucose 17 mg/dL. CSF HSV-1 PCR returned positive. India ink staining was negative, but cryptococcal antigen was positive, suggesting coinfection. The patient was initiated on intravenous amphotericin B, fluconazole, acyclovir, and ceftriaxone. Baseline blood work showed hemoglobin 11 gm/dL, total leukocyte count 7700/µL, platelets 328,000/µL, creatinine 0.8 mg/dL, normal liver enzymes, CRP 1.1 mg/dL, and procalcitonin 0.02 ng/mL. A repeat CD4 count on admission was 138 cells/µL, with a CD4:CD8 ratio of 0.24. Initial blood and urine cultures were sterile (Fig. 2).

After initial clinical improvement over 3–4 days, the patient developed acute respiratory distress. Arterial blood gas analysis confirmed type 1 respiratory failure. High-resolution CT (HRCT) chest showed bilateral ground-glass opacities, peribronchovascular consolidation, and nodular infiltrates (Fig. 3). Bronchoscopy revealed thick purulent secretions, and bronchoalveolar lavage (BAL) fluid tested positive for *Streptococcus pneumoniae*, *Klebsiella* spp., *Pneumocystis jirovecii*, and cytomegalovirus (CMV). CMV PCR quantified 17,800 copies/mL. BAL galactomannan index was 0.80. The patient was started on targeted antibiotics, trimethoprim-sulfamethoxazole, and valganciclovir under infectious disease supervision. Despite negative MTB GeneXpert results from CSF and BAL, the high clinical suspicion led to extended mycobacterial culture testing. 5 days later, the patient developed melena with a hemoglobin drop to 7.5 gm/dL. He was transfused and underwent upper GI endoscopy, which revealed a Mallory–Weiss tear, managed with argon plasma coagulation.

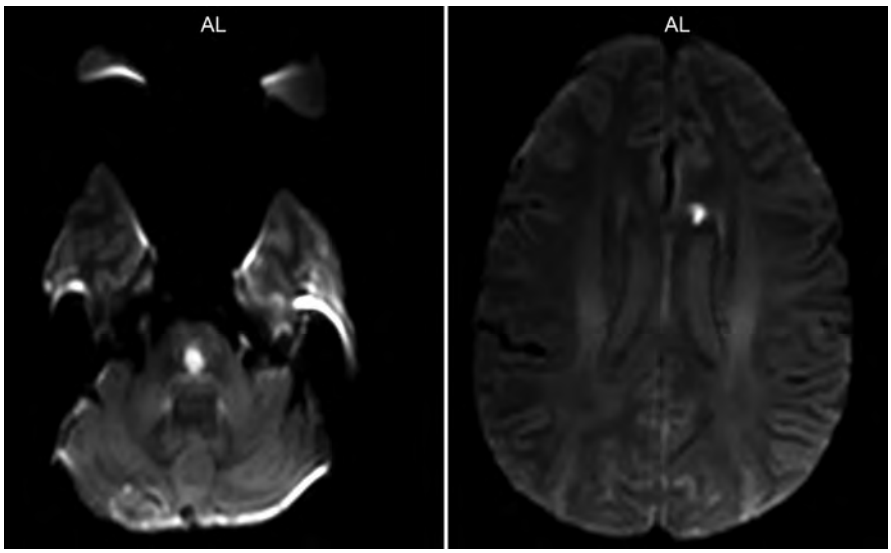

Fig. 2: Diffusion-weighted imaging axial sequences of magnetic resonance imaging of the brain showing acute infarcts in the body of the corpus callosum and central pons—case 11

Soon after stabilization, the patient developed new-onset drowsiness and fever. MRI brain revealed acute infarctions involving the central pons and body of the corpus callosum. Stroke workup, including echocardiography, Holter monitoring, and carotid Doppler, was noncontributory. He was started on dual antiplatelet therapy and a statin, later de-escalated to single antiplatelet therapy following complications.

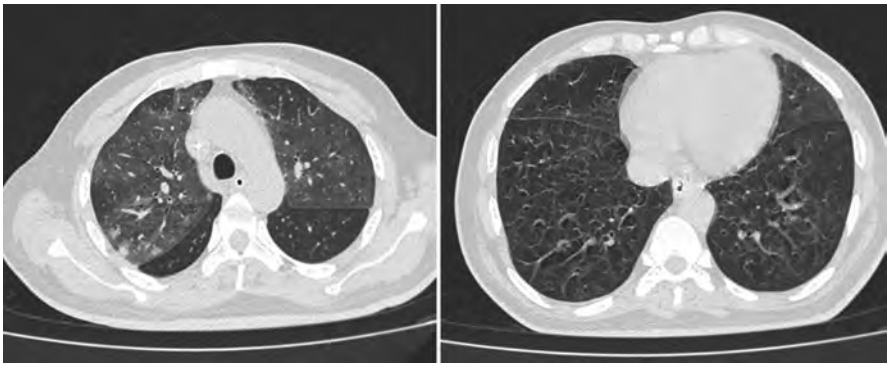

Fig. 3: High-resolution computed tomography section showing ground-glass opacities and infective changes of *Pneumocystis pneumonia* infection—case 11

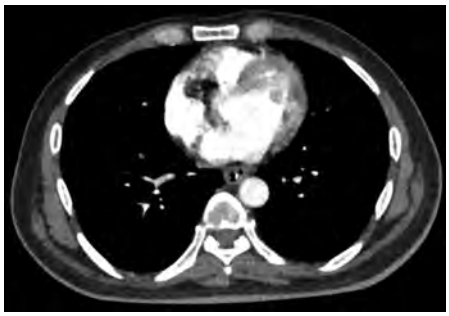

Fig. 4: Computed tomography pulmonary angiography images showing segmental pulmonary emboli

The patient remained febrile, and repeat CSF analysis showed persistent pleocytosis with lymphocytic predominance and vasculitis features. CSF BACTEC culture confirmed *M. tuberculosis*, and antitubercular therapy (ATT) was initiated in accordance with the National Tuberculosis Elimination Program (NTEP).

Neurological evaluation noted progressive limb weakness. Nerve conduction studies confirmed axonal motor polyradiculopathy involving all four limbs, not fully explained by the infarct. Management included supportive care and physiotherapy.

The patient then developed recurrent respiratory distress. CT pulmonary angiography revealed bilateral segmental pulmonary emboli and persistent parenchymal changes (Fig. 4). Anticoagulation was initiated with low-molecular-weight heparin and later transitioned to apixaban, while antiplatelet therapy was adjusted to minimize bleeding risk.

During hospitalization, he also developed diarrhea. Stool studies confirmed *Cryptosporidium* infection, for which metronidazole was added.

Through coordinated multidisciplinary care involving infectious disease, neurology, pulmonology, and gastroenterology teams, the patient showed gradual improvement. At discharge, he was hemodynamically stable, ambulantory with assistance, and able to perform daily activities with support. He was tolerating oral intake without dysphagia.

Discharge Medications

- ART: Tenofovir/lamivudine/dolutegravir (dolutegravir dose adjusted for concurrent ATT).
- ATT: As per NTEP guidelines.
- Antivirals: Valganciclovir.
- Antimicrobials: Trimethoprim-sulfamethoxazole, fluconazole, metronidazole.
- Others: Statin, apixaban, supportive supplements.
- At discharge, his CD4 count had improved to 282 cells/μL, CD3 to 983 cells/μL, and CD4:CD8 ratio to 0.43.

This case illustrates the diagnostic and therapeutic complexities associated with advanced HIV and profound immunosuppression. A high index of suspicion for coexisting opportunistic infections and complications—including CNS vasculitis, pulmonary embolism, and polyneuropathy—is essential. Multidisciplinary coordination and dynamic treatment adaptation are crucial for optimizing outcomes in such critically ill patients.

Discussion

In our case series, we observed a striking cluster of 11 patients presenting with triple-organism-positive meningitis, all identified shortly after the initiation of ART. This clinical scenario underscores the pathophysiological phenomenon of IRIS, wherein the recovery of pathogen-specific immune responses following ART initiation paradoxically results in a pathological inflammatory reaction.

In patients with severe immunosuppression, as seen in advanced HIV, disruption of the blood–brain barrier (BBB) facilitates CNS invasion by multiple opportunistic pathogens. Profoundly low CD4+ T-cell counts impair cell-mediated immunity, and reduced phagocytic function of macrophages and neutrophils further compromises the host defense mechanism, permitting persistent, concurrent infections within the CNS. In such settings, one primary pathogen—often *Cryptococcus neoformans*—may incite local immune and structural changes, predisposing the host to secondary bacterial or mycobacterial infection. Thus, coinfections are not uncommon in PLHIV, particularly those with low baseline immunity.[5–7]

The unmasking form of IRIS further complicates this picture. For instance, in unmasking TBM-IRIS, latent Rich foci become inflamed following ART initiation due to reconstituted TB-specific immune responses. This results in the rupture and dissemination of bacilli into the subarachnoid space, leading to inflammatory meningitis. Importantly, pathogen-specific IRIS phenomena may occur simultaneously or sequentially, contributing to complex and multifactorial presentations involving multiple pathogens.[8]

Diagnosing concurrent infections is particularly challenging due to overlapping clinical features and high early mortality rates. For example, concurrent TB meningitis may go unrecognized in patients with cryptococcal meningitis, leading to underdiagnosis.[9] Therefore, the use of comprehensive diagnostic modalities becomes imperative. As per WHO guidelines, GeneXpert MTB/RIF is the recommended initial diagnostic tool for TB meningitis. Cryptococcal meningitis, which often presents subacutely, is diagnosed using a combination of CSF culture, cryptococcal antigen (CrAg) testing in CSF/serum, and India ink microscopy.[10]

In our series, we ensured a thorough diagnostic workup, including HSV PCR, toxoplasma PCR, and syphilis serology (including treponemal and nontreponemal testing). For suspected neurosyphilis, CSF-VDRL remains the gold standard, though the CSF fluorescent treponemal antibody test may offer sensitivity in certain clinical contexts, albeit with reduced specificity.[11,12]

Neuroimaging was pivotal in our diagnostic approach. MRI findings characteristic of different pathogens were instrumental in detecting coinfections:

- Cryptococcus: Dilated perivascular spaces, gelatinous pseudocysts, leptomeningeal enhancement.
- Tuberculosis: Basal meningeal enhancement, tuberculomas, hydrocephalus.
- Bacterial meningitis: Leptomeningeal enhancement, infarcts, subdural empyema.

- CMV/HSV/VZV: Ependymal enhancement, ventriculitis, infarcts, encephalitis.
- *Toxoplasma gondii*: Multiple ring-enhancing lesions, predominantly in the basal ganglia.

Advanced techniques such as MR Spectroscopy, MRA, and MRV were useful in differentiating abscesses from tumors and identifying vascular complications like infarcts due to vasculitis, particularly in TB meningitis. CT was utilized primarily to rule out contraindications to lumbar puncture and to detect calcifications, mass effect, and hemorrhage. Nonetheless, MRI was superior in detecting early and subtle CNS pathology.

The management of these patients was inherently complex due to polypharmacy, risk of drug interactions, and compounding toxicities. Cryptococcal meningitis was managed per WHO guidelines, using a single dose of liposomal amphotericin B (10 mg/kg) plus 14 days of flucytosine (100 mg/kg/day) and fluconazole (1200 mg/day). This was followed by a consolidation phase with fluconazole 800 mg/day for 8 weeks. HSV encephalitis was treated with acyclovir 10 mg/kg IV every 8 hours for 14–21 days.[13] Patients with tuberculous meningitis received antitubercular therapy per national guidelines (isoniazid, rifampicin, ethambutol, pyrazinamide), with adjunctive corticosteroids. ART was deferred and reinitiated cautiously after clinical stabilization.

Despite optimal management, we observed a mortality rate of 45%, reflecting the severity and complexity of managing opportunistic CNS infections in advanced HIV.[14]

Conclusion

This case series emphasizes the clinical significance of triple-organism meningitis in PLHIV, particularly in the early period following ART initiation, where IRIS-driven unmasking of latent infections is common. The potential for pathogen synergy, CNS immune dysfunction, and overlapping inflammatory responses makes the diagnosis and management profoundly challenging.

The occurrence of stroke in this cohort further highlights the vascular complications of HIV, which may arise due to:

- HIV-associated vasculopathy (nonatherosclerotic vasculitis, arteritis).
- Opportunistic infections such as *M. tuberculosis*, *VZV*, and *CMV*.
- Prothrombotic states (elevated D-dimer, antiphospholipid antibodies).
- Cardioembolic sources.
- ART-associated metabolic derangements.

Some infections, such as tuberculosis, syphilis, and varicella zoster virus, are well-recognized causes of stroke even in non-HIV patients, but HIV-related immunosuppression increases both susceptibility and severity. Additionally, CNS opportunistic infections can be unmasked by cART, presenting with stroke or worsening neurological deficits.

A multidisciplinary approach—including infectious disease, neurology, radiology, and critical care—is essential. Timely and accurate diagnosis using advanced microbiological, molecular, and imaging modalities is critical for improving patient outcomes.

This series also highlights the noninfectious complications of HIV, including pulmonary embolism and peripheral neuropathy, reinforcing the need for holistic patient evaluation and follow-up.

Author Contributions

Sakshi Puri contributed to the concept, design, definition of intellectual content, manuscript preparation, and editing. Insha Aleena contributed to the design, data acquisition, manuscript preparation and editing, and literature search. Rupak Chatterjee contributed to the design, data acquisition, manuscript preparation and editing, and literature search. Sarbajit Das contributed to the concept, manuscript editing, literature review, and data acquisition.

Acknowledgments

We have organized the order of the visits of these patients and interpreted the results. All authors mentioned above have approved the final manuscript as submitted and agree to be accountable for all aspects of the work. The authors have received no financial compensation for this case report.

Source of Funding

None.

Conflict of Interest

None.

Patient Consent Statement

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given consent for the patient's images and other clinical information to be reported in the journal. The patient understands that the patient's name and initials will not be published, and due efforts will be made to conceal the patient's identity, but anonymity cannot be guaranteed.

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