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Case Reports

Contents

CASE REPORT

Head, Shoulders, Knees, and Toes: Unveiling Stroke in Leptospirosis Acute Respiratory Distress Syndrome

Sonal P Karpe[1*], Sidharth K[2], Vishwambar S Khadekar[3], Shivam S Gurme[4], Jairaj P Nair[5]

Received: 14 September 2024; *Accepted:* 28 March 2025

Abstract

Leptospirosis is an infection caused by the bacteria *Leptospira*. The disease presentation varies from self-limited acute febrile illness to complications involving multiple organs such as the liver, kidney, lungs, and bleeding diathesis. We present a case of a middle-aged female admitted with acute febrile illness, thrombocytopenia, and respiratory failure. She was diagnosed with leptospirosis-induced acute respiratory distress syndrome (ARDS) and was on noninvasive mechanical ventilation (NIV). The patient developed a stroke during the course of her admission, which was due to a large cerebral infarction. The patient was treated for leptospirosis, respiratory failure, and the cerebral infarction with antibiotics, steroids, and antiplatelet agents. She eventually recovered from both her ARDS and stroke and was discharged. To the best of our knowledge, this is the first reported case from India of leptospirosis presenting with both ARDS and cerebral infarct. There is a dearth of literature wherein leptospirosis neurological involvement is in the form of ischemic stroke. This would further encourage research and guideline formulation for the management of both leptospirosis ARDS and ischemic stroke occurring as a complication.

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Introduction

Infections with multisystem organ involvement pose a formidable challenge even in this era of modern medical advancements and breakthroughs. Leptospirosis is one such zoonotic disease caused by the gram-negative bacteria *Leptospira*. Leptospirosis presents as a disease mostly affecting multiple organs like the liver, kidneys, and lungs, but involvement of other systems, especially the brain, has also been reported. Acute respiratory distress syndrome (ARDS) is primarily due to pulmonary hemorrhage, whereas brain involvement results from both direct damage caused by the organism and immune complex-mediated injury. We present the first case report from India of leptospirosis with ARDS and cerebral infarction, highlighting a rare complication and the need for further study.

Case Description

A 63-year-old lady with no comorbidities was symptomatic for 8 days with high-grade fever and breathlessness, which progressed from Modified Medical Research Council (MMRC) grade I to grade IV over 3 days. There was dry cough with one episode of streaky hemoptysis. On enquiry, there was a history of wading through rainwater. The patient denied any significant past history or any history of addiction. On examination, the patient was febrile with both tachycardia and tachypnea. Blood pressure was maintained at 110/70 mm Hg with bilateral crepitation on auscultation. Her oxygen saturation was 62% at room air. There was no pallor, but subconjunctival hemorrhage was present. There was no icterus, cyanosis, clubbing, lymphadenopathy, or edema of the feet. Her laboratory investigations are shown in Table 1.

The leptospirosis immunoglobulin M and leptospirosis polymerase chain reaction (PCR) tests of serum were both positive.

The chest radiograph showed reticular opacities diffusely distributed over all zones bilaterally (Fig. 1). The electrocardiogram had normal sinus rhythm with tachycardia.

Reports of her arterial blood gas (ABG) on day 1 are shown in Table 2.

A screening echocardiogram showed a normal ejection fraction of 60%. The patient was diagnosed with leptospirosis ARDS. The patient was given noninvasive mechanical ventilation (NIV) mode. She was administered injection ceftriaxone 1 gm twice a day for a duration of 7 days. Intravenous methylprednisolone 500 mg was given for 3 days, then stopped. Intravenous fluids and correction of dyselectrolemia were done. On day 2, the patient showed an improving trend in her oxygenation with a further increase in the P/F ratio to 295 and a reduction in oxygen requirement to 30%. The patient was conscious, comfortable, and tolerating NIV.

Day 3, the P/F ratio had worsened to 210, and there was an increase in oxygen requirement to 40%. The patient was leaning her head to the left side. There was slurred speech with deviation of the angle of the mouth to the left side. Muscle power was zero at the left shoulder on asking to raise her left hand, along with a very weak hand grip. There was presence of hypotonia both proximally and distally in the upper and lower limb on the left side. The knee jerk was diminished on the left, with upgoing plantar response and fanning of toes. The findings were highly suggestive of an acute stroke, wherein the hypertonia and brisk reflexes had not set in yet. An immediate computed tomography (CT) brain revealed a large subacute nonhemorrhagic infarct involving the corona radiata, right frontoparietal, anterior temporal, and insular cortex along the middle cerebral artery territory on the right side. There was also a subacute infarct in the right cerebellar hemisphere (Fig. 2).

Electrocardiogram showed sinus tachycardia with no changes suggestive of any arrhythmia or recent cardiac insult. Bilateral carotid Doppler was normal. A repeat echocardiogram was also normal. Platelet count had improved to 1,09,000/dL. She was given a loading of atorvastatin, but loading with aspirin and clopidogrel was avoided due to suboptimal platelet count. Heparin was deferred in view of a large infarct and risk of hemorrhagic transformation. She was started on dual antiplatelet therapy for 2 weeks, followed by single antiplatelet therapy thereafter, along with statin for secondary prevention of stroke. The patient gradually recovered both from her ARDS and the stroke. She was shifted to nasal prongs, and then eventually she could maintain saturation at room air. With involvement of a physiotherapist and regular assessment from the neurology

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Table 1: Laboratory investigations reports

Laboratory investigations	*Patient's value and results*	*Normal range*
Hemoglobin	10 gm/dL	Female: 12–16 gm/dL
White cell count	16,500/µL	4,000–11,000/µL
Platelet count	29,000/µL	1,50,000–4,50,000/µL
Blood urea nitrogen	30 mg/dL	6–24 mg/dL
Serum creatinine	1.3 mg/dL	0.7–1.3 mg/dL
Total bilirubin	1.0 mg/dL	<2 mg/dL
Aspartate transaminase	40 U/L	0–40 U/L
Alanine transaminase	50 U/L	0–40 U/L
International normalized ratio (INR)	1.2	1.1 or below
Sodium	129 mmol/L	135–145 mmol/L
Potassium	3.3 mmol/L	3.5–4.5 mmol/L
Triglycerides	100 mg/dL	60–165 mg/dL
Cholesterol	160 mg/dL	150–220 mg/dL
Glycosylated hemoglobin (HbA1c)	5.5%	<5.7%: nondiabetic

Table 2: ABG values on day 1

ABG	*Day 1*	*Normal range*
pH	7.34	7.35–7.45
Partial pressure of carbon dioxide (pCO_2)	26 mm Hg	32–48 mm Hg
Partial pressure of oxygen (pO_2)	76 mm Hg	83–103 mm Hg
Bicarbonates	14 mmol/L	22–29 mmol/L
Oxygen saturation level	94%	95–100%
Fraction of inspired oxygen (FiO_2) requirement	35%	Room air has 21% FiO_2
Inspiratory positive airway pressure (IPAP)	16 mm of water (H_2O)	Millimeter of H_2O
Expiratory positive airway pressure (EPAP)	8	Millimeter of H_2O
PO_2/FiO_2 ratio (P/F ratio)	217	>400

Fig. 1: Chest radiograph showing bilateral reticular opacities distributed diffusely in all the zones

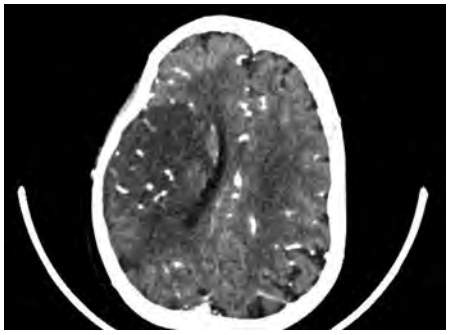

Fig. 2: An ill-defined, hypodense, nonenhancing area with loss of grey-white differentiation is noted involving right corona radiata, right frontoparietal and anterior temporal regions, with effacement of the overlying sulci

team, she was gradually able to walk and was discharged.

Discussion

Leptospirosis is a zoonotic disease found in tropical countries, especially after heavy rains and flooding.[1] The causative agent, *Leptospira*, is present in the urine or feces of rodents and mice. It has been observed that suboptimal sanitary conditions and poor housing contribute to higher chances of infection, especially in cities. Breaks in skin are a common portal of entry, along with contact from mucosa of the mouth, nose, and eyes, and food contamination.[2] The disease manifests as a febrile illness along with headache, myalgia, and pain in the abdomen. Other symptoms include subconjunctival hemorrhage, dry cough, nausea, and vomiting. These symptoms predominate in the initial acute phase, which lasts for a week. The second phase (immune phase) is characterized by a widespread inflammatory response. Complications include involvement of the liver, lungs, kidneys, and brain. Weil's disease is the severe form of the disease, characterized by involvement of the kidney, liver, and bleeding tendency, which occurs in around 5–10% of people.[3] Our patient presented with extensive lung involvement, requiring NIV. On the 3rd day, the sudden onset of cerebrovascular accident (CVA) symptoms raised concerns about a hemorrhagic stroke, given the patient's diagnosed leptospirosis with thrombocytopenia. However, the detection of a thrombotic stroke indicated an inflammatory vascular involvement rather than a bleeding tendency.

The vascular involvement in leptospirosis has a complex pathophysiology. *Leptospira* antigens deposit on host cell membranes, potentially altering cadherin expression. This disruption weakens vascular integrity, triggering extensive leakage, tissue invasion, and widespread dissemination across multiple organs and tissues. Systemic vasculitis serves as one of the main mechanisms of tissue damage. There are several possible reasons for this, such as direct invasion by infectious agents or immune mechanisms, including immune complex deposition, auto-antibodies, and cell-mediated immunity. However, these pathways have unclear documentation in leptospirosis-related vascular involvement.[4] Nicodemo et al. concluded that severe lung involvement in leptospirosis was in the form of hemorrhagic pneumopathy, presenting as injury to capillaries at the core of bleeding diathesis.[5] It is, however, worth noting that spirochetes are found in blood and cerebrospinal fluid (CSF) early in the course of the illness and later in the urine. There are several presentations of neuroleptospirosis; commonly seen are aseptic meningitis,

myositis, mononeuropathies, intracranial hemorrhage, extradural hematoma, and Guillain–Barré syndrome. Leptospirosis causing ischemic stroke and infarction is seldom reported and is considered uncommon.[6]

China first reported cerebral arteritis due to leptospirosis in 1975. A study of postmortem cases of leptospirosis was conducted at Wuhan Medical College, which demonstrated cerebral occlusion secondary to arteritis of major vessels such as middle and anterior cerebral arteries.[7] Our patient had involvement of the middle cerebral artery. Similar involvement of coronary arteries also has been documented before. A study done for cause of cerebral infarction due to infection revealed that a few had developed arterial disease of the intracranial vessels.[8] A study done by Li et al.[9] demonstrated a 2.49-fold risk of stroke among the leptospirosis patients younger than 39 years. However, this study was pertaining to hemorrhagic stroke, so the risk of nonhemorrhagic stroke remains largely unknown.

The treatment of neuroleptospirosis along with nonhemorrhagic stroke can be tricky due to the presence of thrombocytopenia. There are no clearly defined guidelines for the same, and hence reporting of such cases warrants a priority for formulation of the same. Heparin was contraindicated in our patient due to the presence of a large stroke and the possibility of hemorrhagic conversion. Our patient had received intravenous steroids, methylprednisolone 500 mg for 3 days, for the presence of ARDS. The effectiveness of steroids during the immune phase lacks robust evidence. However, steroids have shown to decrease the severity and duration of disease based on previous available literature.[10]

Conclusion

Leptospirosis is a common illness encountered during the monsoons, especially in overcrowded, rat-infested metropolitan cities. A thorough knowledge of the potential complications of the disease is important, as although treatment is available, complications are immense, with a high fatality rate for multiorgan involvement. To the best of our knowledge, this is the first reported case from India of leptospirosis presenting with both ARDS and neurological involvement in the form of cerebral infarct. The importance of such rare complications cannot be overemphasized, as the eyes don't see what the mind doesn't know. This might encourage much-needed randomized controlled trials for both leptospirosis ARDS and ischemic stroke.

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CASE REPORT

Tolosa–Hunt Syndrome: A Rare Case of Painful Ophthalmoplegia in a Young Female

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Abstract

Tolosa–Hunt syndrome (THS) is a syndrome of painful episodic ophthalmoplegia due to nonspecific inflammation around the superior orbital fissure or the cavernous sinus, sometimes associated with paralysis of one or more of the cranial nerves III, IV, or VI. It is usually idiopathic but may have triggers such as tumors, aneurysms, or trauma. Since it is a diagnosis of exclusion, all other differentials such as cavernous sinus thrombosis, carotid-cavernous fistulae, giant cell arteritis, diabetic ophthalmoplegia, or ophthalmoplegic migraines should be ruled out. Diagnosis is mainly based on characteristic findings on clinical and radiological examination. The importance of diagnosing this condition lies in its management with steroids. This is one of the few neurological conditions that can completely resolve upon treatment. Here, we have a case of a young female who presented with painful ophthalmoplegia and ptosis of the left eye. She was diagnosed with THS on the basis of clinical and radiological features and showed complete resolution without any relapse with the administration of glucocorticoids. Therefore, early recognition of the condition and appropriate treatment lead to complete resolution of THS, as can be seen in our patient.

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Introduction

Tolosa–Hunt syndrome (THS), also called painful ophthalmoplegia, recurrent ophthalmoplegia, or ophthalmoplegia syndrome, causes severe, unilateral periorbital headache with restricted eye movements. First reported in 1954, the annual incidence is about one case per million with no reported predilection for any geographical or racial factors. It is uncommon in the younger demographic with the mean age of onset being >41 years, without any gender predilection.[1]

Tolosa–Hunt syndrome is an idiopathic condition usually due to nonspecific inflammation in the orbital apex, superior orbital fissure, or cavernous sinus (CS) areas, often triggered by trauma, tumors, and aneurysms in these areas.[2]

Pain is the defining feature (described as "boring" and "stabbing" in periorbital, retro-orbital regions extending to frontal and temporal regions), which is often associated with the involvement of all three ocular motor nerve nuclei.[2]

Contrast-enhanced magnetic resonance imaging (MRI) with multiple views is the initial investigation to be done, which shows hyperintensity in the T1 and intermediate-weighted images, consistent with an inflammatory process. However, MRI findings in THS lack specificity, which is why a resolution of imaging abnormalities after treatment is considered diagnostic of THS. Cerebrospinal fluid (CSF) findings are usually unremarkable, and neurosurgical biopsy to obtain a diagnosis is an absolute last resort.[2]

Here, we present a case of a young female presenting to the medicine ward with the complaint of painful ophthalmoplegia with ptosis of the left eye and diagnosed with THS. She showed dramatic improvement after the administration of glucocorticoids and had no relapse during 1 year of follow-up.

Case Description

An 18-year-old female without any major medical illness presented to our hospital with a complaint of left-sided ocular pain, double vision, and partial drooping of the left upper eyelid for the past 5 days (Fig. 1). She also complained of headaches localized to the left frontal region for 5 days. There were no complaints of watery discharge from both eyes, pain or diplopia in the right eye, nausea, vomiting or vertigo, convulsions, altered sensorium, and any focal neurological deficits, with normal menstrual function.

On general examination, she was vitally stable and was well-oriented to time, place, and person. However, on ocular examination, restriction of left eyeball movement in the upper and outer direction, and partial ptosis on the left upper eyelid were observed (Fig. 1). Additionally, the right eye showed nystagmus with a fast component toward the left side on the right lateral gaze. The contracted fundus findings were reported as normal. Other neurological, cardiac, respiratory, and abdominal examinations were normal.

On routine investigations, hemoglobin was 13.6 gm/dL. No significant abnormality was reported in hematological investigations. Bilirubin (total) was 0.6 mg/dL, with indirect comprising 0.4 mg/dL and direct being 0.2 mg/dL. Serum total protein, serum albumin, liver enzymes, blood glucose, serum urea, creatinine, and electrolytes including ionized calcium were within normal limits. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were within normal limits. CSF analysis was ordered; however, parameters were reported as normal. Antinuclear antibody (ANA) and antineutrophil cytoplasmic antibodies (ANCA) screening reports also came back with nonsignificant findings.

Magnetic resonance imaging of the brain with the orbit (plain with contrast) reported focal abnormal enhancement at the left inferior orbital fissure, left superior orbital fissure, and left optic canal along the traversing structures, suggestive of possible inflammatory or granulomatous etiology.

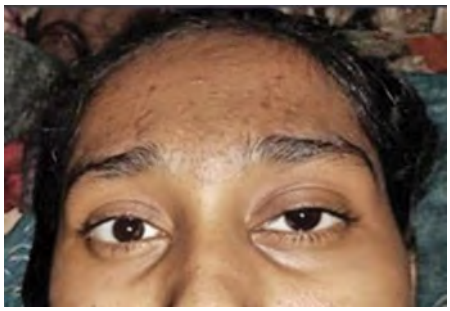

Fig. 1: Ptosis of the left upper eyelid (at the time of presentation)

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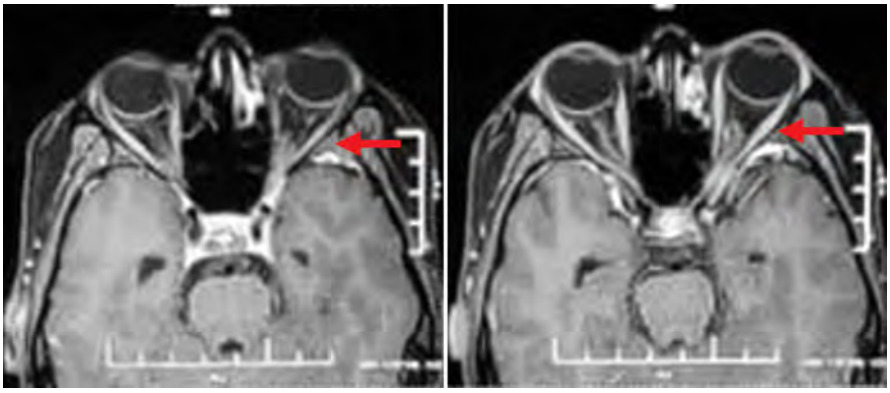

Fig. 2: MRI of the brain + orbit showing enhancement of the left optic canal with traversing structures (marked by red arrow)

No other significant intracranial etiology was observed (Figs 2 and 3).

The patient was fitting into the diagnostic criteria mentioned by the International Headache Society[3] and therefore was diagnosed with THS based on combined clinical and radiological findings.

Upon neurophysician reference, she was initially started on injection of methylprednisolone 1 gm intravenously diluted in 100 mL normal saline once a day for 5 days, to which she showed a dramatic response in the form of resolution of ophthalmoplegia, headache, and ptosis (Fig. 4). After that, she was shifted to oral prednisolone 1 mg/kg/day.

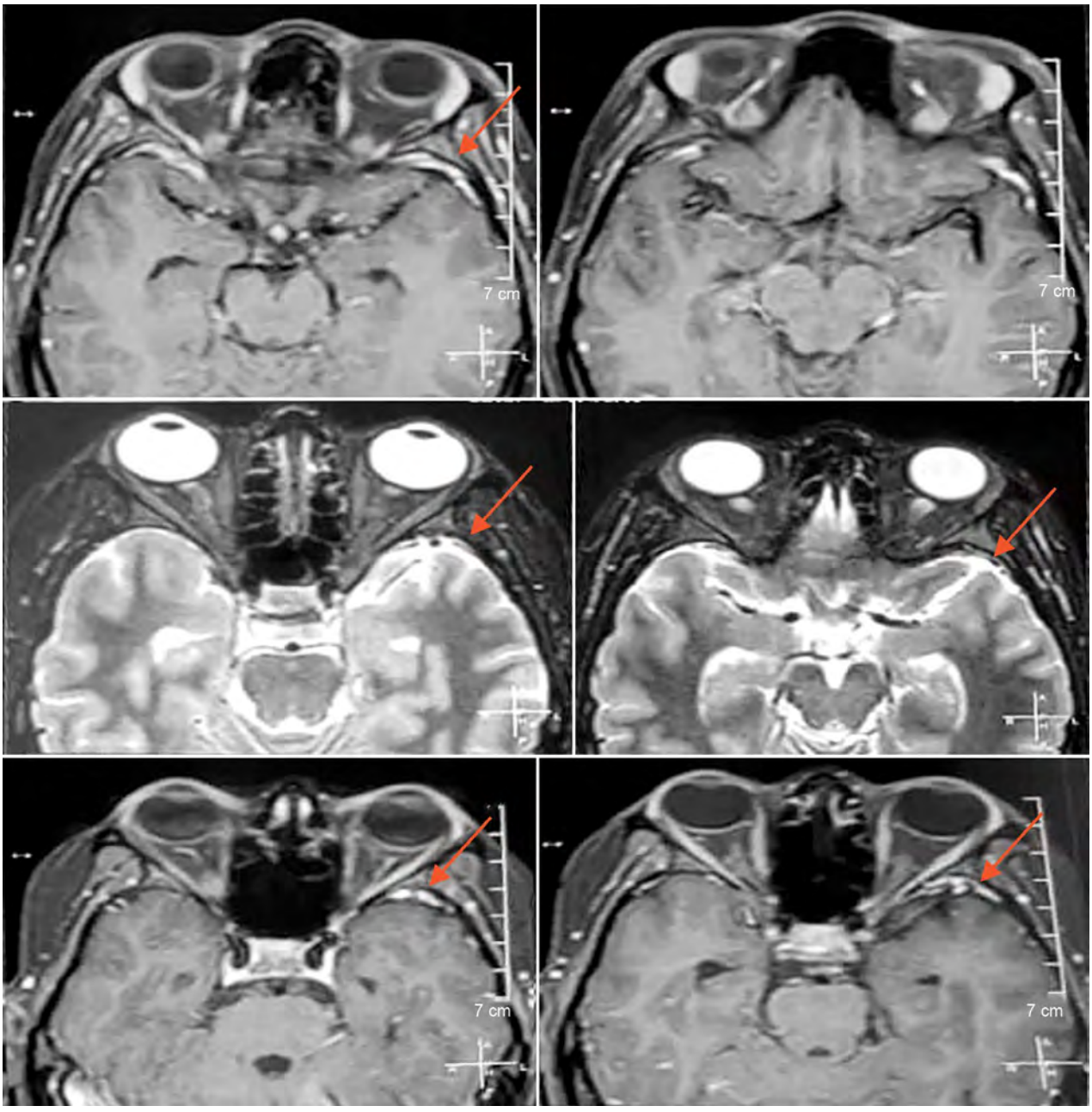

Fig. 3: MRI of the brain + orbit showing focal abnormal enhancement at the left inferior orbital fissure, left superior orbital fissure, and left optic canal (marked with red arrow)

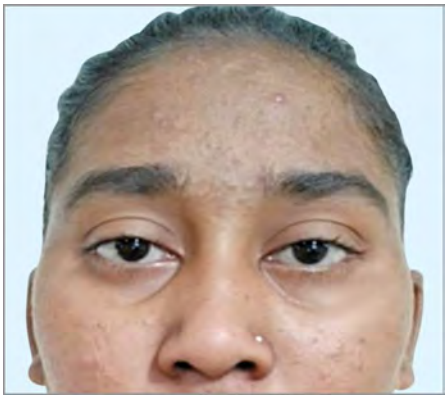

Fig. 4: After treatment with glucocorticoids

She was further started with tablet Neurobion Forte twice daily, tablet folic acid 500 mg once daily, tablet pantoprazole once daily, and domperidone as and when required. Tablet Calcium and vitamin D3 were also prescribed twice daily along with oral steroids. Oral steroids were tapered gradually over a period of 2.5 months, without developing any symptoms or signs of relapse. Thus, steroids were stopped after 2.5 months, and during 1 year of follow-up, she did not relapse.

Discussion

Tolosa–Hunt syndrome is a rare disorder of severe periorbital unilateral headaches along with decreased painful eye movements (ophthalmoplegia). Patients may also present with features such as ptosis, diplopia, enlarged pupil, and localized facial numbness consistent with palsies of certain cranial nerves distributing to those regions.[2,4] THS pathophysiology was first described as nonspecific chronic inflammation of the septa and walls of the CS along with the proliferation of fibroblasts and infiltration of lymphocytes and plasma cells. These changes, in turn, exert pressure on the nerves located in the CS (usually cranial nerves III, IV, VI, and V1), leading to most of the symptoms. Even though THS sometimes presents with systemic and autoimmune illnesses such as systemic lupus erythematosus (SLE), sarcoidosis, and Wegener's granulomatosis.[1,5]

Due to the exceedingly rare nature of THS, it is a diagnosis of exclusion. It is initially important to rule out causes of parasellar syndromes and other causes of ophthalmoplegia.[2,4]

Intracavernous carotid artery aneurysm may produce painful ophthalmoplegia. Carotid-cavernous fistulae (CCF) and cavernous sinus thrombosis (CST) have acute onset symptoms; however, CCF patients have a dramatic presentation with pain seldom being their defining feature and bruits often being present. CST, if infective, is associated with a history of sinusitis, otitis, gingivitis, or orbital cellulitis, whereas the noninfective type is associated with polycythemia, sickle cell disease, trauma, vasculitis, or intracranial surgery. It also has symptoms such as chemosis, proptosis, orbital congestion, lacrimation, and eyelid swelling (none seen in this patient). Diabetic ophthalmoplegia may also produce an acute painful neuropathy in a long-running case of poorly controlled diabetes mellitus, but it usually does not respond to corticosteroid therapy and has a positive response to proper glycemic control.[2,4]

Giant cell arteritis may sometimes present as painful ophthalmoplegia, but cranial motor nerve functions are normal in such cases.[2,4] Ophthalmoplegic migraines are also a possible differential; however, patients have a family history of the same, and attacks are associated with sensitivity to light, nausea, vomiting, irritability, and constipation or diarrhea. Restricted eye movements are not a characteristic feature of ophthalmoplegic migraine.[6]

Since diagnosis is largely on the basis of radiological findings (MRI plain with contrast) with the corroborating clinical picture, the MRI report in this patient showed focal abnormal enhancement on the affected left side of the left inferior and superior orbital fissure and optic canal of a possible inflammatory or granulomatous cause. The patient was treated with an injection of methylprednisolone, and upon finishing 5 days, she was shifted to oral prednisolone. Multivitamins, folate, and vitamins C and D3 were also started.

Conclusion

Painful ophthalmoplegia is commonly found in clinical practice; however, THS is one of the rare causes of painful ophthalmoplegia, which could be missed while making the diagnosis. As THS is a diagnosis of exclusion, all other causes need to be ruled out before labeling the patient to have THS. The importance of correctly diagnosing THS lies in its management, as it is one of the few neurological conditions that is completely reversible on appropriate treatment. We have presented one such case of THS in a young female who completely recovered from treatment and showed no relapse during 1 year of follow-up.

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CASE REPORT

Neurophysiology of Acute Quadriparesis

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Received: 11 January 2025; *Accepted:* 05 May 2025

Abstract

Background: Acute respiratory failure is a life-threatening emergency requiring intensive care. Nerve conduction and repetitive nerve stimulation studies are invaluable to solve dilemmas related to the diagnosis and management. The results of these tests are available immediately, and prompt treatment can be given as illustrated in this case.

Clinical description: A 7-year-old boy presented in circulatory shock and impending respiratory failure to the casualty without any preceding illness.

Management and outcome: The clinical picture, blood reports, and neurophysiological findings of repetitive compound muscle potentials on nerve conduction and a progressive decremental pattern on repetitive nerve stimulation were suggestive of acute organophosphate poisoning. This led to prompt institution of appropriate treatment comprising Ryle's tube aspiration, respiratory support, and administration of neostigmine and pralidoxime. The diagnosis was later confirmed by low serum pseudocholinesterase levels.

Conclusion: This case exemplifies the importance of neurophysiological study in the diagnosis of organophosphate poisoning.

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Introduction

In 2018, WHO estimated that of 2,50,000 poison-related deaths per year globally, organophosphate poisoning contributed to 1,50,000 deaths per year.[1] Organophosphate-induced neurological syndromes were consequent to accidental or suicidal intake of organophosphorus compounds in the community.[2] Urgent first aid, removal of soiled clothes, hospitalization, stomach wash, prevention of aspiration pneumonia, ventilatory support, atropine, and anticholinesterases reduced morbidity and mortality of affected patients.[2] Complications include an acute cholinergic crisis, intermediate syndrome, delayed polyneuropathy, and organophosphate-induced neuropsychiatric disorders.[2]

Clinical Description

A 7-year-old boy was rushed to the emergency department of our hospital at 10 pm on August 16, 2023, with weakness of all four limbs, abdominal pain, and persistent vomiting. At 3 am, he was intubated and ventilated for impending circulatory and respiratory failure. He received Ryle's tube aspiration, inotrope infusion, intravenous dexmedetomidine, intravenous antibiotics, and ventilatory and circulatory support. This child was unconscious with cold extremities, bradycardia, and persistent hypotension despite inotropes. There was no history of trauma, fever, headache, rashes, seizures, or antecedent events that caused a catastrophic illness. Suspecting poisoning, red blood cell (RBC) pseudocholinesterase levels and urine toxicology screen were sent, and the patient was administered intravenous atropine 0.02 mg/kg every 10–20 minutes till the cholinergic signs reversed. The next day, there was areflexic quadriparesis, bilateral bulbar palsy, ptosis, miosis, external ophthalmoplegia, skew deviation of both eyes, and extensor plantar response.

Management and Outcome

Nerve conduction study revealed repetitive compound muscle action potentials (CMAPs) of normal amplitude after single stimulation in bilateral median, ulnar, common peroneal, and posterior tibial nerves (Fig. 1). Repetitive nerve stimulation at 3 Hz showed a decremental response in trapezius and orbicularis oculi muscles (Fig. 2). On seeing repetitive CMAPs and electrodecremental response on repetitive nerve stimulation, the neurophysiologist was convinced of organophosphate poisoning-induced acute respiratory failure followed by intermediate syndrome, for which the patient was treated appropriately with intravenous neostigmine at 0.01 mg/kg and infusion of pralidoxime 2.5 gm in 20 mL normal saline at 1 mL/hour. Serum pseudocholinesterase obtained 2 days later confirmed reduced levels <1.50 kU/L (normal 4.62–11.50 kU/L). Miosis, external ophthalmoplegia, and absent gag reflex improved in 2 weeks; however, weakness of neck, trunk, and leg muscles persisted for 1 month. The patient recovered with supportive treatment and physiotherapy and was discharged a month later without neurological deficits.

Discussion

Respiratory failure due to an acute cholinergic crisis is caused by persistence of acetylcholine at the motor end plate, resulting in synaptic failure at the neuromuscular junction.[2] The safety margin of the neuromuscular junction is compromised by nicotine receptor hyperstimulation, leading to prolonged action of acetylcholine at the nicotinic receptors, which sustain self-repeating antidromic and orthodromic excitable impulses resulting in fasciculations and an intermediate syndrome.[2,3] The delayed neurological sequel is caused by phosphorylation and aging of neuropathy target esterase in the peripheral

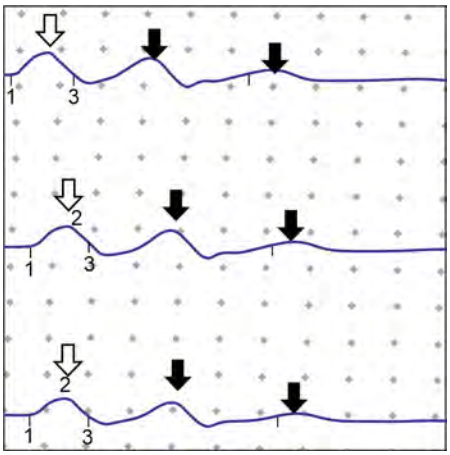

Fig. 1: Characteristic nerve conduction study findings showing single supramaximal electrical stimulus-induced repetitive response, depicted by arrows in median nerve on recording from the abductor pollicis brevis muscle; open arrow—single normal response; closed arrows—repetitive CMAPs

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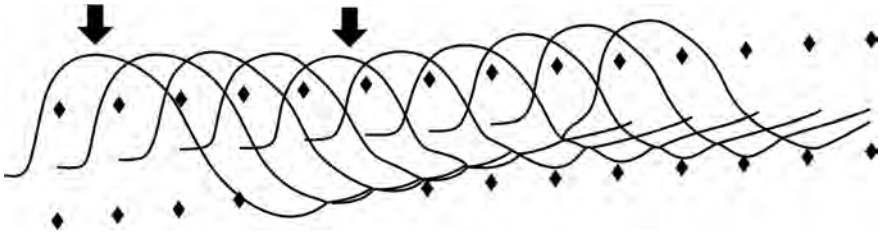

Fig. 2: At 3 Hz stimulation, decremental response of –17% maximal between the first and fifth waveforms recorded in the trapezius muscle

nerves.[2,3] There is axonal degeneration, Schwann cell proliferation, and macrophage accumulation in nerves, resulting in a delayed polyneuropathy.[4,5]

Nerve conduction studies and repetitive nerve stimulation are sensitive tests to detect organophosphate poisoning in critically ill patients.[2,3] Organophosphorus compounds irreversibly inhibit acetylcholinesterase, leading to prolonged contact of excess acetylcholine at the synaptic cleft, increased muscle membrane excitation, prolonged channel opening, and delayed end plate potentials.[4] Thus, nerve conduction tests are invaluable in early diagnosis of acute organophosphate poisoning with the recording of repetitive CMAPs due to acetylcholinesterase inhibition.[4] The repetitive firing of action potentials causes impulses to propagate orthodromically to adjacent nerve endings through the axon reflex, resulting in repetitive end plate depolarization.[4,5] The characteristic patterns of repetitive nerve stimulation during organophosphorus-induced intermediate syndrome enable early diagnosis in unexplained cases of neuromuscular failure even before blood results of poisoning are available.[4] In acute organophosphate poisoning, four types of neuromuscular transmission defects are recorded: a decrement–increment pattern, a repetitive fade pattern after decrement–increment pattern, a severe decrement pattern, and a progressive decrement pattern.[4,5] In the decrement–increment pattern, amplitude of the second motor unit potential is reduced, while there is progressive increase in amplitude from the third to the sixth motor unit at high-rate stimulation.[4,5] The decrement–increment response noted after tetanic stimulation is due to antidromic backfiring of nerves, influx of calcium, and prolonged desensitization of acetylcholine postsynaptic receptors that damage the neuromuscular junction, resulting in a subacute neuromuscular syndrome.[5] The severity of the decrement reflects the degree of inhibition by butyrylcholinesterase at the motor end plate, and treatment with pancuronium facilitates presynaptic decrease in neurotransmitters with subsequent recovery of neuromuscular function.[5,6]

Conclusion

This 7-year-old boy presented to the emergency department with unexplained cardiogenic shock and respiratory failure. However, the electrodiagnostic studies were suggestive of organophosphate poisoning, and immediate lifesaving measures of decontamination, atropinization, use of pralidoxime, and life-supportive care were able to reverse the toxic effects of the poison after he developed an intermediate syndrome with delayed neurological sequelae. Electrophysiology enabled early diagnosis and treatment even before blood levels of pseudocholinesterase were available. This case showcases the importance of applying neurophysiological tests in unexplained acute medical emergencies to gain insight into the nature of the illness.

Lessons Learned

- A high index of suspicion should be entertained in cases of unexplained neuromuscular failure as in the abovementioned case.
- There should be an emphasis on nerve conduction studies and repetitive nerve stimulation in cases of quadriparesis with respiratory involvement to institute lifesaving treatment.

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CASE REPORT

Burkholderia cepacia Splenic Abscess in a Newly Diagnosed Multiple Myeloma Patient

Arpan[1], Navrajbir Singh[2*], Kusum Bali[3], Tarundeep Singh[4]

Received: 15 April 2025; *Accepted:* 13 May 2025

Abstract

Introduction: Splenic abscesses are rare and primarily affect immunocompromised patients. *Burkholderia cepacia*, an opportunistic, multidrug-resistant pathogen, is an uncommon cause of such infections. This case describes a 69-year-old male with multiple myeloma, diabetes mellitus, and chronic kidney disease who developed a *B. cepacia* splenic abscess, emphasizing the pathogen's emerging role in immunocompromised individuals.

Case presentation: A 69-year-old male with type 2 diabetes mellitus and chronic kidney disease was admitted with fever and generalized weakness. Notably, he had been hospitalized 3 months earlier for bacteremia due to *B. cepacia*, which was treated with intravenous antibiotics. During the current admission, imaging revealed multiple splenic abscesses. Blood and splenic aspirate cultures confirmed *B. cepacia*. The patient was diagnosed with multiple myeloma based on a history of recurrent infections, hypercalcemia, anemia, A:G reversal, and bone marrow biopsy findings. He was treated with intravenous antibiotics and supportive care, leading to clinical improvement.

Conclusion: This case highlights the importance of considering *B. cepacia* as a causative agent in splenic abscesses, particularly in patients with newly diagnosed hematologic malignancies. Early recognition and appropriate antimicrobial therapy are crucial for improving patient outcomes.

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Introduction

Splenic abscesses are uncommon, occurring in 0.14–0.7% of autopsy cases, with mortality rates as high as 47% in untreated individuals.[1] The most common causative organisms include *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* spp., and *Klebsiella pneumoniae*.[2] *Burkholderia cepacia*, a gram-negative, aerobic bacillus, is a well-known microorganism for causing opportunistic infections in patients with cystic fibrosis and chronic granulomatous disease, but it has rarely been reported as a cause of splenic abscesses.[3]

Patients with hematologic malignancies, such as multiple myeloma, are at increased risk of infections due to disease-related immunosuppression and chemotherapy-induced neutropenia.[4] In such individuals, bacterial infections can be life-threatening, necessitating early diagnosis and targeted therapy. While respiratory and bloodstream infections are well-documented in these patients, intra-abdominal abscesses due to *B. cepacia* remain exceptionally rare. This report presents a newly diagnosed case of multiple myeloma with *B. cepacia* splenic abscess, emphasizing diagnostic challenges and management strategies.

Case Presentation

A 69-year-old male with a history of type 2 diabetes mellitus, chronic kidney disease (CKD), and coronary artery disease (CAD) was admitted with fever and altered sensorium from January 3, 2025, to January 12, 2025. Initial investigations revealed pancytopenia with an acute febrile illness. Blood cultures from January 3, 2025, were positive for *B. cepacia*, which was sensitive to meropenem, minocycline, ceftazidime, and cotrimoxazole. The patient was managed with intravenous meropenem (1 gm every 8 hours) and teicoplanin (200 mg every 24 hours), along with supportive care and blood transfusions. He showed improvement and was discharged.

On January 30, 2025, he was readmitted with complaints of generalized pain, weakness for 1 month, and fever for 2 days. On examination, his vitals were stable: random blood sugar (RBS) 370 mg/dL, pulse 90/min, blood pressure (BP) 110/70 mm Hg, respiratory rate 24/min, and SpO_2 99%. Abdominal examination revealed splenomegaly. Urine culture from January 19, 2025, showed *E. coli* sensitive to levofloxacin, amikacin, aztreonam, ampicillin, ciprofloxacin, ofloxacin, nitrofurantoin, imipenem, and azithromycin. Repeat urine cultures after antibiotics showed no growth.

Radiological investigations during the hospital stay included:

- Ultrasound of the abdomen (January 30, 2025): Splenomegaly (13.2 cm) with multiple cystic lesions containing internal echoes (largest 2.3 cm), suggestive of chronic splenic abscesses.
- Computed tomography (CT) of the abdomen (January 4, 2025): Splenomegaly (16.7 cm) with scattered air foci in splenic parenchyma and perisplenic location, with a thin layer of perisplenic fluid indicating infective etiology (Fig. 1).

The patient had a prior ultrasound on July 23, 2024, showing splenomegaly with a heterogeneous echopattern and small cystic lesions (15 × 14 mm). A follow-up ultrasound on March 3, 2025, revealed splenomegaly (15.4 cm) with multiple hypoechoic areas measuring 1.1 cm in the splenic parenchyma.

As the patient had persistent fever despite previous antibiotic therapy and a history of *B. cepacia* bacteremia, the splenic cysts were suspected to be secondary to chronic infection. Echocardiography showed CAD with regional wall motion abnormality (RWMA) and left ventricular ejection fraction (LVEF) of 40% but no vegetations, ruling out infective endocarditis.

Further evaluation revealed newly diagnosed multiple myeloma:

- Serum protein electrophoresis: Hypoalbuminemia with a suspicious monoclonal gammopathy.
- Immunofixation electrophoresis: Confirmed monoclonal gammopathy.
- Bone marrow aspiration: Hypercellular marrow with 12% plasma cells.
- Flow cytometry: 3% abnormal monoclonal plasma cells with CD19 loss and kappa predominance.
- β2-microglobulin: 20583 ng/mL (elevated).
- Immunoglobulin G (IgG) levels: 3334 mg/dL (elevated).

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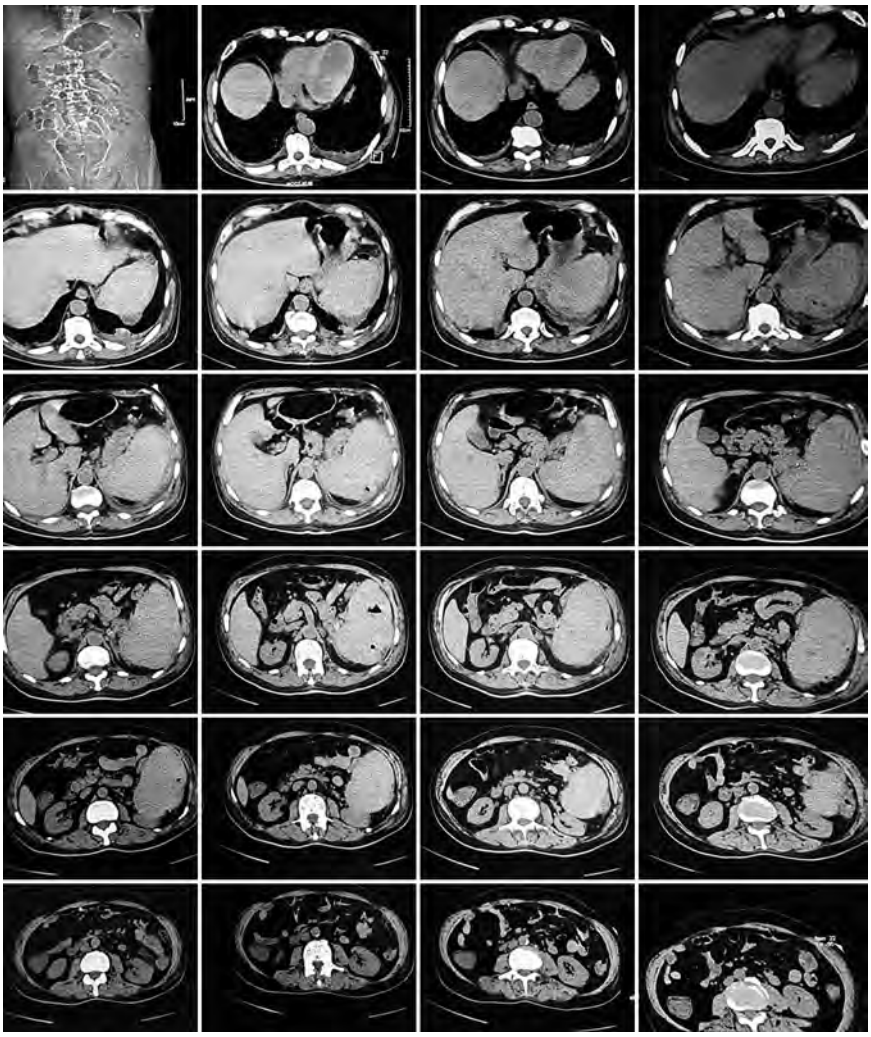

Fig. 1: Computed tomography of the abdomen showing splenomegaly with scattered air foci in splenic parenchyma and perisplenic location, with a thin layer of perisplenic fluid indicating infective etiology

A final diagnosis of multiple myeloma with chronic splenic cysts caused by *B. cepacia* was made. However, there were no lytic lesions on skull X-ray. The patient was initiated on myeloma-directed therapy (high-dose steroids and bortezomib) and continued on appropriate antimicrobial coverage. He showed clinical improvement with resolution of fever (Fig. 2).

Discussion

Burkholderia cepacia is an opportunistic pathogen that primarily affects immunocompromised patients. It has an intrinsic resistance to multiple antibiotics, including aminoglycosides and first-generation cephalosporins.[5] *B. cepacia* is a gram-negative, nonfermenting bacillus found in soil and water. It is a recognized nosocomial pathogen due to its ability to survive in disinfectants and hospital water systems.[6] Its virulence is attributed to biofilm formation, efflux pumps, and the ability to evade host immune responses.[7] In multiple myeloma, immunosuppression is multifactorial: (1) Impaired humoral immunity: Hypogammaglobulinemia leads to defective opsonization, (2) Neutropenia: Chemotherapy-induced or disease-related neutropenia increases bacterial infection risk, (3) Altered splenic function: Myeloma-associated splenic dysfunction predisposes to encapsulated and opportunistic infections. While primarily associated with pneumonia in cystic fibrosis patients, *B. cepacia* is increasingly recognized as a cause of bloodstream infections and abscesses in immunocompromised individuals.[8]

Diabetes mellitus also contributes to increased infection risk by impairing neutrophil function and reducing cytokine production.[9] Additionally, multiple myeloma patients are highly susceptible to infections due to hypogammaglobulinemia and impaired innate immunity.[10]

Similar cases of *B. cepacia* splenic abscesses have been reported in patients with cystic fibrosis and chronic granulomatous disease, but their occurrence in multiple myeloma remains rare.[11,12] Most documented cases required prolonged intravenous antibiotic therapy and, in some instances, splenectomy for persistent infection.

Splenic abscesses typically require a combination of antimicrobial therapy and, in some cases, percutaneous or surgical drainage. However, our patient responded well to conservative management, emphasizing the importance of early detection and targeted antibiotic therapy.[2]

Given *B. cepacia*'s multidrug resistance, carbapenems remain the mainstay of treatment for severe infections.[3] Alternative agents include ceftazidime and trimethoprim-sulfamethoxazole, which have demonstrated efficacy in some cases.[13]

A recent study also highlights the increasing incidence of *B. cepacia* infections in hematologic malignancies, underscoring the importance of early detection and targeted antimicrobial therapy.[14] Multidrug resistance remains a major concern, with some strains exhibiting resistance even to carbapenems, necessitating alternative approaches such as combination therapy with colistin or ceftazidime–avibactam.[15]

Given *B. cepacia*'s intrinsic resistance and ability to form biofilms, treatment strategies must be carefully tailored, emphasizing the need for susceptibility testing to guide therapy.[8] *B. cepacia* is intrinsically resistant to aminoglycosides and first-line β-lactams.[10] Meropenem remains the drug of choice, though combination therapy with trimethoprim-sulfamethoxazole may be considered in severe cases. In our case, the patient responded to meropenem, avoiding the need for surgical intervention.

Conclusion

This case highlights the rare occurrence of *B. cepacia* splenic abscesses in patients with multiple myeloma and diabetes mellitus, the diagnostic challenge of an underlying hematologic malignancy presenting with atypical infections, and the need for early antimicrobial susceptibility testing and targeted therapy.

Clinicians should maintain a high index of suspicion for multidrug-resistant pathogens in immunocompromised patients. Early diagnosis and appropriate antimicrobial

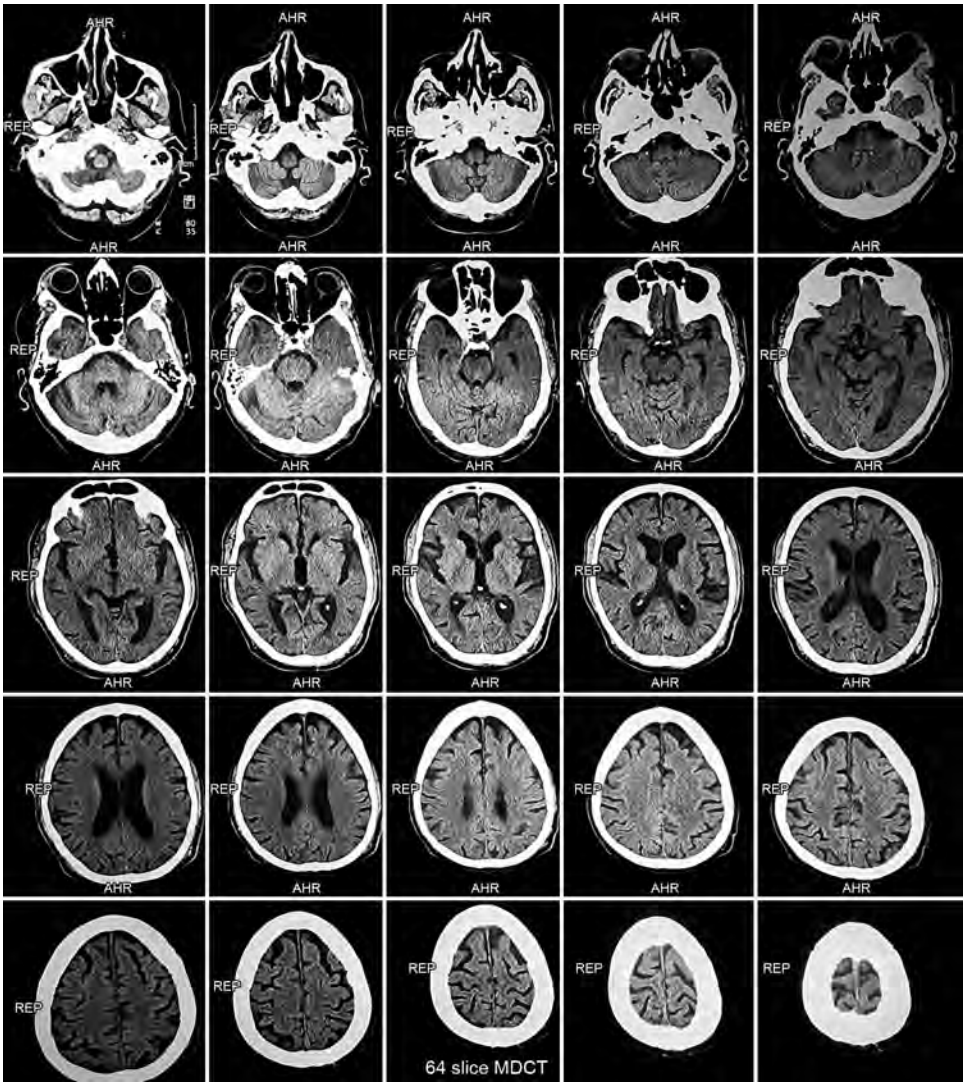

Fig. 2: Computed tomography of the head

therapy are crucial for favorable outcomes. Further research is needed to establish optimal management guidelines for *B. cepacia* infections in multiple myeloma patients.

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CASE REPORT

The Rhythm of Stress: A Case of Dancing Electrocardiography in Partial Hanging

Saleh A Bashadi[1], Rahul R Mamidi[2,*], Mohammed Mubashir A Subhani[3], Ashima Sharma[4], Mohammed I Nizami[5]

Received: 10 April 2025; *Accepted:* 13 May 2025

Abstract

We present the case of a 45-year-old woman who survived a suicide attempt with partial hanging and presented with electrocardiographic (ECG) abnormalities that mimicked acute coronary syndrome (ACS). She exhibited ST-segment abnormalities and QT interval prolongation, all of which resolved within 1 month. This case highlights the importance of recognizing stress-induced cardiomyopathy, such as Takotsubo cardiomyopathy, which can present with ECG changes similar to ACS, particularly in patients experiencing extreme emotional distress or suicide attempts.

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Case Description

A 45-year-old woman was brought to the emergency room after attempting suicide by partial hanging. She was found hanging from the ceiling using her saree, with only her feet touching the ground. She was unconscious and had a known history of psychiatric illness and a prior suicide attempt. She was on chronic antipsychotic therapy. On examination, she was in an altered mental state, exhibiting tachypnea and bilaterally sluggishly reactive pupils. Her vital signs were a pulse rate of 100/minute, blood pressure of 100/70 mm Hg, and normal oxygen saturation. A 6 × 2.5 cm ligature mark (Fig. 1) was noted on the left side of her neck above the thyroid cartilage. There were no signs of head trauma, bleeding, or abnormal movements.

Investigations revealed unremarkable findings on chest X-ray (PA view), cervical spine X-rays (AP and lateral), and a computed tomography (CT) scan of the head and neck. Arterial blood gas (ABG) analysis (Fig. 2) showed metabolic alkalosis, and serum electrolytes indicated hypernatremia and hypokalemia. Routine laboratory tests were within normal limits. The initial electrocardiographic (ECG) demonstrated normal sinus rhythm with a heart rate of 100/minute, QRS axis of 60°, PR interval of 140 ms, and a corrected QT interval (QTc) of 0.61 seconds. Due to concerns about airway compromise, the patient was intubated with ketamine and rocuronium and placed on synchronized intermittent mandatory ventilation (SIMV) mode in the intensive care unit (ICU).

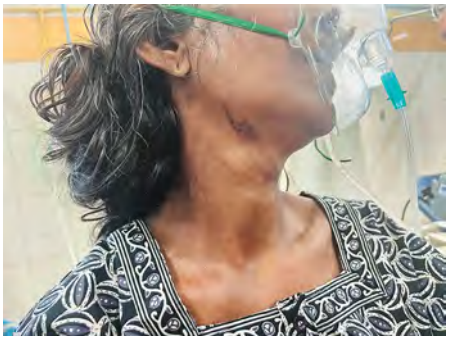
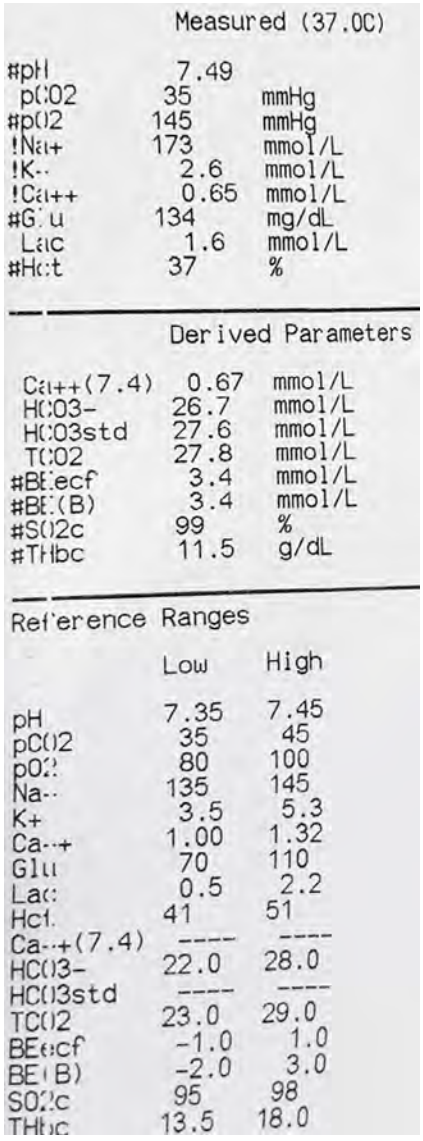


Fig. 1: Ligature mark



Measured (37.0C)

#pH	7.49	
pC02	35	mmHg
#pO2	145	mmHg
!Na+	173	mmol/L
!K+	2.6	mmol/L
!Ca++	0.65	mmol/L
#Glu	134	mg/dL
Lac	1.6	mmol/L
#Hct	37	%

Derived Parameters

Ca++(7.4)	0.67	mmol/L
HCO3-	26.7	mmol/L
HCO3std	27.6	mmol/L
TCO2	27.8	mmol/L
#BEecf	3.4	mmol/L
#BE(B)	3.4	mmol/L
#SO2c	99	%
#THbc	11.5	g/dL

Reference Ranges

	Low	High
pH	7.35	7.45
pCO2	35	45
pO2	80	100
Na+	135	145
K+	3.5	5.3
Ca++	1.00	1.32
Glu	70	110
Lac	0.5	2.2
Hct	41	51
Ca++(7.4)	----	----
HCO3-	22.0	28.0
HCO3std	----	----
TCO2	23.0	29.0
BEecf	-1.0	1.0
BE(B)	-2.0	3.0
SO2c	95	98
THbc	13.5	18.0

Fig. 2: ABG—metabolic alkalosis

Clinical Course

Following intubation, the patient's vitals stabilized, but her ECG showed persistent sinus tachycardia (Fig. 3). About 6 hours later, ECG monitoring revealed global ST-segment depression (Fig. 4). Given these findings, non-ST-elevation myocardial infarction (NSTEMI) was initially suspected, and troponin levels were ordered. However, before an echocardiogram could be performed, her ECG unexpectedly demonstrated global ST-segment elevation (Fig. 5), raising concerns for acute coronary syndrome (ACS).[3,4]

Following ACS protocols, the patient was administered aspirin, clopidogrel, and statins, and the catheterization lab was prepared. However, echocardiography subsequently revealed apical ballooning of the left ventricle (Fig. 6) with global hypokinesia, findings consistent with Takotsubo cardiomyopathy (stress-induced cardiomyopathy).[5,6] Coronary angiography confirmed normal coronary arteries, ruling out an acute myocardial infarction. She was then managed conservatively with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and supportive care. Over the next 9 days, the patient's condition improved gradually. Serial ECGs demonstrated a return

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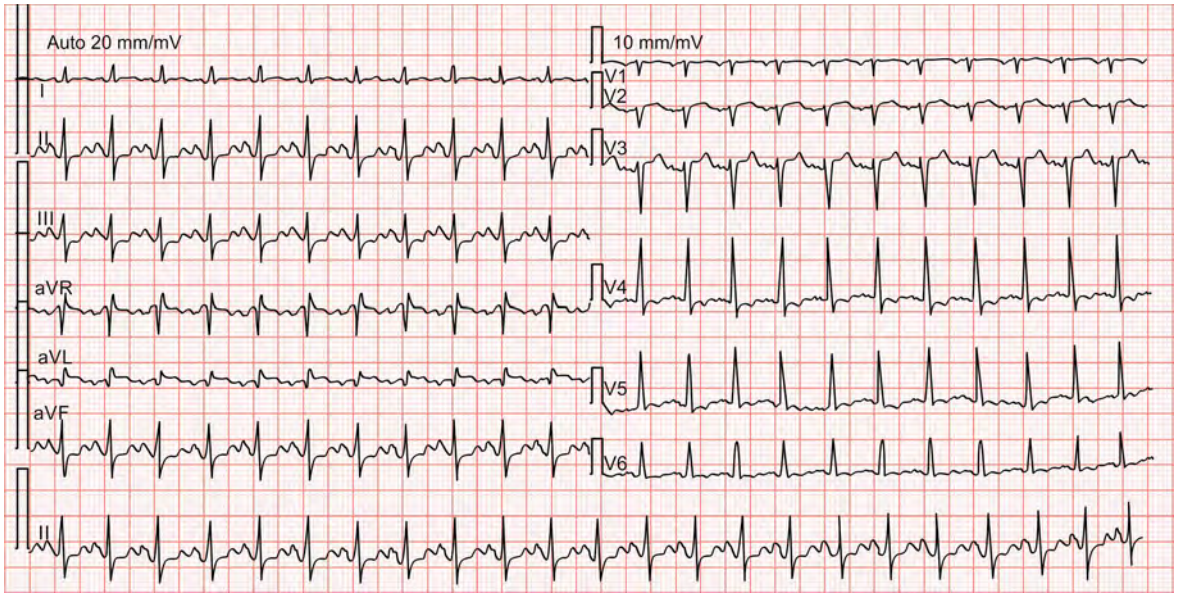

Fig. 3: Sinus tachycardia

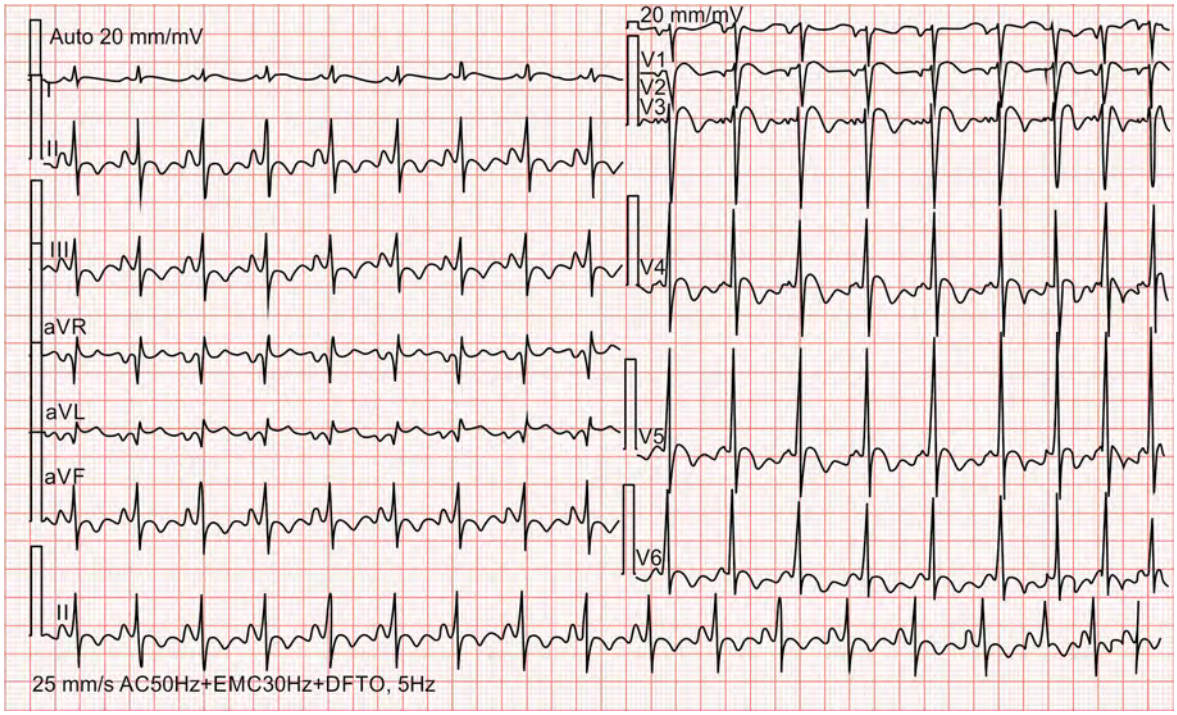

Fig. 4: ST depressions

to normal sinus rhythm without further significant abnormalities.

Discussion

Partial hanging, as in this case, can cause extreme physiological stress, leading to significant ECG changes, including ST-segment elevation, depression, and QT prolongation.[7] These findings can closely resemble those seen in ACS or cerebrovascular events. The fluctuating ECG abnormalities, often described as "dancing ECGs," are commonly associated with severe stress-related cardiac events.

In this case, initial ST-segment depression suggested NSTEMI or myocardial ischemia. However, the subsequent development of ST-segment elevation raised strong concerns for ACS. Stress-induced cardiomyopathy (Takotsubo cardiomyopathy) occurs in response to intense emotional or physical stress, leading to transient cardiac dysfunction that closely mimics myocardial infarction.[8] Key diagnostic criteria for Takotsubo cardiomyopathy include the absence of significant coronary artery disease on angiography, the presence of apical ballooning and global hypokinesia on echocardiography, and ECG abnormalities such as ST-segment changes and QT prolongation, which resolve as the patient recovers.

The pathophysiology of Takotsubo cardiomyopathy is believed to result from catecholamine-induced myocardial stunning, which temporarily impairs left ventricular function. Suicide attempts, particularly hanging, can generate profound emotional and physiological stress,

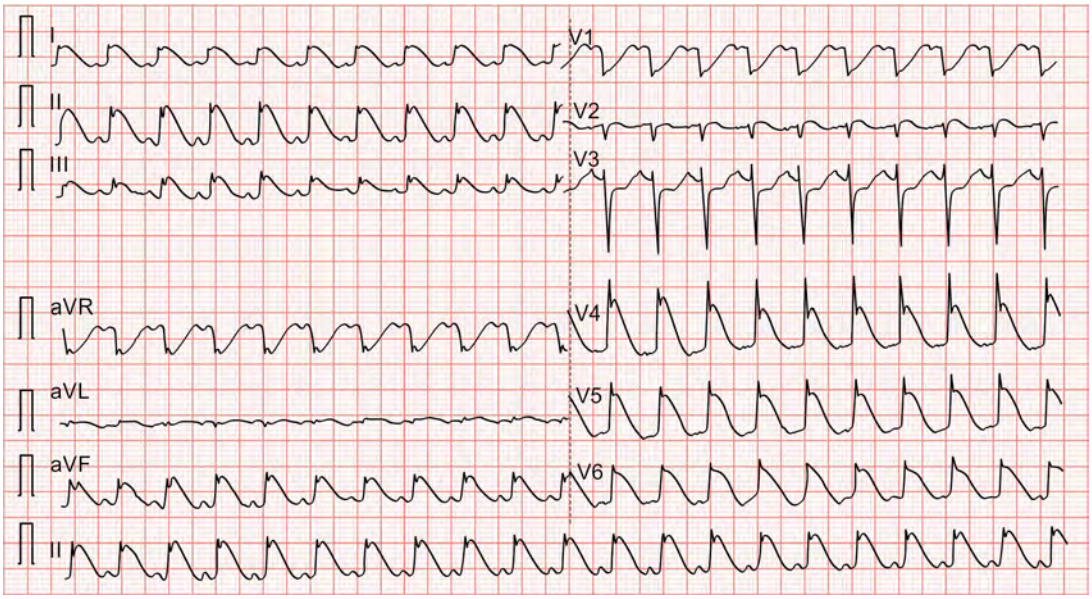

Fig. 5: Global ST elevations

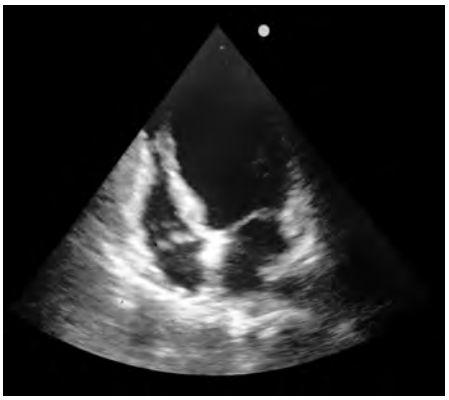

Fig. 6: ECHO suggestive of apical ballooning of left ventricle

increasing the likelihood of developing this condition.[9] Recognizing stress-induced cardiomyopathy is crucial to avoid unnecessary interventions such as invasive coronary angiography. Suicide attempts may have severe cardiovascular effects beyond the mechanical impact of strangulation. Understanding a patient's psychiatric history is essential, as those with mental health disorders are at increased risk for stress-related cardiac events.

Conclusion

In cases of partial hanging, clinicians must consider stress-induced cardiomyopathy as a potential cause of ECG changes resembling acute myocardial infarction. While initial findings in this case were concerning for ACS, the absence of coronary artery disease and characteristic echocardiographic findings ultimately confirmed Takotsubo cardiomyopathy.

Timely recognition of stress-related cardiac syndromes can help prevent unnecessary invasive procedures and ensure better patient outcomes. A comprehensive approach, including ECG monitoring, echocardiography, and coronary angiography, is essential for accurate diagnosis and optimal patient management.

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CASE REPORT

Revisiting Treatment-free Remission: A Case of Late Molecular Recurrence in Chronic Myeloid Leukemia

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Abstract

We present the case of a woman in her early 70s with chronic-phase chronic myeloid leukemia (CML-CP), initially diagnosed in 2002. After achieving deep molecular response (DMR) with imatinib for over a decade, the patient discontinued treatment, entering treatment-free remission (TFR) for around 7 years. She later presented with fever, fatigue, and abnormal blood counts. Restarting imatinib led to a near-complete molecular response, emphasizing the potential for late molecular recurrence (LMRec) in TFR, and underscoring the importance of long-term monitoring in CML patients who discontinue tyrosine kinase inhibitor (TKI) therapy.

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Background

Chronic myeloid leukemia (CML) is caused by abnormal myeloid cell growth, often involving neutrophils, basophils, and eosinophils, due to a chromosomal translocation creating the Philadelphia chromosome. This translocation produces the BCR::ABL1 fusion gene, resulting in a continuously active tyrosine kinase that drives unregulated cell proliferation in hematopoietic stem cells.[1]

The prognosis for CML patients is evaluated using three scoring systems—Sokal, EUTOS, and ELTS—which draw from basic clinical and hematologic parameters. CML treatment relies on tyrosine kinase inhibitors (TKIs), with imatinib (first-generation) and other options like dasatinib and nilotinib (second-generation) forming the main therapeutic approach.[1]

Monitoring BCR::ABL1 levels at specific intervals is essential, particularly within the first 12 months, to determine treatment effectiveness and guide subsequent decisions. In cases of stable DMR, some patients may discontinue TKI treatment and enter treatment-free remission (TFR), maintaining low or undetectable BCR::ABL1 levels without therapy. Nevertheless, even patients in long-term TFR require sustained follow-up, as late molecular recurrence (LMRec), while rare, is increasingly documented.[2]

Case Description

We present the case of a female patient in her 70s who was admitted to our medical facility with complaints of fever and persistent fatigue for a period of 5 months. The patient had previously been diagnosed with chronic myeloid leukemia in the chronic phase (CML-CP) 22 years ago, in 2002. Initially, she underwent treatment with hydroxyurea for 8 months before being transitioned to the newly FDA-approved imatinib when it became available at her center.

The patient exhibited an excellent response to imatinib. Within just 3 months of therapy initiation, her BCR::ABL1 count was reported to be less than 0.1%. Subsequent follow-up assessments at 6 months indicated a further decrease in BCR::ABL1 count to undetectable levels. This undetectable status persisted through regular follow-up appointments every 6 months for 2 years, followed by annual visits for the next decade.

She continued on imatinib until 2016. After thorough evaluation and consistent undetectable BCR::ABL1 counts, her physician decided to discontinue therapy, supported by the emergence of the concept of TFR for CML patients at that time.

Following therapy completion, the patient underwent regular follow-up as per established guidelines. This included monthly monitoring for the initial 6 months, followed by bimonthly monitoring for the next 6 months. Thereafter, the monitoring schedule transitioned to quarterly visits for a total of 7 years. Throughout this period, the patient remained free of symptoms, indicating a potentially deep molecular response. After that, the patient was lost to follow-up due to personal reasons but presented 2 months ago with new symptoms, raising concerns about a potential loss of complete hematologic response, prompting further investigations.

Laboratory assessments, including complete blood count and peripheral blood analysis, were conducted, the results of which are presented in Table 1.

Investigations

Differential Diagnosis

Given the patient's past diagnosis of chronic myeloid leukemia in the chronic phase (CML-CP), along with recent symptoms consistent with CML and supportive findings in the complete blood count and peripheral blood analysis, a relapse of chronic myeloid leukemia was the most likely diagnosis.

Treatment and Outcome

The patient restarted imatinib at 400 mg daily, showing a positive response and near-complete molecular remission within 6 months.

Table 1: Blood investigations

Parameters	*Values*	*Reference values*
Hemoglobin	11.3 gm/dL	12.0–16.0 gm/dL
RBC	3.98 million/mm^3	3.5–5.5 million/mm^3
Platelets	109.6×10^9/L	$150–400 \times 10^9$/L
WBC	171×10^3/mm^3	$4.5–11 \times 10^3$/mm^3
Neutrophils	60%	55–70%
Lymphocytes	3%	20–40%
Eosinophils	4%	1–4%
Monocytes	3%	2–8%
Basophils	7%	0.5–1%
Blasts	4%	<0.5%
Metamyelocytes	19%	<1%
BCR::ABL1 transcripts	48.164% IS	

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Discussion

Recent advances in chronic myeloid leukemia (CML) therapy, especially through the use of tyrosine kinase inhibitors (TKIs), have markedly improved patient outcomes, often aligning life expectancy with that of the general population. The primary treatment goals now extend beyond survival to achieving a stable deep molecular response (DMR), with some patients able to discontinue TKIs to reach treatment-free remission (TFR), with increasing focus on quality of life and minimizing chronic toxicity associated with lifelong TKI use.[1,3] As a result, strategies are being developed to enable more patients to discontinue TKI therapy safely. However, only a small proportion of those treated with TKIs reach sustained DMR, necessary for TFR consideration. In these patients, molecular recurrence-free survival rates are around 43% at 6 months and 38% at 5 years.[4]

Studies have explored TFR, generally applying similar criteria to stop TKIs: patients who maintained DMR for over 2 years on TKIs (such as imatinib) for at least 3 years may attempt stopping therapy. A relapse, commonly defined by loss of major molecular response (MMR), necessitates TKI resumption.[5] Current guidelines, such as from the European Society for Medical Oncology (ESMO), suggest monthly qPCR monitoring for the first 6 months after TKI cessation, with the frequency decreasing over time as molecular stability is confirmed.[6]

Molecular recurrence patterns exhibit a two-phase curve: most relapses occur within the initial 12–18 months, while instances of late molecular recurrence (LMRec) are rare but possible beyond 2 years posttherapy. In such cases, fluctuating molecular response (FlucMR) has been identified as a factor; patients with recurrent readings above MR4 (>0.0032%) or undetectable levels have shown varied long-term remission outcomes.[7] One possible explanation for such recurrences, including associated rises in WBC count, is the persistence of a small population of quiescent leukemic stem cells that are resistant to TKI therapy. Over time, they may slowly resume activity, contributing to low-level molecular signals and, in some cases, subtle clinical changes.[8]

Extended follow-up in cases like this is relatively rare, given the scarcity of long-term patient monitoring and consensus on recurrence criteria. This particular case exemplifies LMRec after sustained DMR, highlighting the importance of prolonged follow-up to detect late relapses in TFR patients. Despite the recurrence, the patient's prognosis remained stable, underlining that late molecular recurrence does not necessarily indicate a progression in disease severity.

Learning Points/Take Home Messages

- This case exemplifies LMRec after prolonged TFR, underscoring the need for sustained posttreatment monitoring in CML.
- Extended follow-up may be critical to managing patients who achieve TFR, even after several years of DMR stability.

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CASE REPORT

A Case Report of Unilateral Pleural Effusion in a Middle-aged Woman: A Rare Coexistence

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Abstract

A 39-year-old woman with a 1-year history of seronegative arthritis was admitted for shortness of breath, left-sided chest pain, and joint pains. Upon physical examination, the tips of her right leg's fifth toe showed dry gangrene. Laboratory results revealed proteinuria and positivity for antinuclear antibody, ribonucleoprotein/Smith (RNP/Sm) antibody, Smith, and anti–double-strand deoxyribonucleic acid (DNA) antibody. The chest radiograph showed cardiomegaly, and computed tomography (CT) of the chest revealed pleural effusion. Initial pleural investigations revealed exudative pleurisy, low adenosine deaminase (ADA), and pleural effusion with cytology positive for lupus erythematosus (LE) cells. Rigid thoracoscopy revealed necrotic parietal pleura. Acid-fast bacillus (AFB) yielded positive results with Ziehl–Neelsen stains. Based on the above clinical, cytohistological, and serological findings, a coexistence of lupus pleuritis with tuberculous serositis (TS) was diagnosed in the background of systemic lupus erythematosus (SLE) with renal crisis. After 2 months of antitubercular therapy (ATT) with maintenance dose of steroids, following symptomatic improvement, pulse steroids and cyclophosphamide were initiated for SLE with renal crisis, and ATT was continued for 6 months. Postcompletion of ATT, the patient had complete resolution and was in remission of SLE.

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Introduction

Systemic lupus erythematosus (SLE) is an unknown autoimmune disease that can affect any organ. The reported prevalence of SLE in India ranges from 14 to 60 per 1,00,000.[1] In more than half of patients, lupus manifests as musculoskeletal, cutaneous, and hematological involvement. Nephritis and neuropsychiatric lupus are two other important organ involvements. Digital gangrene is rare and seen in patients with long-term disease with Raynaud's phenomenon.[2] The prevalence of tuberculosis (TB) in SLE has been reported to range from 5 to 15% in several studies, while the data from India is limited.[3] Fever, constitutional symptoms, lymphadenopathy, pleural and pericardial effusion, and other TB clinical manifestations can mimic lupus and pose a diagnostic challenge, particularly in the setting of active lupus. Although the lupus erythematosus (LE) cells test has been declared obsolete, its presence is still significant and provides an important clue to the diagnosis of SLE.[4] Here we report a case of seronegative arthritis diagnosed as SLE, tuberculous serositis (TS), with gangrene of the fifth toe.

Case Description

A 39-year-old female with seronegative arthritis for 1 year presented with shortness of breath, left-sided chest pain, joint pains, and discoloration of the right fifth toe for 1 month. A general physical examination revealed afebrile, pulse 120 beats/minute, blood pressure 138/90 mm Hg, and respiratory rate 28 breaths/minute. She had localized dry gangrene in the tip of her right fifth toe. Physical examination of the chest demonstrated dullness on percussion and decreased breath sounds in the left middle and lower lung fields. Baseline blood investigations produced unremarkable results. Urine examination showed few red blood cells (RBCs) and proteinuria (3+, >500 mg/dL). The C-reactive protein was <5 mg/L, and anti-cyclic citrullinated peptide (anti-CCP antibody) level was normal (0.90 U/mL). The computed tomography (CT) of the chest revealed mild to moderate pleural effusion on the left, underlying collapse consolidation, and an enlarged subcarinal lymph node (Fig. 1). The chest radiograph showed cardiomegaly and left-side costophrenic angle blunting (Fig. 1). The arterial color Doppler of the right lower limb was normal. Thus, the differential diagnoses considered clinically and radiologically for this patient were lupus pleuritis, TB, malignancy, parapneumonic effusion, and pulmonary embolism.

Ultrasound-guided thoracentesis was done, and 700 mL of hemorrhagic fluid was aspirated (Fig. 2). Evaluation by rigid thoracoscopy revealed nodule-studded pleura. The pleural fluid total count showed 200 cells/mm^3 with many RBCs. The biochemical adenosine deaminase (ADA) level was 26.80 U/L. The pleural effusion cytology revealed neutrophils, lymphocytes, and few homogeneous, round, pink eosinophilic material (LE body) engulfed by neutrophils (LE cells) (Fig. 2), with a microscopy of LE (Fig. 2). A pleural-based nodule biopsy demonstrated numerous epithelioid granulomas with Langhans-type large cells and localized necrosis during histological analysis (Figs 3A and B). The results of the Ziehl–Neelsen stains for acid-fast bacillus (AFB) were positive (Fig. 4). The presence of LE cells alerts lab physicians to the possibility of SLE. Serological antinuclear antibody (ANA) with indirect immunofluorescent assay yielded positive results with 3+ intensity (1:160), nuclear homogeneous pattern, and ribonucleoprotein/Smith (RNP/Sm),

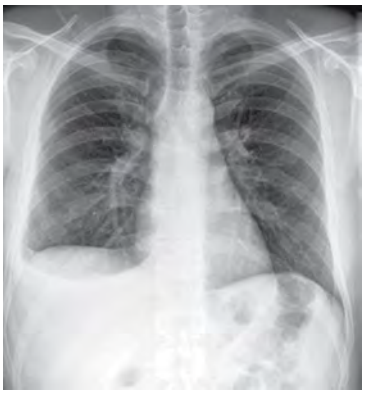

Fig. 1: Chest X-ray showing costophrenic angle blunting

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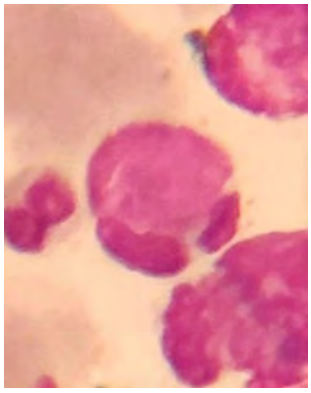


Fig. 2: Microscopic examination of LE cell

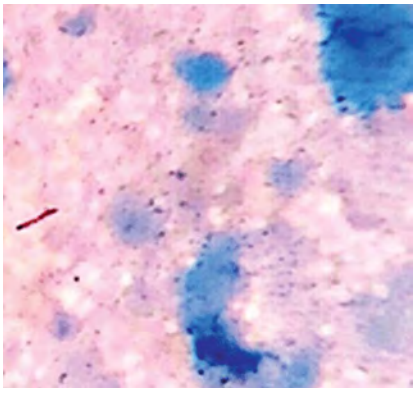
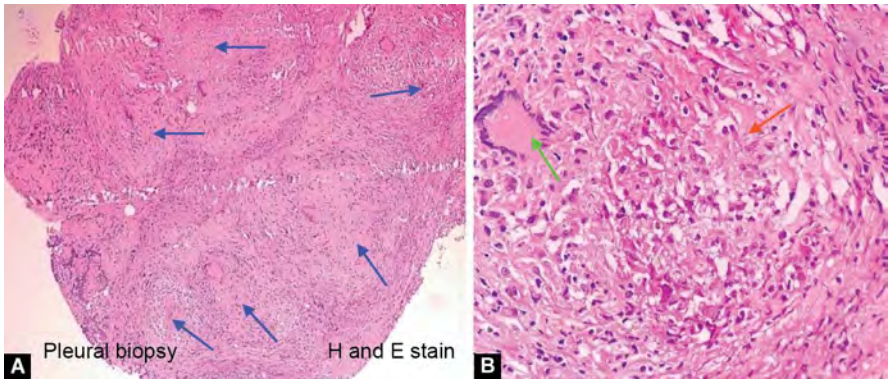


Fig. 4: AFB smear of pleural fluid stained with Ziehl–Neelsen



Figs 3A and B: Pleural based nodule biopsy: (A) Showing many granulomas (blue arrow) and; (B) Langhans giant cell (green arrow) and focal necrosis (orange arrow)

Smith, and double-strand deoxyribonucleic acid (dsDNA) antibody profile. Tests for antiphospholipid antibodies (anticardiolipin, lupus anticoagulant, and beta-2 glycoprotein) were negative.

Based on clinical, cytohistological, and serological findings, she was diagnosed with SLE with TS and was initiated on antitubercular therapy (ATT) (HRZE), steroids, and supportive therapy. On completion of 2 months of the intensive phase of ATT, monthly IV cyclophosphamide for gangrene and lupus activity was initiated. After 6 months of ATT, there was resolution of the pleural effusion. She is currently on azathioprine maintenance and is symptomatically doing well.

Discussion

Clinical Discussion

Systemic lupus erythematosus is a chronic multisystemic autoimmune disease that primarily affects young females, with clinical manifestations varying from mild to life-threatening illness. The most common cause of pleural effusion in lupus is the disease itself, followed by parapneumonic effusions, pulmonary embolism, nephrotic syndrome, heart failure, and malignancy. They are usually bilateral and mild to moderate, rarely with a large effusion.[5] In the index case, the patient complained of breathing difficulties and chest pain; thus, congestive heart failure, pulmonary embolism, parapneumonic effusion, TB, and collagen vascular disorders are all possible differential diagnoses. Infection risk is increased in lupus patients due to a dysregulated immune system and the use of immunosuppressive drugs. The prevalence of TB in lupus patients ranges from 0.7 to 13%. TB is more common in lupus patients, especially those who had nephritis, arthritis, or were on high doses of steroids.[6] Our patient has been on low-dose steroids for arthritis for a year, and urine tests are positive for proteinuria. Digital gangrene is seen in our patient at a late stage of the disease and is suggested to be the result of poor perfusion caused by vasculitis, vasospasm, thromboembolism, or atherosclerosis.

Radiologic Discussion

Respiratory disease affects approximately 60–80% of patients with rheumatoid arthritis (RA) and can involve the airways, lung parenchyma, and pleura.[7] Pleural disease is usually subclinical; pleural effusions and pleurisy are the most common pleural manifestations. In the acute presentation, effusions are unilateral and small in volume, associated with pleural enhancement on contrast imaging. Chronic pleural inflammation causes thickening of parietal and visceral pleura, leading to loculation, which appears like empyema. Pleural thickening and fibrosis have a nodular appearance, imitating malignancy, and thus necessitating a biopsy for diagnosis. When untreated or recurrent, severe pleuritis can result in fibrothorax, leading to restrictive pulmonary physiology.[8]

Pathologic Discussion

The presence of LE cells in the pleural fluid is highly specific for SLE. The pathogenesis of LE cell formation *in vivo* begins with the interaction of serum gamma globulin with the nucleus in the presence of complement, causing loss of molecular structure in the nucleus and swelling of the nucleus, resulting in the formation of denatured homogeneous structures (LE bodies), which are then engulfed by polymorphonuclear cells (rarely monocytes) and give rise to LE cells.[9] Incubation of pleural fluid for several hours at room temperature can enhance the LE cell phenomenon. LE cells are also found in bone marrow aspirate, synovial fluid, cerebrospinal fluid, and pericardial fluid in patients with SLE. The presence of LE cells in any of these samples, together with the appropriate clinical and laboratory findings, would aid in the diagnosis of SLE.[10] In our case, a simple cytological preparation revealed a high number of LE cells in pleural effusion, resulting in the diagnosis of SLE, which was confirmed by serum ANA tests and specific antibody testing.

Here, in lupus pleuritis, pleural fluid is frequently exudative, has normal glucose and pH levels, and elevated LDH (though not specifically) with *Mycobacterium tuberculosis*. In our case, a high pleural ANA titer (>1:160) may help distinguish lupus pleuritis from other types of pleuritis. Low pleural-to-serum anti-dsDNA and C3 ratios were also more favorable to lupus pleuritis than other causes, suggesting that complement-mediated immune complex formation from antibodies dispersed into the pleura from serum is the pathophysiology implicated in lupus serositis. The detection of *M. tuberculosis* in pleural fluid or pleural biopsy specimens, either by microscopy and/or culture, or the histological demonstration of caseating granulomas in the pleura along with positive AFB, remains the gold standard for tuberculous pleuritis diagnosis. The Ziehl–Neelsen stains for AFB yielded positive results in this instance. Numerous cases of active TB in individuals

with autoimmune illnesses receiving severe immunosuppressive medication have increased the risk of TB in these patients.[11] In individuals with SLE, the combination of infection and autoimmunity increases the risk of TB, which is reliant on the disease entity's local incidence and prevalence.[12] Patients with SLE who have TB are treated similarly to those who have the disease. The course of treatment typically consists of a 2-month combination of isoniazid, rifampin, ethambutol, and pyrazinamide, followed by at least 4 months of isoniazid and rifampin. TB should always be tested for before beginning immunosuppressive medication, and patients should undergo physical examination, risk assessment, and chest radiograph.[13]

Conclusion

Pleuropulmonary involvement is common in both SLE and TB. Cytological examinations of pleural fluid revealing the presence of LE cells provide important clues to the diagnosis of SLE. Thoracoscopic pleural biopsy plays a crucial role for suspicious pleural-based nodules, especially in hemorrhagic pleural effusion. The prognosis for lupus serositis is generally good. Serositis usually responds to low- to medium-dose oral steroids. Intravenous methylprednisolone pulses, intravenous immunoglobulin, and cyclophosphamide may be required for refractory cases. Digital gangrene in lupus is treated with steroids and cyclophosphamide in cases of vasculitis, and lipid-lowering drugs and anticoagulants for atherosclerosis and thrombotic occlusion, respectively.

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CASE REPORT

Beta Thalassemia Manifesting as a Leukemoid Reaction: A Rare Case Report

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Abstract

The occurrence of marked leukocytosis in hemoglobinopathies is generally uncommon. Herein, we describe a 41-year-old male patient with a history of chronic alcoholism who presented for the first time with shortness of breath and abdominal distension. On complete blood counts and peripheral smear examination, there was a microangiopathic hemolytic anemia with leukemoid reaction, which turned out to be beta thalassemia trait on hemoglobin high-performance liquid chromatography. He was ultimately diagnosed with beta thalassemia trait in conjunction with chronic alcoholic liver disease and spontaneous bacterial peritonitis. The presence of leukocytosis accompanied by cytopenias in other hematopoietic cell lines and organomegaly presents a considerable diagnostic challenge. Increased leukocyte counts do not invariably indicate leukemia. A comprehensive analysis of the hemogram, which includes an examination of each cell line, relevant indices, and a thorough peripheral smear evaluation in relation to the clinical presentation, is essential for determining suitable investigations and management strategies.

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Introduction

Leukocytosis presents a broad spectrum of differential diagnoses, with infections being the most prevalent etiology.[1] Hemoglobinopathies are linked to an increased presence of nucleated red blood cells (nRBC) in peripheral blood, which can result in artificially elevated leukocyte counts, creating a clinical challenge. The presence of nRBC is particularly notable in cases of beta thalassemia major (BTM), especially in infants; however, a white blood cell (WBC) count exceeding 50,000/cumm is rare. Significant leukocytosis is an unusual presentation in cases of hemoglobinopathies.[2] We present a case of an adult patient who, upon first presentation with a leukemoid reaction, was diagnosed with beta thalassemia trait (BTT) alongside chronic alcoholic liver disease and spontaneous bacterial peritonitis.

Case Description

A 41-year-old male patient with a history of chronic alcoholism presented with shortness of breath and abdominal distension. There was generalized weakness and decreased appetite. On examination, there was pallor, icterus, ascites, and hepatomegaly. Clinically, the provisional diagnosis was alcoholic liver disease.

Liver function tests showed decreased serum albumin of 1.8 gm/dL with a normal reference range (NRR) of 3.5–5.2 gm/dL. There was also a decrease in serum levels of albumin-globulin ratio (0.5 gm/dL, NRR is 0.8–2 gm/dL), total protein (5.3 gm/dL, NRR is 6–8 gm/dL), sodium (121 mEq/L, NRR is 135–145 mEq/L), and potassium (3.4 mEq/L, NRR is 3.5–5.0 mEq/L). Total bilirubin was elevated to 16.5 mg/dL (NRR is 0.2–1 mg/dL) with predominantly direct bilirubin of 15.1 mg/dL (NRR is ≤0.2 mg/dL) and indirect bilirubin of 1.4 mg/dL (NRR is 0.2–0.8 mg/dL). Serum alkaline phosphatase was elevated to 315 U/L (NRR is 38–126 U/L) with normal serum levels of aspartate aminotransferase and alanine transaminase.[3,4]

Complete blood count was performed using the electronic automated six-part hematology analyzer, Sysmex XN 1000. Hemoglobin (Hb) was 8.8 gm/dL, red blood cell (RBC) count 4.03 million/µL, total white blood cell (WBC) count 113,480/cumm, and platelet count 455,000/cumm (Fig. 1). RBC indices were reduced. In the WBC scattergram, white blood cell differential (WDF): side scattered light (SSC)–side fluorescent light (SFL) plot, a significant cluster was observed above the neutrophil zone within the area of immature granulocytes. Conversely, no notable cluster was detected in the basophil region (Fig. 2).

On peripheral smear (PS) examination, the RBCs were microcytic hypochromic, with anisopoikilocytosis +++, target cells +++, schistocytes 6%, macrocytes, polychromatophils, and occasional nRBC. There was marked neutrophilic leukocytosis with shift to left: 6% myelocytes and metamyelocytes, 77% neutrophils and band cells, 11% eosinophils, 1% monocytes, 3% lymphocytes, and 2% basophils. Dysplasia or blasts were absent on smear. The neutrophilic series showed cytoplasmic vacuolations and toxic granulations. Platelet count was mildly increased on smear. Findings were suggestive of microangiopathic hemolytic anemia (MAHA) with leukemoid reaction (Fig. 3). Prothrombin time (PT) was increased to 19.3 seconds (mean normal PT was 11.5 seconds) and activated partial thromboplastin time (APTT) was also elevated to 31 seconds (control APTT was 26.4 seconds).

Bone marrow examination and reverse transcriptase-polymerase chain reaction (RT-PCR) for BCR-ABL was advised to rule out chronic myeloid leukemia (CML). Neutrophil alkaline phosphatase (NAP) score was 110, indicating leukemoid reaction. In view of the presence of reduced RBC indices, target cells +++, and hemolytic anemia, hemoglobinopathies/thalassemia needed to be ruled out. Hence, for further analysis, Hb high-performance liquid chromatography (HPLC) was performed utilizing the ARKRAY ADAMS HA-8180T HPLC automated analyzer. The HA-8180T conducts an analysis of HbA1c, HbA2, and HbF concentrations in blood utilizing reversed-phase cation exchange chromatography.[5] HbA2 was 4.5%, HbF was 0.8%, and HbA 87.9% (Fig. 4). Elevation of HbA2 (NRR is 2.2–3.5%) was diagnostic of beta thalassemia trait[6].

Injection albumin was transfused intravenously, following which ascitic tapping was done and showed 700 cells/cumm, comprising 60% polymorphs and 40% lymphocytes. Hence, the patient was diagnosed to be a case of beta thalassemia trait with chronic alcoholic liver disease manifesting as spontaneous bacterial peritonitis leading to disseminated intravascular coagulation and leukemoid reaction.

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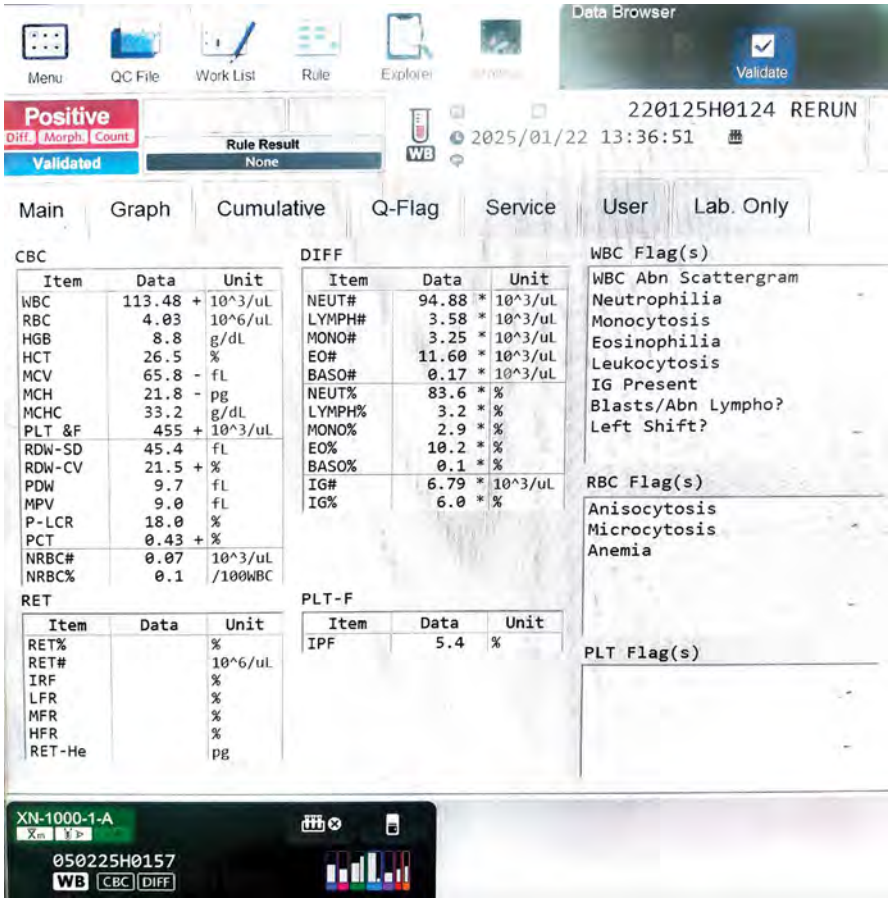
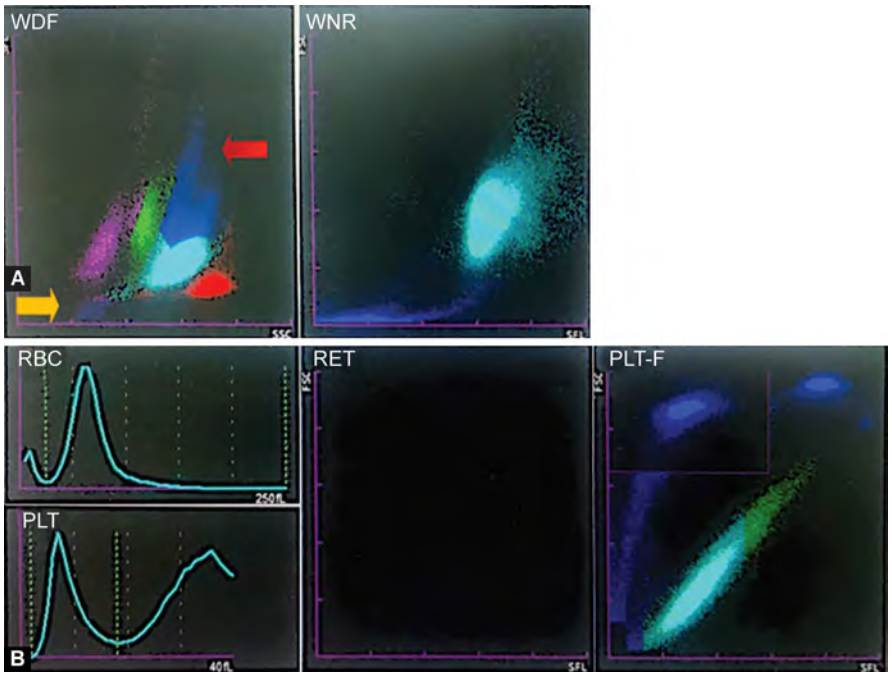


Fig. 1: Complete blood count findings showing microcytic hypochromic anemia, marked leukocytosis, and mild thrombocytosis

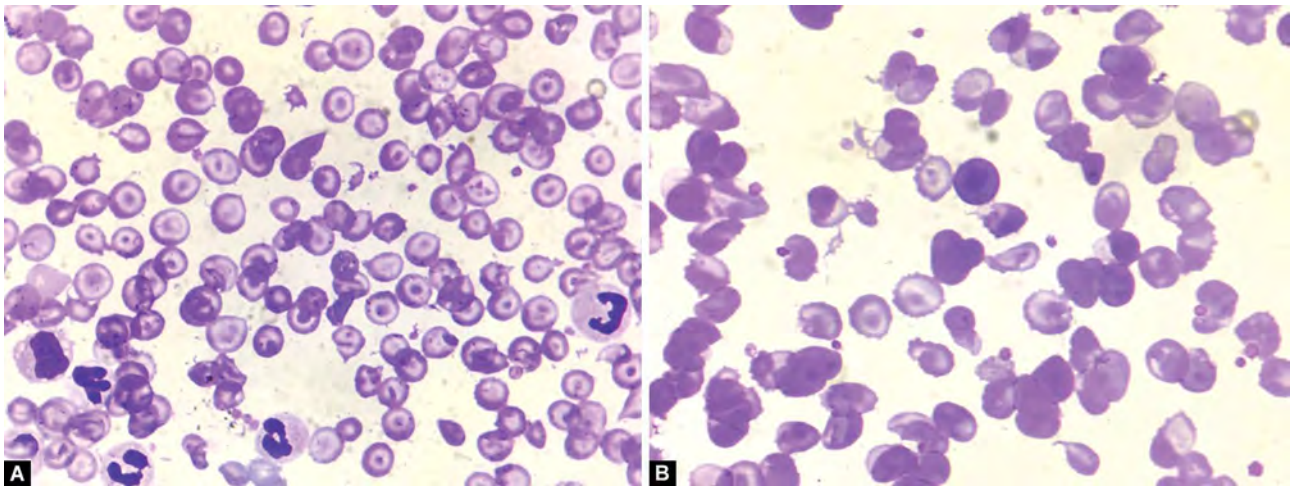


Figs 2A and B: Scattergram showing (A) WDF (SSC-SFL) plot with a prominent cluster above the neutrophil area in the region of immature granulocytes and (B) WNR (SFL-FSC) with no prominent cluster in the basophil region; FSC, forward scattered light; SFL, side fluorescent light; SSC, side scattered light; WDF, white blood cell differential; WNR, white cell nucleated

The patient was started on intravenous antibiotics including injection cefotaxime, oral rifaximin, and norfloxacin. Injection thiamine along with oral folic acid and lactulose was also started. On follow-up CBC after 1 week, the total count reduced to 50,000/cumm and the patient improved clinically as well. Due to complete recovery of the patient and normalization of total leukocyte count within 15 days, the RT-PCR for BCR-ABL was not done.

Discussion

Leukocytosis is characterized by a WBC count exceeding 11,000 cells/cumm in adults and 20,000/cumm in children.[1,6] Neutrophilia can develop due to infections, stress-related factors, and inflammation, in contrast to lymphocytosis, which is commonly seen in cases of pertussis, syphilis, viral infections, and also in leukemia or lymphoma.[1,7] The term leukemoid reaction describes a condition where there is a substantial rise in the leukocyte count, exceeding 50,000/cumm, along with the presence of immature WBC in the peripheral blood. This condition mimics leukemia but arises in nonleukemic contexts,



Figs 3A and B: Peripheral blood smear showing microcytic hypochromic RBCs with anisopoikilocytosis +++, target cells +++, schistocytes, neutrophilic leukocytosis, and occasional late normoblast (Leishman stain, 1000× magnification)

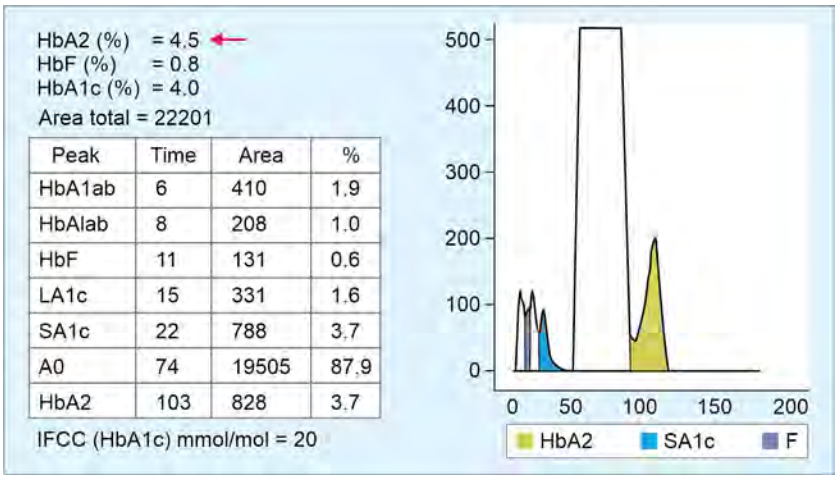


Fig. 4: HPLC chromatogram showing an elevated peak of 4.5% in the A2 window suggestive of beta thalassemia trait

Table 1: Differences between leukemoid reaction and chronic myeloid leukaemia (CML)

	Leukemoid reaction	*CML*
Massive splenomegaly	Usually absent	Present
Leukocyte count	Usually <50,000/cumm	Usually >100,000/cumm
Myelocyte bulge	Absent	Present
Basophilia, eosinophilia	Usually absent	Present
Toxic granules	Present	Absent
Neutrophil alkaline phosphatase score	Normal or increased	Low
Genetic study	Normal	t(9,22); BCR-ABL gene rearrangement

frequently as a result of severe infections, acute hemolysis, hemorrhagic events, burns, inflammatory diseases, cancers that have metastasized to the bone marrow, eclampsia, and mercury toxicity. A notable feature of this reaction is the predominance of neutrophils and a leftward shift in the WBC differential, which distinguishes it from leukemia.[2,8]

There are two types of leukemoid reactions: myeloid and lymphoid. The myeloid type exhibits a blood profile that may resemble either acute or chronic myeloid leukemia. A notable neutrophilic leukocytosis, along with the presence of immature white blood cells at various stages, from myeloblasts to segmented neutrophils, can imitate CML. Table 1 depicts the distinguishing features that set leukemoid reaction apart from CML.[8] The NAP score is a simple and effective tool for ruling out CML. A normal range for the NAP score is between 40 and 100. During the chronic myeloid leukemia–chronic phase (CML-CP), mature neutrophils exhibit a notable decrease or total absence of NAP. In contrast, a normal or increased NAP score is often observed in leukemoid reactions associated with infections, polycythemia vera, and agnogenic myeloid metaplasia with myelofibrosis.[9]

Hematology analyzers generate scattergrams that depict the characteristics of cells, focusing on the presence of a nucleus, size, and granularity. Nonnucleated cells, which comprise RBCs and platelets, are distinguished by their size, with RBCs ranging from 70 to 80 fL and platelets from 7 to 9 fL. Conversely, nucleated WBCs are classified into various types based on their size and granularity.[2] The Sysmex XN automated hematology analyzer utilizes fluorescence flow cytometry for the assessment of leukocyte differentials, nRBCs, reticulocytes, and fluorescence platelet counts. The WDF count is performed *via* flow cytometry, which analyzes specific characteristics of the cells, including their size, internal complexity, and nucleic acid content. The WDF channel successfully differentiates all WBC populations, with the exception of basophils, while the white cell nucleated (WNR) channel serves to distinguish nucleated red blood cells and basophils from other nucleated cell types.[10,11] The WDF (SSC-SFL) plot in a leukemoid reaction is comparable to that of CML-CP, with a marked absence of considerable events in both the basophil and blast regions.[11] The presence of nRBCs, platelet aggregates, cryoglobulins, or lipids can be mistakenly identified as WBC by analyzers, resulting in an inaccurate diagnosis of leucocytosis.[12]

A thorough and detailed examination of PS, along with the correlation of abnormalities observed in each cell line, enables us to distinguish between leukemia, leukemoid

reactions, and spurious leucocytosis.[2] It is imperative to perform a hemolytic workup prior to RBC transfusions, which frequently delay the diagnosis by 8–12 weeks or may lead to the need for expensive genetic testing to establish the diagnosis. In our patient, the lack of blasts in the context of elevated WBC counts, a near-normal platelet count, and a low MCV suggested the possibility of hemolytic anemia even before the examination of the PS.

The prevalence of BTT in India is approximately 2.78%, with specific state variations observed between 1.48 and 3.64%.[13] Evaluating HbA2 concentrations is vital in screening programs aimed at identifying BTT. A result above 4% implies that the individual is probably a carrier of β-thalassemia.[14] In BTT, there is consistent elevation of HbA2 levels, which typically range from 3.5 to 9%. Additionally, in approximately 50% of these cases, HbF levels are also elevated, generally falling between 1 and 3%.[15]

Spurious leukocytosis in individuals with thalassemia may be induced by hypoxia resulting from severe anemia. This situation leads to compensatory erythropoiesis occurring in the bone marrow, alongside extramedullary erythropoiesis in the spleen and liver, which subsequently releases immature red blood cells into the peripheral blood. Hyperuricemia, frequently associated with leukemia, can also manifest in hemolytic anemia. This condition arises from elevated cell turnover and diminished renal function, which is a consequence of free Hb resulting from intravascular hemolysis. Additionally, proximal tubular dysfunction may occur due to oxidative stress, hemodynamic changes, and an inflammatory response triggered by the release of immune complexes.[2]

There exist a few case reports highlighting the development of hematological malignancies, including leukemia and lymphoma, in patients with thalassemia. This situation may represent a random occurrence or may arise from a complex interaction of genetic and environmental factors.[16] Nonetheless, the specific relationship between malignancies and thalassemia syndromes remains to be determined.

Conclusion

Leukocytosis, when associated with cytopenias in other hematopoietic cell lines and organomegaly, creates a notable diagnostic difficulty. Elevated leukocyte levels are not always indicative of leukemia. It is crucial to conduct a systematic examination of the hemogram, encompassing each cell line, indices, and a meticulous PS examination, all within the context of the clinical presentation, to effectively plan further investigations and management.

Author Contributions

Garima Anandani conceptualized the study, collected the case data, conducted the literature review, and drafted the manuscript. Vaishali Bhankhodia and Komal Kumar Jangir helped in reviewing and editing the manuscript. All authors contributed to the article and approved the submitted version. The manuscript has been read and approved by all the authors, and each author believes that the manuscript represents honest work.

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Ethical Statement

Approval of the research protocol: Approved by the institutional ethics committee of AIIMS Rajkot. Approval number: AIIMS.Rajkot/IEC/47/2023. The authors confirm that they have adhered to the ethical policies of the journal. No identification details of the patients are shared.

Consent

Written informed consent was taken from the patient.

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CASE REPORT

Beyond the Norm: Recognizing Uncommon Presentations of Large Vessel Vasculitis

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Abstract

Large vessel vasculitis (LVV) is known to affect the aorta and its branches. Takayasu arteritis (TAK) is a well-recognized LVV. TAK typically manifests with limb claudication, syncope, angina, absent pulses and unequal blood pressure. These symptoms stem from fibrotic and irreversible processes like stenosis and contribute to morbidity and mortality. Early atypical presentations may lead to delayed diagnosis. This underscores the importance of early diagnosis to arrest inflammation and prevent permanent damage. We present three cases where LVV was identified in patients with unusual symptoms, emphasizing the necessity for a high index of suspicion among healthcare providers. This is especially crucial in the primary care setting where patients first encounter general practitioners.

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Introduction

Large vessel vasculitis (LVV) primarily affects the aorta and its major branches. Typical symptoms include limb claudication, syncope, constitutional features, and angina. Diagnosis usually relies on the detection of asymmetrical or absent pulses and blood pressure discrepancies in both limbs. However, when patients present with atypical symptoms in a busy clinic, the diagnosis may be overlooked. Moreover, these findings may be absent in isolated abdominal involvement and in the systemic phase, as pulses may be intact. Early detection in the systemic phase is crucial to prevent irreversible damage. Maintaining a high suspicion for Takayasu arteritis (TAK) and LVV with an unusual presentation is essential.

Case 1

A 33-year-old female presented with 2 months of burning pain in the left fingertips, without Raynaud phenomenon or sensory loss. All pulses were well felt. C-reactive protein (CRP) was elevated (7.7 mg/dL) (Table 1). Suspecting digital ischemia, she was evaluated for thoracic outlet syndrome (TOS). A dynamic Doppler suggested left subclavian artery impingement during 180-degree abduction, but MRI revealed 90% focal stenosis with irregular wall thickening in the proximal left subclavian artery (Figs 1A and B), without evidence of TOS. An MR aortogram showed no additional aortic involvement. At 2-month follow-up, her left radial and brachial pulses were feeble, with a faint left subclavian bruit. The occlusion progressed rapidly, as evidenced by the pulse loss within 2 months. Her antinuclear antibody (ANA) was weakly positive, but ANA blot was negative. She was diagnosed with LVV and started on prednisolone 0.5 mg/kg and methotrexate 15 mg every week. At 1-month follow-up, her symptoms had resolved. Presently she is being treated as LVV.

Case 2

A 30-year-old female with hypothyroidism and Hodgkin's lymphoma in remission (since 2015) presented with a 2-year history of sharp, shooting pain over the right mandible and cheek. She underwent multiple dental treatments, received carbamazepine for suspected trigeminal neuralgia, and analgesics, but without relief. Due to persistent pain extending to the neck, a neck ultrasound was done which revealed thickening of the right common carotid artery (CCA). A Doppler showed diffuse thickening of the right CCA from its origin to bifurcation, including the brachiocephalic trunk at the right CCA origin.

MR angiography and CT angiography confirmed diffuse thickening of the right CCA, attenuation of the right intracranial and cervical internal carotid artery (ICA), mild attenuation of the right cervical vertebral artery, and thickening at the origin of the left subclavian artery (Figs 2A and B). No other vascular involvement was seen. Her right radial, brachial, and carotid pulses were weak, with carotidynia and raised CRP (8.8 mg/dL). She was diagnosed with TAK and started on 30 mg prednisolone with tapering doses and 20 mg weekly methotrexate. Pain resolved in a week. She is presently well on a combination of methotrexate and mycophenolate mofetil.

Case 3

A 45-year-old male presented with 10 days of severe epigastric pain radiating to the back, unrelated to meals. He did not complain of fever, nausea, vomiting, weight loss, sweating, or angina. Cardiac and gastroenterological evaluations, including gastroesophagoscopy, were normal. Despite analgesics and proton pump inhibitors, his pain persisted. CT angiography revealed long-segment circumferential wall thickening with luminal narrowing in the superior mesenteric artery (8 cm) (Figs 3A and B), and PET CT showed curvilinear uptake along the ascending aorta. Inflammatory markers were normal, and ANA and viral markers (Hepatitis B, C and HIV) were negative. He was diagnosed with LVV, likely TAK. Pain resolved with 30 mg prednisolone taper and weekly 15 mg methotrexate. He did not complain of the typical post-prandial pain seen in mesenteric ischemia.

Discussion

Takayasu arteritis, a large-vessel vasculitis, is often described as having three phases, though not all patients experience this progression. Phase I (systemic) involves constitutional symptoms. This phase may precede pulse loss. Phase II (vasculitis stage) includes vessel tenderness (angiodynia) and possible ischemia. At this stage, the disease may spontaneously resolve or progress. Phase III (fibrotic/pulseless) is characterized by arterial stenosis, typical of TAK.[1]

In a study by Alnabwani et al. of 43 case reports, fever was the most common

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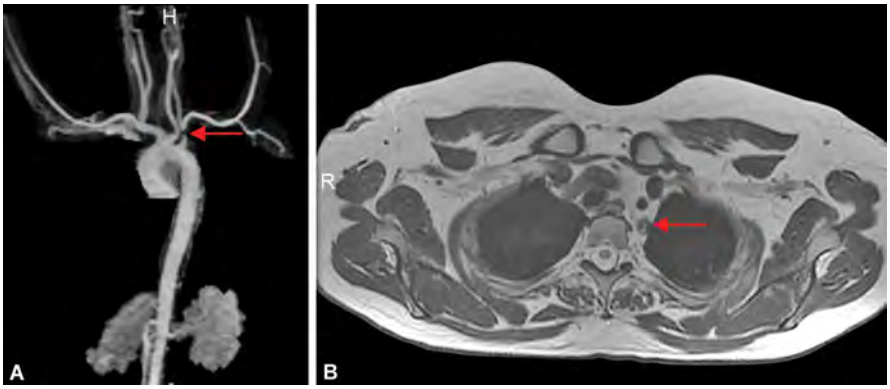
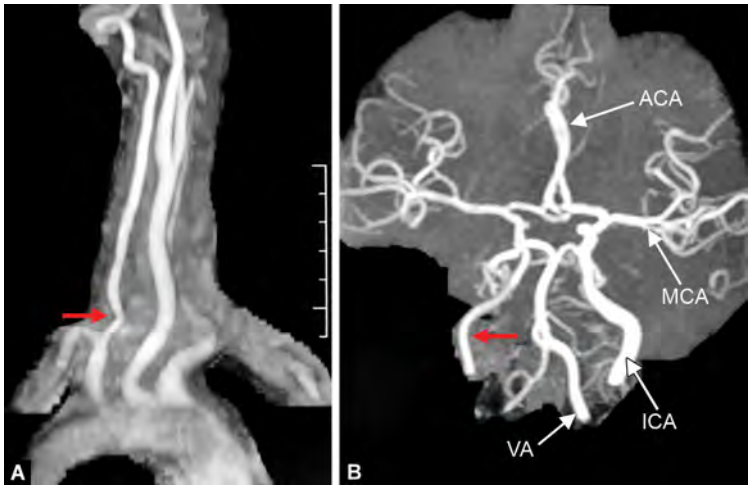
Table 1: Baseline investigations

	Case 1	*Case 2*	*Case 3*	*Reference values*
Hb (gm/dL)	11.6	11.4	14.7	12–15
TLC (10^6/L)	7640	11130	7570	4000–10000
Platelet (10^9/L)	292	417	259	150–410
ESR (mm/hour)	19	28	14	0–20
CRP (mg/L)	7.7	8.8	3	0–5
Creatinine (mg/dL)	0.75	0.5	0.7	0.5–0.95
ALT (U/L)	34	18	0.8	0–35

ALT, alanine transaminase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; TLC, total leukocyte count



Figs 1A and B: (A) Red arrow shows the left subclavian artery stenosis; (B) Red arrow shows subclavian artery thickening



Figs 2A and B: (A) Attenuation in caliber of entire cervical right ICA; (B) Diffuse attenuation of intracranial right ICA

symptom (20.93%), followed by chest pain, limb claudication, and headache (each 13.95%). Less frequent symptoms included shortness of breath (11.62%), weight loss (9.30%), syncope (6.98%), and night sweats (4.65%).[2] None of these symptoms were present in our patients. This highlights the rarity of symptoms that led to diagnosis in our cases.

Thoracic outlet syndrome typically presents with neurological symptoms from brachial plexus compression, such as finger paresthesias, neck, trapezius, shoulder, or arm pain. A rarer form involves subclavian artery compression, causing distal upper extremity ischemia, making it a potential mimic of TAK.[3]

Given the overlap of symptoms between TOS and TAK, there have been instances where TAK was mistaken for TOS[4] and vice versa.[5] TAK usually causes limb pain with repetitive activity, making a thorough clinical assessment crucial to differentiate it from TOS.

Our patient presented with digital ischemia rather than limb claudication, which made TAK an unexpected initial diagnosis. However, severe acute vascular inflammation could explain the symptoms. What makes this case unique is the persistent pain and paresthesias, uncommon in vasculitis unless acute vessel occlusion occurs.

TAK typically progresses slowly with collateral vessel formation. In rare cases, patients may experience acute vascular stenosis, leading to critical ischemia or gangrene of the extremities.[6]

A case similar to our second case involved a 25-year-old female with a 3-year history of left mandibular pain radiating to the neck and temple after dental extraction. ENT consultation was unhelpful. Examination revealed neck tenderness with a left carotid bruit, and ultrasound showed concentric thickening with 90% luminal narrowing of the left CCA. CT angiography confirmed involvement of the descending thoracic, abdominal aorta, and left CCA. She fully recovered with 50 mg prednisolone, tapered and discontinued over 2 months.[7]

In a large study of 1,372 patients with TAK, 22.6% of patients complained of head and neck symptoms, such as dizziness, anterior neck pain, and masseter claudication.[8]

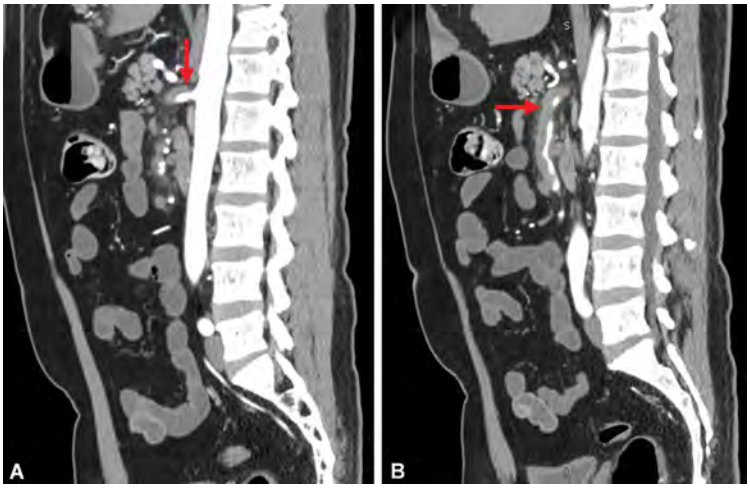
A multicenter study of 318 patients found carotidynia in 10% of subjects and that it was independently associated with relapse.[9]

Orofacial or jaw pain may indicate carotid artery involvement in TAK. Neck pain or tenderness (carotidynia) is a key sign of active vascular inflammation. It is important for dentists, ENT specialists and general physicians to be aware of these uncommon symptoms for early detection.

A close differential in this case could be giant cell arteritis, as it can present with new-onset or worsening headache and jaw claudication. However, the age of our patient and absence of temporal artery involvement make this diagnosis unlikely.

A case similar to our third case involved a 20-year-old female with 3 months of fatigue, low-grade fever, and nonpostprandial periumbilical pain. Initial examination showed mild fever with normal pulse and blood pressure. Her inflammatory markers were high. Imaging revealed thickening and stenosis in the celiac, superior mesenteric, and renal arteries, as well as the thoracic aorta, brachiocephalic, carotid, and left subclavian arteries. She was diagnosed with TAK, and her symptoms resolved with prednisolone.[10]

Abdominal pain is an uncommon manifestation of TA.[11] Postprandial pain arouses suspicion of intestinal ischemia, which can also be seen in the context of systemic vasculitis like granulomatosis with polyangiitis or secondary vasculitis due to rheumatoid arthritis or lupus. Thus, it warrants evaluation. But the pain may not always be postprandial, as depicted by our



Figs 3A and B: (A and B) Red arrows show thickening at the origin and whole length of the superior mesenteric artery with stenosis

case and the above mentioned case report. Abdominal pain in TAK can stem from either ischemia in the mesenteric artery distribution or inflammation-related vascular pain.[10]

Back pain is another atypical manifestation of TAK, which can result from aortitis affecting the upper, mid, or lower back and is often overlooked.[12] Thoracic and upper abdominal aortic involvement may occur without pulse loss. Aortitis should be considered in unexplained back pain, especially with elevated inflammatory markers, as early treatment can reduce complications like stenosis and aneurysms.

Other notable mimics of TAK and LVV include atherosclerosis, fibromuscular dysplasia (FMD), IgG4 disease, cardiac emboli, and antiphospholipid syndrome.[13]

Atherosclerosis and TAK can both cause arterial stenosis, ischemia, and bruits, but they differ significantly. Atherosclerosis affects older individuals with metabolic risk factors and is driven by lipid-rich plaques, while TAK affects young women. Inflammatory markers are often elevated in TAK but not in atherosclerosis.[13] TAK shows concentric, homogeneous, long-segment vessel wall thickening with less early calcification, predominantly involving the aorta and its main branches. In contrast, atherosclerosis shows eccentric, focal wall thickening, prominent calcifications, and preferential involvement of areas like the carotid bifurcation and abdominal aorta. On imaging, Takayasu shows diffuse FDG uptake on PET and wall enhancement on MRI, while atherosclerosis shows patchy FDG uptake and no significant wall enhancement.[14]

FMD is a close differential of TAK, as it also presents in young females. It is a noninflammatory vascular disease characterized by stenoses and aneurysm formation in multiple vascular territories, giving a "string of beads" appearance. Acute-phase reactants are usually normal in FMD. Renal and carotid arteries are most commonly involved, but other arteries may be involved in 10% of cases. FMD is unlikely to involve multiple vascular territories.[13,15]

Antiphospholipid syndrome (APS) is an autoimmune procoagulant disorder marked by recurrent arterial or venous thrombosis, pregnancy loss, thrombocytopenia, and persistently positive anticardiolipin or lupus anticoagulant antibodies. It can mimic vasculitis angiographically due to multifocal arterial thrombi. APS may be primary or associated with SLE and can also present with hematologic, neurologic, cutaneous, cardiac, and renal manifestations. Diagnosis requires clinical features plus persistent antiphospholipid antibody positivity on serial testing.[13]

IgG4-related disease (IgG4RD) is a multisystem fibroinflammatory disorder known to cause periaortitis and periarteritis. This can occur in isolation and cause a diagnostic conundrum as a mimic of LVV/TAK. IgG4-related perivascular lesions mainly affect adult males, often involving the aorta and its branches. Perivascular lesions of IgG4RD are common in the abdominal aorta, thoracic aorta, and coronary artery. They show arterial wall thickening and homogeneous late-phase enhancement on CT, with frequent multi-organ involvement. Elevated serum IgG4 and imaging findings suggest the diagnosis, but histology is needed for confirmation. Histologically, they show sclerosing inflammation mainly in the adventitia, matching the CT findings.[16]

Other important mimics of TAK that warrant discussion include infections such as syphilitic aortitis, tuberculous aortitis, and mycotic aneurysms from infective endocarditis. They result from direct microbial invasion of the vessel wall. Infectious arteritis tends to cause aneurysms, vessel erosion, and systemic infection signs like fever or positive cultures, whereas primary vasculitis shows granulomatous inflammation without pathogens.[13]

Conclusion

Diagnosing large-vessel vasculitis early helps in preventing catastrophic outcomes. The patients often approach physicians during early phases of their illness with apparently vague and nonspecific symptoms. It is therefore imperative to be well-versed in recognizing the early/atypical manifestations of the disease.

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CASE REPORT

Acute Cerebellar Ataxia in a Case of Enteric Fever

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Received: 13 April 2025; *Accepted:* 05 June 2025

Abstract

Isolated acute cerebellar ataxia is a rare neurological complication of enteric fever. It usually presents with speech and gait abnormalities. Cerebellar ataxia is generally masked by various other neurological complications, such as delirium. Here, we report a case of a 24-year-old male with no known comorbidities, who presented with complaints of high-grade fever, slurred speech, and unsteady gait, which was broad based. He also had abnormal cerebellar signs. Initial laboratory investigations showed thrombocytopenia, and blood cultures detected *Salmonella* Typhi. cerebrospinal fluid (CSF) examination and brain imaging were unremarkable. The patient recovered with ceftriaxone, and a final diagnosis of enteric fever with encephalopathy was made.

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Introduction

Enteric fever, caused by *Salmonella* Typhi and *Salmonella* Paratyphi, manifests with a wide variety of complications involving hematological, gastrointestinal, hepatobiliary, and neurological systems.[1,2] Despite advancements in antibiotic therapy that have significantly reduced the incidence of complications, these complications continue to contribute substantially to the morbidity and mortality associated with the disease. Neurological complications in enteric fever are less common, but they are well documented and can range from mild confusion and delirium to severe forms of encephalopathy. Other neurological complications include meningitis and myelitis, with cerebellar ataxia being a rare but recognized manifestation.[3,4] Radiologically, CT and MRI scans are often reported as normal in acute cerebellar ataxia.[5]

History

A 24-year-old man, hailing from Assam and working in a tech start-up in New Delhi, presented to casualty with high-grade fever, slurred speech, and unsteady gait for 2 days. There were no complaints of headache, abdominal pain, or diarrhea. He also gave a history of high fever and loose stools 2 weeks prior and had recently traveled to Mumbai 7 days ago. On examination, he was conscious but intermittently confused. He was febrile (temperature 103.2°F), tachycardic (heart rate 120/minute), and had normal oxygen saturation. Neurological examination revealed sluggish response, dysdiadochokinesia, and incoordination in the form of abnormal heel-shin and finger-nose tests. His gait was broad based and unsteady. The patient also exhibited dysarthria, although comprehension was fully intact. The rest of the systemic examination was normal. There was no rash or eschar. He was empirically started on intravenous ceftriaxone.

Initial laboratory tests showed normal total leukocyte count, thrombocytopenia, elevated liver enzymes, and raised serum creatinine (Table 1). Infective workup was done to rule out dengue, malaria, scrub typhus, and leptospirosis. CT head was normal. Cerebrospinal fluid (CSF) examination showed mildly elevated protein levels with no other abnormality. CSF meningitis/encephalitis panel and cultures were sterile. On the 3rd day, blood cultures identified *Salmonella* Typhi, resistant to chloramphenicol and ciprofloxacin. The patient was diagnosed with enteric encephalopathy and treated for the same. He became afebrile by the 7th day, with significant improvement in dysarthria and ataxia by the 10th day. He was discharged in stable condition and is currently doing well on follow-up, with no residual focal deficit.

Discussion

Enteric fever remains a significant public health concern in India.[1] The disease typically presents with systemic symptoms, such as prolonged fever, abdominal discomfort, and gastrointestinal disturbances, including diarrhea.[1,2] Complications of enteric fever are generally seen in the second week of illness.

Neurological complications in enteric fever occur in approximately 3–10% of cases, but isolated cerebellar ataxia is very rare.[3,4] It often goes overshadowed by more severe neurological manifestations, such as toxic delirium and encephalopathy. When cerebellar ataxia does occur, it typically presents in the second week of illness, mirroring the timing of most other complications associated with enteric fever, as was the case with our patient. Clinically, cerebellar ataxia generally presents with complaints of difficulty in speech and unsteady gait.[4]

The pathophysiology of cerebellar ataxia in enteric fever is not well understood. The nonspecific inflammation of the cerebellum is believed to play a very important role in pathogenesis.[4,6] Several mechanisms have been proposed, including bacteremia with systemic dissemination, an immune response to enterotoxin that triggers cytokine release, cerebral hypoperfusion, metabolic and electrolyte imbalances, and direct involvement of the central nervous system.[6]

Radiologically, CT and MRI scans are often reported as normal in acute cerebellar ataxia. Occasionally, CT may show mild cerebral edema or subtle findings. Rarely, MRI brain may show diffuse cerebral edema, meningeal enhancement, or focal lesions.[5] In our case, noncontrast computed tomography (NCCT) brain was done, and it was reported to be within normal limits. Typical findings from lumbar puncture in cases of acute cerebellar ataxia include mildly elevated protein levels without pleocytosis or microbial growth on cultures. In our case, the CSF examination also showed mildly elevated protein, and no organism was detected in culture or biofire panel.[7] These CSF findings support the hypothesis of an inflammatory process rather than an infectious one directly involving the central nervous system (CNS).

Cerebellar ataxia associated with enteric fever is usually self-limiting, resolving completely within a few weeks. Treatment focuses on the appropriate antibiotic therapy for enteric fever as per sensitivity, with no additional specific treatment required for the ataxia itself. However, some case reports suggest the

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Table 1: Laboratory investigations

	Day 1 (on admission)	*Day 7 (at discharge)*	*Normal range*
Hb (gram/dL)	11.2	9.3	13.5–17.5 g/dl (M), 12.0–15.5 g/dl (F)
Total leukocyte count ($\times 10^9$/L)	3.20	6.78	4000–11000 /µL
Platelets ($\times 10^9$/L)	0.64	164	150,000–450,000 /µL
Creatinine (mg/dL)	1.18	0.74	0.6–1.3 mg/dL
Sodium (mEq/L)	138	139	135–145 mEq/L
Potassium (mEq/L)	3.71	3.66	3.5–5.0 mEq/L
Total/direct bilirubin (mg/dL)	0.53/0.32	0.48/0.21	0.1–1.2/0–0.3 mg/dL
Total protein/albumin (gm/dL)	4.6/2.40	5.0/2.50	6.0–8.3/3.4–5.4 g/dL
SGOT/SGPT (IU/L)	400/191	231/215	5–34/0–55 IU/L
ALP/GGT (IU/L)	147/179	109/113	44–147/9–48 IU/L
ESR (at the end of 1st hour)	5	–	<21 mm/hour
CRP	62.4	–	<6 mg/dL
Blood culture	*Salmonella* typhi	–	Negative

SGOT, Aspartate Aminotransferase; SGPT, Alanine Aminotransferase; GGT, Gamma-Glutamyl Transferase; ALP, Alkaline Phosphatase; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein

potential benefit of high-dose systemic steroids in cases with severe neurological manifestations, although complete recovery was seen without their use in our case.

Orcid

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CASE REPORT

Keloidal Dermatofibroma: A Rare Diagnostic Entity

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Abstract

Dermatofibroma, also referred to as benign fibrous histiocytoma, is a cutaneous tumor frequently occurring on the extremities. Its occurrence on the neck is linked to atypical clinicopathologic characteristics and a more aggressive clinical course compared to typical cases. Furthermore, prior studies have recognized benign fibrous histiocytoma as the predominant subtype, while the keloid variant is extraordinarily rare, constituting approximately 1% of documented cases. In this case study, the exhibited nodular lesion is on the neck region. Upon histopathological examination, the tumor demonstrated well-circumscribed features with keloid-like regions, occasional spindle cells with elongated nuclei and eosinophilic cytoplasm, and a prominent inflammatory infiltrate. The objective of this study was to report our experience with a case of keloidal dermatofibroma occurring on the neck, a condition frequently overlooked in clinical practice, and to critically examine the management strategies for keloidal dermatofibromas at this anatomical site.

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Introduction

Dermatofibroma, also referred to as benign fibrous histiocytoma, is a cutaneous lesion predominantly observed in young individuals and those in early to late adulthood, exhibiting a slight female predilection.[1] The diagnosis is fairly straightforward when classical clinicopathological features are evident. Dermatofibromas most commonly develop on the limbs but are rarely found on other locations such as the neck, face, breasts, palms and soles, scalp, mucosal surfaces, and genital areas. Some of the variants are atrophic, keloidal, granular cell, myxoid, lichenoid, balloon cell, aneurysmal, hemosiderotic, cellular, epithelioid, atypical, lipidized, clear cell, palisading, and signet-ring cell variants, among which the keloidal variant is exceptionally uncommon, accounting for <1% of all cases.[2] First described in 1998, this uncommon variant has been documented in only 15 reported cases to date.[3]

Case Description

A 12-year-old boy came to the surgery OPD with a complaint of swelling over the lateral aspect of the neck for 2 months. The swelling measured 3 × 2 cm in size with a solitary nodular appearance, insidious in onset, gradually progressive, smooth, firm in consistency, non-tender, and without local rise in temperature, with overlying skin that was unremarkable. There is no past history of medication or trauma. No other significant family history was noted. The patient did not undergo any scans or other additional investigations. The sample was sent for histopathological examination with the clinical diagnosis of an epidermoid cyst.

In the department of pathology, we received a single skin-covered firm tissue piece measuring 2.2 × 1.5 × 1 cm for histopathological examination. The tissue was formalin-fixed and processed under paraffin. A hemisection was cut and stained with hematoxylin and eosin stain. Microscopic examination revealed epidermis and dermis. The epidermis was thinned out and flattened (Fig. 1). The superficial dermis showed a few lymphocytes in the perivascular region along with occasional spindle cells with elongated nuclei and eosinophilic cytoplasm (Fig. 2). The deep dermis showed thick hyalinized keloidal collagenous tissue (keloidal change). The collagenous material was interspersed with a few spindle-shaped cells (Fig. 3). Occasional adnexal structures were noted in the periphery. Based on these histopathological findings, a diagnosis of keloidal dermatofibroma was made. Masson's trichrome stain was performed, which confirmed the presence of collagen (Figs 4 and 5).

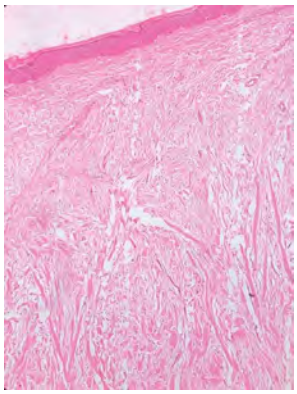

Fig. 1: Epidermis and dermis. Epidermis was thinned out and flattened (10×)

Discussion

Dermatofibromas generally manifest as solitary or multiple firm, pigmented papules or nodules that exhibit slow, progressive growth. These lesions are predominantly found on the lower extremities. The lesions typically measure between a few millimeters and 2 cm in diameter, with pigmentation ranging from light brown and dark brown to yellow-red, brown-red, or black.[4]

Dermatofibroma encompasses a spectrum of histopathological variants, such as atrophic, keloidal, granular cell, myxoid, lichenoid, balloon cell, aneurysmal, hemosiderotic, cellular, epithelioid, atypical, lipidized, clear cell, palisading, and signet-ring cell forms.[5] Among the various subtypes, keloidal dermatofibroma comprises approximately 1% of all occurrences.[2] Precise diagnosis of these subtypes is imperative to avert misclassification as an aggressive neoplasm. Keloidal dermatofibroma is an exceptionally rare entity, with neck involvement being exceedingly uncommon.[1]

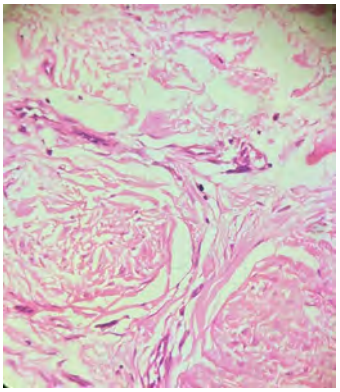

Fig. 2: Superficial dermis showed few lymphocytes in the perivascular region, along with occasional spindle cells with elongated nuclei and eosinophilic cytoplasm

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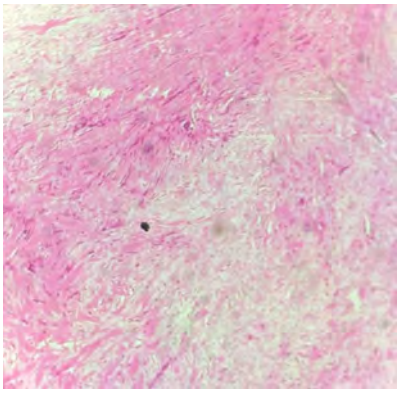

Fig. 3: Deep dermis showed thick, hyalinized, keloidal collagenous tissue (keloidal change). The collagenous material was interspersed with few spindle-shaped cells

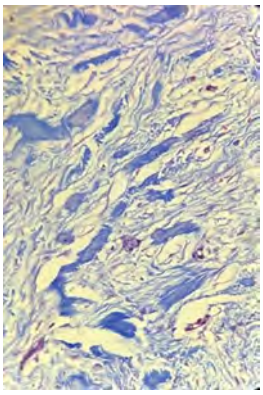

Fig. 4: Masson's trichrome stain was performed, which confirmed the presence of collagen

On microscopic examination, dermatofibromas are distinguished by a sharply defined dermal mass, often accompanied by epidermal thickening and increased pigmentation in the basal layer.[6] Key features include the growth of spindle cells, histiocytes, Touton giant cells, and lipidized siderophages. Cytological atypia, pleomorphism, and mitotic activity may vary, with the potential for collagen entrapment to also be observed.[5]

Keloidal dermatofibroma, on the other hand, is a rare condition that infrequently affects the neck. These well-defined

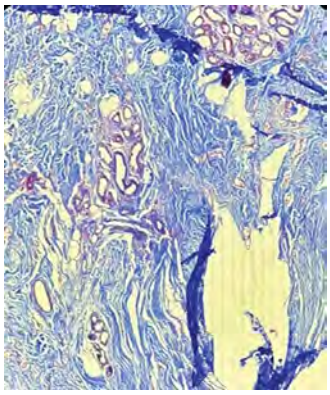

Fig. 5: Masson's trichrome stain was performed, which confirmed the presence of collagen

lesions are characterized by an irregular arrangement of thick, hyalinized collagen fibers in the superficial dermis. Unlike keloid scars, they lack elastic fibers.[5] The nature of dermatofibroma remains uncertain, with ongoing controversy regarding whether it constitutes a reactive inflammatory response or a genuine neoplastic disorder. Compelling evidence suggests that dermatofibroma may represent an inflammatory reactive process, potentially triggered by injuries such as insect bites, ruptured folliculitis, or the rupture of infundibular cysts.[4] In our case, the patient did not have any of these conditions.

Clinically, the differential diagnosis encompasses epidermal inclusion cyst, nodular fasciitis, dermatofibrosarcoma protuberans, keloids, cutaneous leiomyoma, and basal cell carcinoma.[4]

Differential diagnosis of keloidal dermatofibroma can be differentiated histologically by the following findings. Epidermal inclusion cyst includes evidence of stratified squamous epithelium along with keratin. Nodular fasciitis, characterized by the rapid proliferation of undifferentiated cells resembling sarcomatous fibroblasts interspersed with inflammatory cells, should also be included in the differential diagnosis. Dermatofibrosarcoma protuberans is an aggressive neoplasm that infiltrates the subcutaneous tissue, lacking the keloid-like collagen. In keloids, the fibroblasts are arranged in a disorganized manner. Cutaneous leiomyoma is defined by spindle-shaped cells organized in a fascicular configuration, lacking inflammatory and multinucleated cells. In basal cell carcinoma, basaloid cells are organized into lobular configurations, displaying peripheral palisading, retraction artifacts, and an abundance of mitotic profiles.[5]

Conclusion

Keloidal dermatofibroma is a rare condition that is often difficult for the clinician to diagnose accurately. Hence, histopathology along with special stains plays an important role in morphological assessment and achieving a precise diagnosis. In instances of typical dermatofibromas on the lower extremities, marginal or partial excision fails to result in a heightened incidence of local recurrence, whereas in dermatofibromas on the neck, resection with more expansive margins is required to avert repeated recurrence and alleviate patient distress. Hence, the case study seeks to underscore the paramount importance of cultivating heightened awareness of this entity among pathologists and surgeons to arrive at an accurate diagnosis.

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CASE REPORT

Cryptogenic Organizing Pneumonia: A Case Report

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Abstract

Cryptogenic organizing pneumonia (COP) is an idiopathic interstitial lung disease affecting the distal airways, characterized by the development of granulation tissue that obstructs the bronchioles and alveoli, leading to respiratory failure. This case report describes a 63-year-old female patient with a history of diabetes, hypertension, and hypothyroidism who presented with persistent productive cough and dyspnea, initially treated as community-acquired pneumonia. Despite empirical antibiotic therapy, the patient's symptoms persisted. Further investigation, including high-resolution CT (HRCT) scans and a CT-guided lung biopsy, revealed fibrotic exudates, interstitial fibrosis with inflammatory infiltrates, and epithelioid granuloma. A diagnosis of COP was made after multidisciplinary discussion, and corticosteroid therapy was initiated, leading to significant clinical improvement and resolution on repeat imaging. This case highlights the importance of considering COP in patients with nonresolving pneumonia and underlines the efficacy of corticosteroids in its management. It also emphasizes the need for a multidisciplinary approach combining clinical, radiological, and histological assessments to reach a definitive diagnosis. Early recognition and appropriate treatment are crucial in preventing complications such as fibrosis and respiratory failure.

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Introduction

Cryptogenic organizing pneumonia (COP) is a subtype of interstitial lung disease and the idiopathic form of organizing pneumonia (OP) (formerly called bronchiolitis obliterans organizing pneumonia), affecting distal bronchioles, respiratory bronchioles, alveolar ducts, and alveolar walls. It is marked by the development of organized clusters of granulation tissue that block the alveolar spaces and bronchioles, leading to respiratory failure.[1–3] The exact etiology of OP is unknown. Several potential causes have been proposed for OP, including viral infections, exposure to toxic gases, certain medications, gastroesophageal reflux, radiation therapy, and connective tissue disorders.[4] OP is considered a clinicopathological condition, meaning that while clinical and radiological findings can raise suspicion for the diagnosis, histological confirmation through tissue biopsy is necessary for a definitive diagnosis. As such, diagnosing OP requires a combination of clinical presentation, imaging studies, and pathological examination.[5,6] Here, we outline a case of an elderly female presenting with nonresolving pneumonia diagnosed as COP and treated successfully with corticosteroids.

Case

A 63-year-old female, known case of type 2 diabetes, systemic hypertension, and hypothyroidism, presented with complaints of productive cough and dyspnea for 5 days and fever for 2 days. Her chest X-ray PA view showed left lower zone alveolar inhomogeneous opacities. HRCT thorax showed left lower lobe consolidation (Fig. 1). Sputum and BAL evaluation were negative for tuberculosis. She was diagnosed with community-acquired pneumonia, treated with empirical antibiotics, and discharged.

The patient revisited our OPD after 4 weeks with persistent cough and occasional fever; hence, an alternative diagnosis was considered for nonresolving pneumonia, including tuberculosis, OP, and malignancy. She was reevaluated with CECT thorax (Fig. 2), which showed persistent, denser consolidation in the left lower lobe with no contrast enhancement. Antinuclear antibody (ANA) profile was negative.

The patient underwent CT-guided biopsy, which showed many fibrotic exudates filling the alveolar sacs and ducts. Dense interstitial fibrosis with mixed inflammatory cells was noted; some alveoli were dilated and showed foamy macrophages. Many well-formed epithelioid cell granulomas with central suppurative inflammation and foci of necrosis were seen. Few Langhans-type giant cells were also noted (Fig. 3). Biopsy specimen GeneXpert was negative. There was a diagnostic dilemma between tuberculosis and OP. After a multidisciplinary discussion involving pulmonology, infectious disease specialists, and pathology, the team decided to initiate corticosteroid therapy tapered over 8 weeks. During follow-up, both the bronchoalveolar lavage (BAL) and biopsy mycobacteria growth indicator tube (MGIT) cultures remained negative, and repeat imaging showed resolution (Fig. 4).

Discussion

The primary objective of this case study was to evaluate the diagnosis and treatment of a 63-year-old female patient with nonresolving pneumonia, ultimately diagnosed as COP after a thorough clinical, radiological, and histopathological examination. The case emphasizes the importance of considering COP in patients presenting with persistent pneumonia. The patient initially presented with productive cough, dyspnea, and fever, which persisted despite empirical treatment for community-acquired pneumonia. Follow-up imaging revealed persistent lung consolidation. After ruling out tuberculosis and malignancy, a CT-guided biopsy revealed features characteristic of COP, including fibrotic exudates and interstitial fibrosis. The patient was successfully treated with corticosteroids, resulting in clinical and radiological resolution.

Cryptogenic organizing pneumonia generally affects individuals in their 50s or 60s, with the onset of symptoms being gradual and often mistaken for other respiratory conditions. Commonly, patients present with nonspecific symptoms like fever, malaise, persistent cough, and progressive shortness of breath, which can last for several weeks. These symptoms often lead to misdiagnosis as bacterial pneumonia, especially since they do not respond to standard antibiotic treatments.

In most cases, the severity of symptoms is mild to moderate, but there are instances where patients may experience more severe

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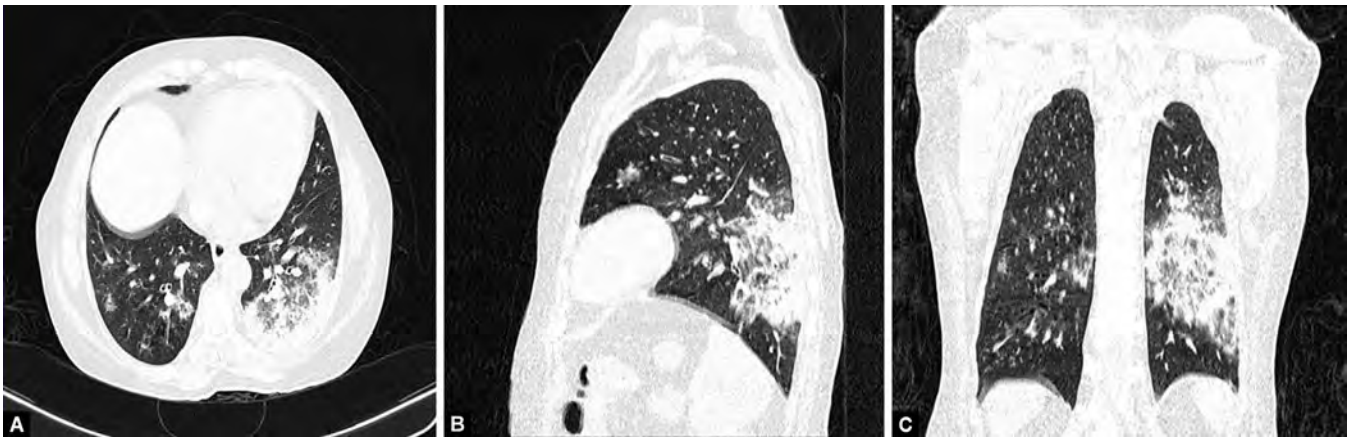
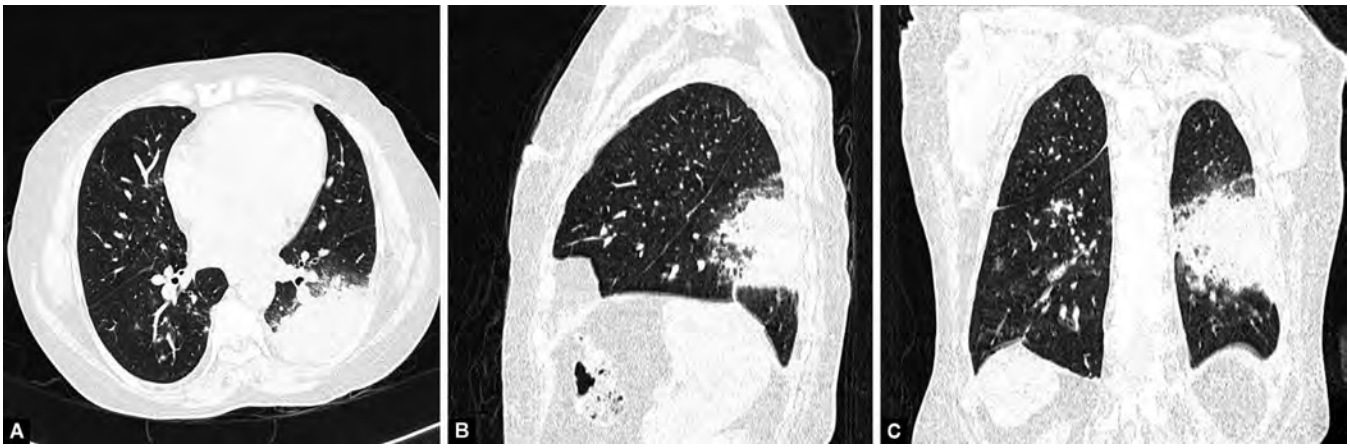


Figs 1A to C: HRCT thorax (6th April 2024)—left lower lobe consolidation



Figs 2A to C: CECT thorax (4th May 2024)—left lower lobe dense persistent consolidation

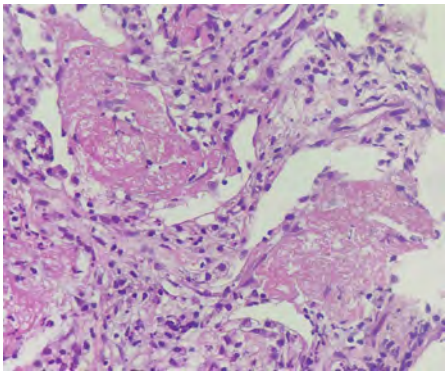


Fig. 3: HPE of CT-guided lung biopsy (4th May 2024)—many polypoidal fibrotic plugs filling the alveolar sacs and ducts (Masson bodies) with dense interstitial fibrosis and mixed inflammatory cells

complications, including significant shortness of breath (dyspnea) and low blood oxygen levels (hypoxemia). These severe cases can become concerning, as they might require more aggressive treatment, including hospitalization and oxygen therapy.

Less commonly, individuals with COP may experience additional symptoms like chest pain, unexplained weight loss, night sweats, and joint pain (arthralgias). These atypical symptoms can make diagnosis challenging, especially when they mimic other conditions such as tuberculosis, lung cancer, or interstitial lung disease.

The precise cause of COP remains unknown, earning it the term "cryptogenic." However, it is widely believed that the condition results from injury to the alveolar epithelium, the thin cells lining the air sacs of the lungs. This damage might be triggered by an underlying factor that remains unidentified. Several potential triggers have been proposed, including viral infections (such as those caused by influenza or other respiratory viruses), inhalation of toxic gases, adverse reactions to certain medications, or even gastroesophageal reflux. Other possible triggers include prior radiation therapy and connective tissue disorders like rheumatoid arthritis or lupus.[4]

The pathogenic mechanism involves alveolar epithelial injury causing plasma protein leakage, which recruits inflammatory cells. This process progresses in three stages: fibrin formation and inflammation, fibroblast proliferation with re-epithelialization, and organization of fibroblasts and connective tissue matrix. Vascular endothelial growth factor (VEGF) and fibroblast growth factors play key roles, while glucocorticoids can inhibit granulation tissue formation in experimental models.[7–10]

This case is consistent with established studies on COP, where the condition is frequently misdiagnosed as bacterial pneumonia initially. The patient's presentation aligns with documented symptoms of COP, such as persistent cough, fever, and respiratory difficulty despite treatment. The use of corticosteroids in this case also mirrors standard management protocols found in existing literature, which advocate for their effectiveness in resolving COP-related inflammation.[11]

Before confirming the COP diagnosis, other potential causes for nonresolving pneumonia, such as tuberculosis and malignancy, were carefully considered and ruled out. Although these conditions can present similarly, the absence of supportive clinical, microbiological, and radiological findings for these alternative diagnoses directed attention toward COP.

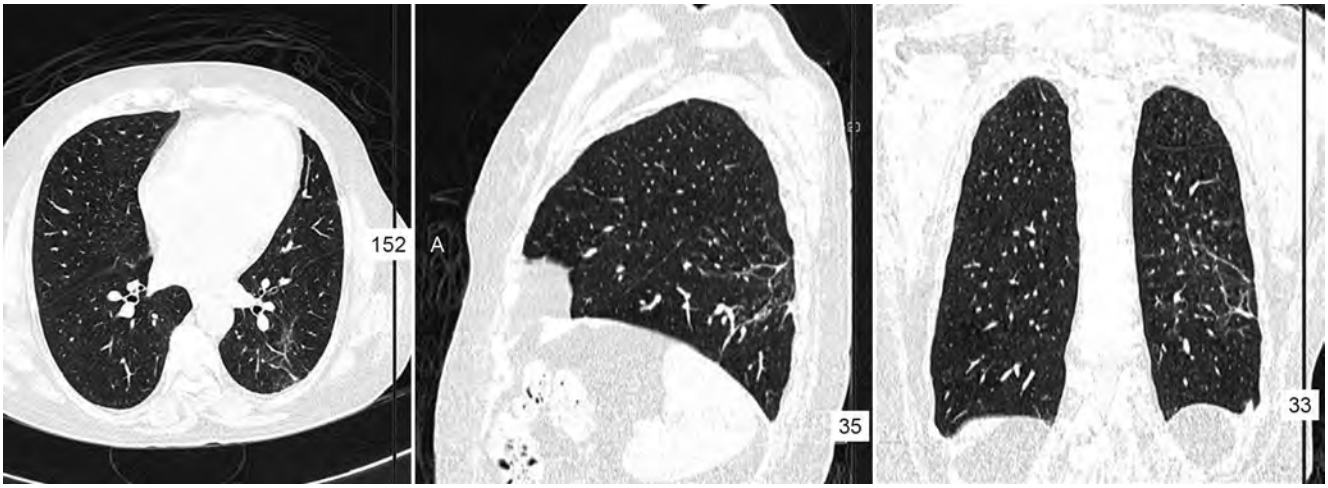


Fig. 4: CECT thorax (26th July 2024)—resolution after corticosteroid treatment

This case highlights the importance of considering COP in patients with nonresolving pneumonia and emphasizes the value of a multidisciplinary approach involving clinical, radiological, and histopathological assessments. Early recognition and treatment with corticosteroids can lead to symptom resolution and prevent complications such as fibrosis and respiratory failure.

A limitation of this case is the inability to identify a definitive etiology for the OP, as the condition remained cryptogenic. Additionally, while corticosteroid treatment was successful, the long-term follow-up to monitor for potential relapse or steroid-related side effects was not detailed in this case. Future research could focus on identifying potential triggers or early biomarkers for COP to aid in earlier diagnosis. Studies on the long-term outcomes of patients treated for COP, including relapse rates and steroid-related complications, would provide valuable insights into optimizing treatment strategies.

Conclusion

This case underscores the importance of considering COP in patients with persistent pneumonia-like symptoms that do not respond to standard treatments. The prompt use of corticosteroids led to a successful outcome, reinforcing their role as the primary treatment for COP. Early and accurate diagnosis remains key to managing the condition effectively and preventing long-term complications.

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CASE REPORT

Unmasking Addison's Disease: A Case of Acute Adrenal Crisis

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Abstract

Addison's disease is a rare endocrine disorder causing adrenal insufficiency and inadequate cortisol production. A 56-year-old chronic smoker presented with recurrent vomiting, abdominal pain, and severe hyponatremia. He had a 20 kg weight loss over 2 months, generalized weakness, dizziness, and hyperpigmentation. Laboratory tests showed hyponatremia (108 mEq/L), hyperkalemia (6.1 mEq/L), low fasting cortisol (0.65 µg/dL), and elevated adrenocorticotropic hormone (ACTH) (705 pg/mL). Imaging revealed bilateral adrenal enlargement and lymphadenopathy, confirming Addison's disease with adrenal crisis. Immediate IV hydrocortisone led to clinical improvement, stabilizing blood pressure and electrolyte balance. He was transitioned to oral steroids and discharged in stable condition with counseling and an emergency medical information card. This case highlights the need for early recognition and prompt treatment of adrenal crisis to prevent fatal outcomes. Increased clinician awareness can facilitate timely diagnosis and intervention, improving patient prognosis and reducing mortality risk.

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Background

Addison's disease is a rare endocrine disorder characterized by adrenal insufficiency, leading to inadequate cortisol and aldosterone production. It commonly presents with fatigue, weight loss, nausea, vomiting, and hyperpigmentation. In severe cases, it can progress to adrenal crisis, marked by hypotension, hyponatremia, and hyperkalemia.[1] The most frequent cause is autoimmune adrenalitis, but infections such as tuberculosis remain significant in endemic regions.[2] Electrolyte imbalances result from aldosterone deficiency, impairing sodium retention and potassium excretion. Despite its rarity, Addison's disease must be considered in patients with persistent nonspecific symptoms and unexplained electrolyte abnormalities. Early recognition and prompt corticosteroid replacement are crucial to preventing life-threatening complications.[3]

Case Description

A 56-year-old man, a chronic smoker, presented with recurrent vomiting and abdominal pain for the past month. He reported a low-grade evening fever for 4 months, loss of appetite, generalized weakness, and an unintentional weight loss of 20 kg over 2 months. He also experienced dizziness for the past month and multiple episodes of nausea and vomiting daily for the last 15 days. On examination, he had diffuse hyperpigmentation, including on the face and palms, and leukonychia (Figs 1 to 3). His blood pressure was 80/48 mm Hg, with a low-volume pulse. He appeared fatigued and had a low mood, but systemic examination was otherwise unremarkable. He was initiated on intravenous hydrocortisone (100 mg stat, followed by 50 mg every 6 hours) with gradual clinical improvement. After 5 days, he was transitioned to oral hydrocortisone (20 mg/day in three divided doses) and was discharged in stable condition. He was provided with an emergency medical information card and was counseled on lifelong steroid therapy and adrenal crisis management.

Investigations

Comprehensive laboratory evaluations, including hematological and biochemical parameters, revealed severe hyponatremia (Na^+ 108 mEq/L) and hyperkalemia (K^+ 6.1 mEq/L), indicative of adrenal insufficiency. Renal and liver function tests remained within normal limits. Further endocrinological assessment demonstrated a markedly reduced fasting serum cortisol level of 0.65 mcg/dL, coupled with elevated plasma adrenocorticotropic hormone (ACTH) (705 pg/mL), confirming primary adrenal insufficiency.

Imaging studies were conducted to assess structural abnormalities of the adrenal glands. Ultrasonography (USG) of the abdomen yielded unremarkable findings, necessitating further radiological evaluation. Contrast-enhanced computed tomography (CECT) of the abdomen delineated bilateral adrenal gland enlargement (left: 34 × 24 mm, right: 22 × 14 mm), accompanied by enlarged paracaval and para-aortic lymph nodes (12 mm), suggestive of an underlying adrenal pathology.

In light of the patient's profound electrolyte imbalances, hypotension, and hyperpigmentation, the clinical suspicion of Addison's disease presenting as adrenal crisis was substantiated through the corroborative biochemical and radiological findings. The patient was promptly initiated on hydrocortisone therapy, leading to significant clinical improvement (Figs 4 to 6).

Differential Diagnosis

- Sepsis and septic shock: The patient's hypotension, generalized weakness, and electrolyte imbalances raised suspicion for sepsis. However, the absence of fever spikes, normal leukocyte count, and a rapid hemodynamic response to corticosteroid therapy makes an infectious cause less likely. Additionally, no focus of infection was identified on imaging or cultures, further ruling out sepsis as the primary diagnosis.
- Tuberculous adrenalitis: In regions with a high prevalence of tuberculosis, adrenal insufficiency due to tuberculous adrenalitis must be considered. The presence of bilateral adrenal enlargement on imaging supports this possibility. However, the lack of constitutional TB symptoms, a negative tuberculin skin test, and the absence of pulmonary or extrapulmonary TB evidence in radiological and microbiological investigations makes this diagnosis less probable.
- Primary gastrointestinal malignancy with adrenal metastasis: Significant weight loss, anorexia, and persistent nausea raised concerns about an underlying malignancy. Adrenal metastases from primary cancers such as lung, gastric, or pancreatic carcinoma could explain the adrenal enlargement seen on imaging. However, the absence of a

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Fig. 1: Facial pigmentation, especially around the lips and forehead, with signs of fatigue[4]

Fig. 2: Hyperpigmentation of hands and nails, characteristic of Addison's disease[4]

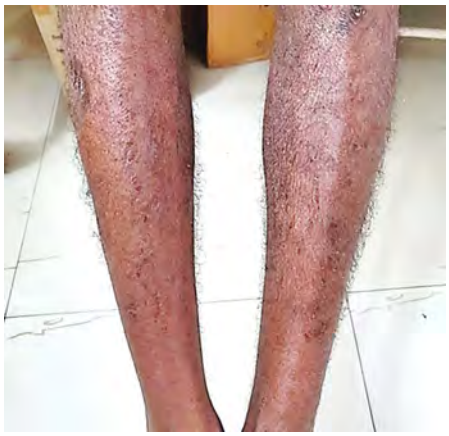

Fig. 3: Bilateral lower limb hyperpigmentation and dryness, suggestive of adrenal insufficiency[4]

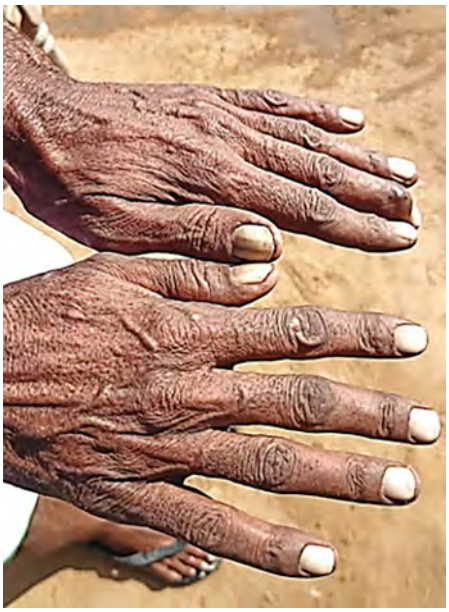

Fig. 4: Reduced hand hyperpigmentation, healthier nails[4]

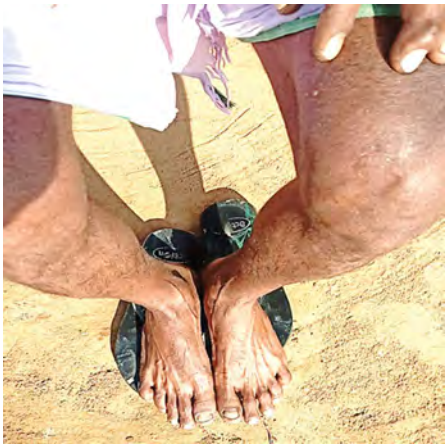

Fig. 5: Improved lower limb pigmentation and skin texture[4]

Fig. 6: Significant facial depigmentation[4]

detectable primary malignancy on further investigations and the dramatic response to steroid therapy makes metastatic disease unlikely in this case.

- Syndrome of inappropriate antidiuretic hormone secretion: Hyponatremia with associated symptoms such as fatigue and dizziness suggested syndrome of inappropriate antidiuretic hormone secretion (SIADH) as a differential. However, the presence of concurrent hyperkalemia, low serum cortisol, and high ACTH levels confirms a primary adrenal insufficiency rather than an isolated disorder of sodium balance.
- Hypothyroidism and myxedema crisis: Adrenal insufficiency shares several features with severe hypothyroidism, including fatigue, hypotension, hyponatremia, and depressive symptoms. However, the absence of bradycardia, periorbital edema, delayed reflexes, and hypothermia, along with normal thyroid function tests, rules out myxedema crisis.
- Pheochromocytoma with adrenal insufficiency: Although rare, pheochromocytoma-associated adrenal insufficiency can present with hypotension, autonomic dysfunction, and electrolyte disturbances. However, the absence of paroxysmal hypertension, episodic palpitations, and normal plasma metanephrine levels makes pheochromocytoma an unlikely cause.
- Isolated ACTH deficiency (secondary adrenal insufficiency): In cases of adrenal insufficiency, secondary causes due to pituitary dysfunction must be considered. However, the markedly elevated plasma ACTH levels in this patient confirm a primary adrenal insufficiency, ruling out central causes such as pituitary adenomas, chronic steroid withdrawal, or Sheehan's syndrome.

Treatment

The patient was initially managed with intravenous hydrocortisone 100 mg stat, followed by 50 mg every 6 hours to address adrenal insufficiency. Intravenous fluids were administered to correct hypotension and electrolyte imbalances, specifically targeting severe hyponatremia (108 mEq/L) and hyperkalemia (6.1 mEq/L). Supportive therapy, including close monitoring of vital signs, metabolic parameters, and fluid balance, was provided. Over the next few days, his blood pressure stabilized, electrolyte levels normalized, and his general condition improved. By day 5, intravenous steroids were tapered, and the patient was transitioned to oral hydrocortisone 20 mg/day in three divided doses.

Outcome and Follow-up

The patient showed significant clinical improvement, with resolution of dizziness,

appetite recovery, and normalization of mood and energy levels. Upon discharge, he was counseled on lifelong steroid replacement therapy, stress dose adjustments, and the importance of medication adherence. An emergency medical information card was provided, detailing his diagnosis, prescribed medications, and emergency contact information. Follow-up visits were scheduled at 4–6-week intervals to monitor adrenal function, electrolyte balance, and overall clinical status. Education on recognizing adrenal crisis symptoms and the need for prompt medical intervention was emphasized. Long-term management included dose adjustments based on stress levels, infection risk assessment, and regular endocrinology reviews. By the 4th week, the patient remained stable, and continued outpatient follow-up ensured optimal disease management and quality of life.

Discussion

This case describes a 56-year-old man presenting with severe hyponatremia, hypotension, and hyperpigmentation, ultimately diagnosed as Addison's disease with adrenal crisis. Addison's disease is a rare but potentially life-threatening condition of primary adrenal insufficiency, where destruction of the adrenal cortex leads to deficient cortisol and aldosterone production.[1] The insidious onset of symptoms like fatigue, weight loss, nausea, and dizziness often leads to delayed diagnosis and increased morbidity.[2] In this case, adrenal crisis was the most severe manifestation, presenting with hypotension, electrolyte imbalances, and cardiovascular instability, necessitating urgent corticosteroid therapy.

A key diagnostic feature in this case was the electrolyte imbalance, particularly hyponatremia with hyperkalemia, a hallmark of primary adrenal insufficiency due to aldosterone deficiency.[3] Hyperpigmentation, absent in secondary adrenal insufficiency, results from excessive ACTH stimulating melanocortin receptors. The patient's elevated ACTH and low cortisol levels confirmed the diagnosis, while CECT findings of bilateral adrenal enlargement raised suspicion of an infectious etiology, particularly tuberculosis, which remains a major cause of Addison's disease in endemic regions.[4]

Management of adrenal crisis requires immediate corticosteroid replacement and fluid resuscitation. Hydrocortisone is preferred due to its glucocorticoid and mineralocorticoid activity, unlike dexamethasone, which lacks the latter. The patient showed rapid improvement with IV hydrocortisone, followed by oral maintenance therapy. Lifelong steroid replacement is essential, with patient education on stress dosing and emergency preparedness being crucial to prevent recurrent adrenal crises.[5]

This case highlights the importance of recognizing adrenal insufficiency as a potential cause of persistent hyponatremia, unexplained weight loss, and hypotension. A high index of suspicion, particularly in tuberculosis-endemic regions, is essential for timely diagnosis and management.

Patient's Perspective

I had been feeling unwell for months—always exhausted, dizzy, and losing weight without understanding why. No matter how much I ate, I felt weaker every day. My skin had also started darkening, but I did not think much of it. Then the vomiting started. At first it was occasional, but soon I could not keep anything down. My body felt like it was shutting down, and I had no idea why. When I was taken to the hospital with severe abdominal pain and dangerously low blood pressure, I was scared. The doctors ran multiple tests, and when they told me I had Addison's disease and was in adrenal crisis, I did not know what it meant. All I knew was that my body was not making enough of an important hormone, and without immediate treatment things could get worse.

They started me on medication right away, and within a few hours I felt stronger. My blood pressure stabilized, my dizziness reduced, and for the first time in months I had an appetite. After a few days I was able to sit up, walk, and even feel hopeful again. The doctors explained that I would need lifelong medication, but as long as I took it regularly and stayed prepared for emergencies, I could live a normal life. They even gave me an emergency medical information card so that if I ever had another crisis, any doctor would know how to help me. Now I take my medication every day and listen to my body more carefully. It is a big adjustment, but I feel grateful that my condition was diagnosed in time. Looking back, I wish I had paid more attention to my symptoms earlier, and I hope my story helps others recognize the warning signs before it becomes critical.

Learning Points

- Recognizing adrenal crisis in Addison's disease: Adrenal crisis should be suspected in patients presenting with severe hyponatremia, hyperkalemia, hypotension, and nonspecific symptoms such as fatigue, nausea, and weight loss, as early diagnosis is essential to prevent life-threatening complications.
- Timely corticosteroid replacement is lifesaving: Immediate intravenous hydrocortisone administration is crucial for hemodynamic stabilization and electrolyte correction, highlighting the need for early and aggressive intervention in suspected adrenal crisis.
- The role of a multidisciplinary approach in diagnosis: Collaboration across specialties is vital in cases with nonspecific or misleading presentations, as timely referral can prevent misdiagnosis and ensure appropriate management.
- Long-term management and patient education: Lifelong steroid replacement, stress-dose adjustments, and emergency preparedness, including a medical alert card, are essential for preventing adrenal crises and optimizing long-term care.

Author Contributions

The following authors were responsible for drafting the text, sourcing and editing clinical images, investigation results, drawing original diagrams and algorithms, and critical revision for important intellectual content: MM, NE, DM, and JR. The following authors gave final approval of the manuscript: MM, NE, DM, and JR. The guarantor was JR.

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Patient Consent for Publication

Consent obtained directly from patient(s).

Provenance and Peer Review

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CASE REPORT

A Raw Crabby Tale: Paragonimiasis Unmasked

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Abstract

Paragonimiasis is a parasitic infection endemic in the northeastern states of India. Because the infection is largely restricted to endemic areas, suspecting and establishing a diagnosis are challenging in nonendemic areas. Here, we describe a rare case of paragonimiasis in a nonendemic area. We highlight the importance of meticulous history as well as the practical issues in establishing the diagnosis. We also describe the management and outcome of the patient.

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Introduction

Paragonimiasis is a trematode (fluke) infection predominantly transmitted *via* consumption of raw or undercooked crab or crayfish. Almost 50 species of *Paragonimus* have been described.[1] Not all are pathogenic to humans; approximately 11 species have been reported to cause disease in humans.[1] Of the different species of *Paragonimus*, *Paragonimus westermani* and *Paragonimus heterotremus* are the ones found in the Indian subcontinent.[1] Estimates suggest that about 23 million people are infected globally.[2,3] In India, certain endemic and hyperendemic areas are described.[1,3] Because the infection is largely restricted to endemic areas, suspecting and establishing a diagnosis are challenging in nonendemic areas. Here, we describe a case where the diagnosis was suspected based on meticulous history. It highlights the importance of meticulous history. It also highlights the difficulties in establishing the diagnosis and potential solutions.

Case Description

A 30-year-old male with no known comorbidities presented to our hospital with complaints of intermittent fever episodes of 3 months duration associated with right hypochondriac pain and weight loss. There was no history of cough, breathlessness, hemoptysis, loose stools, nausea, vomiting, jaundice, itching, or any urinary symptoms. On clinical examination, he was hemodynamically stable. The general physical examination was unremarkable. Systemic examination was significant for right hypochondriac tenderness on deep palpation.

The initial blood investigations showed leukocytosis with eosinophilia [total white blood cell (WBC) count 15,170 cells/mm^3 with 54% eosinophils]. The absolute eosinophil count was 9,690 cells/mm^3. The liver function tests were mildly deranged. Because of the presence of right hypochondriac tenderness and deranged liver function tests, a contrast-enhanced computed tomography (CECT) scan of the abdomen was requested. This showed a few small to medium-sized ill-defined hypoenhancing areas in segments IVA, VII, VIII of liver showing delayed progressive enhancement in the delayed phase (Fig. 1). On further detailed history taking, he gave history of going on trekking with friends and having exotic meat (raw snails and crabs) almost 3–4 months prior to the onset of symptoms. Considering this history in the background of peripheral eosinophilia and liver lesions, a working diagnosis of parasitic infection—probable *Fasciola hepatica* infection—was considered. Subsequent clinical and laboratory evaluation including fundoscopy for coexisting ocular parasitic infection, CT scan of thorax, neuroimaging, and stool examination for ova/cysts were all normal. Peripheral smear did not show any hemoparasites. Serum echinococcus serology and schistosoma serology were negative. Serological test for *F. hepatica* could not be done due to the nonavailability of this test in the local area. He was given empiric treatment with ivermectin and subsequently with nitazoxanide due to difficulty in procuring triclabendazole and anecdotal reports of nitazoxanide use in a few *Fasciola* infections. There was an improvement in his symptoms with nitazoxanide over the next few days; therefore, he was discharged with a plan to continue 10-day course of nitazoxanide.

Two weeks following discharge, he came back with complaints of hemoptysis and chest pain. A repeat CT of the thorax showed a thick cavitary lesion in the left lung (Fig. 2). Workup for tuberculosis [GeneXpert for *Mycobacterium tuberculosis* and mycobacteria growth indicator tube (MGIT) culture] was negative. Sputum for parasites and ova was negative. A possibility of paragonimiasis (considering history of consuming raw crab and liver and lung lesions) was considered. He was started on praziquantel 25 mg/kg thrice daily for 2 days. Considering the possibility of dual infection (*Fasciola* and paragonimiasis), a veterinary preparation of triclabendazole was procured and administered at 10 mg/kg once a day for 2 days.

Subsequently, the patient remained clinically well. He followed up 2 months later. By then we were able to establish contact with the National Reference Laboratories, and his serum sample was sent for testing. Meanwhile, his follow-up CECT of the abdomen and high-resolution computed tomography (HRCT) of the thorax were suggestive of resolving lesions (Fig. 3). Repeat blood workup showed resolution of eosinophilia and normalization of liver function tests. By this time, we had received the reports of serology for *F. hepatica* and *Paragonimus* infection; the serology for *Paragonimus* antibody was positive, thereby confirming the diagnosis of paragonimiasis.

Discussion

Paragonimiasis is a rare disease. The first reported human case in India was from Mumbai (then known as Bombay) in 1919.[1] However, this was not an indigenous case; the first indigenous case was reported more than half a century later in 1981 from Manipur.[1] Globally, it is estimated that approximately 23 million people are infected.[2] In India, the disease is endemic in the northeastern states. A previous study carried out in Manipur identified a seroprevalence rate of 6.7% among a large cohort of >3,000 individuals.[4] This study also identified that people who consumed crabs had a significantly higher seroprevalence compared to those who

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did not. Other studies have also identified endemic foci in Arunachal Pradesh.[3]

It is estimated that over 290 million people are at risk worldwide. The prevalence of infection increases in areas with numerous human and animal reservoir hosts, an abundance of first and second intermediate hosts (snail and crab or crayfish, respectively), and in social customs of eating raw or undercooked seafood. Transmission has also been reported *via* contaminated utensils, such as knives or chopping boards.[5,6]

The life cycle of *Paragonimus* passes through many forms (unembryonated egg, miracidia, sporocysts, rediae, cercaria, and metacercaria) in the first and second intermediate hosts (snail and crab/crayfish, respectively). It is the metacercaria that are the infective forms for mammalian hosts (humans, pigs, dogs, cats, and rodents). Infection is most commonly acquired by eating inadequately cooked or pickled crab or crayfish. The metacercaria excyst in the duodenum, penetrate the intestinal wall, and migrate through the abdominal wall and diaphragm into the lung parenchyma, where they mature into adults over 5–6 weeks.[7]

The most typical clinical manifestations include cough and hemoptysis.[8] However, there are several not-so-typical presentations that make a timely diagnosis difficult. Like in most parasitic infections, peripheral eosinophilia is common. The key to suspecting paragonimiasis lies in a detailed history of diet for exotic meats. The main modalities for diagnosis are detection of *Paragonimus* species immunoglobulin G (IgG) antibodies and *Paragonimus* eggs in sputum.[9–11] Once a diagnosis is made, triclabendazole is the preferred treatment regimen. In addition, educating common people, especially people in endemic areas, not to consume raw or undercooked freshwater crabs or crayfish is important. Community education (along with treatment) has been shown to be associated with a decline in seroprevalence of this infection, which highlights the importance of community education in preventing this illness.[3]

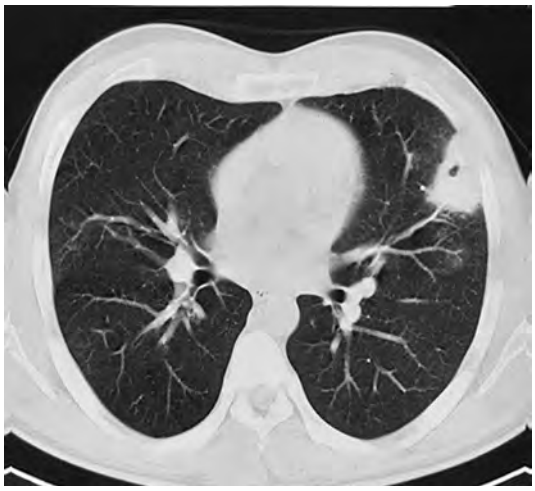
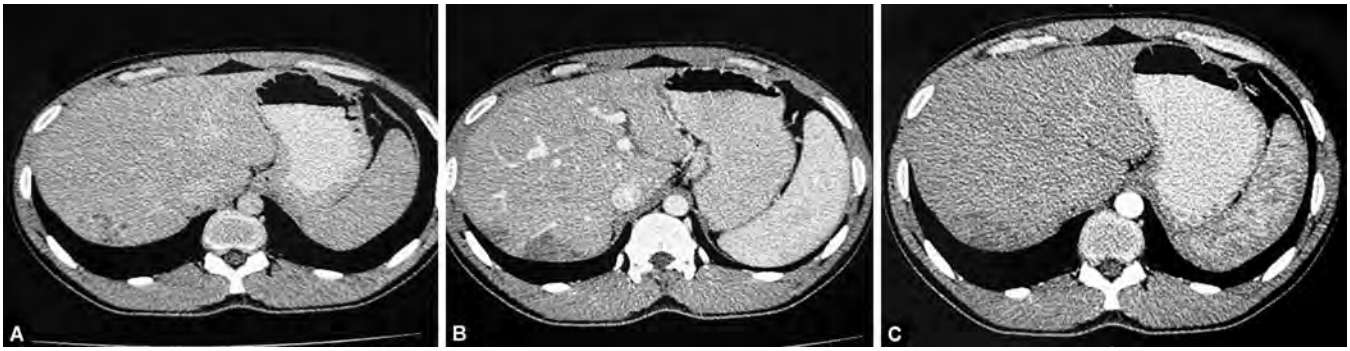


Fig. 2: Computed tomography scan of the thorax showing a thick-walled cavitary lesion



Figs 1A to C: Contrast-enhanced computed tomography scan of the abdomen: (A) Arterial phase; (B) Venous phase; (C) Delayed phase

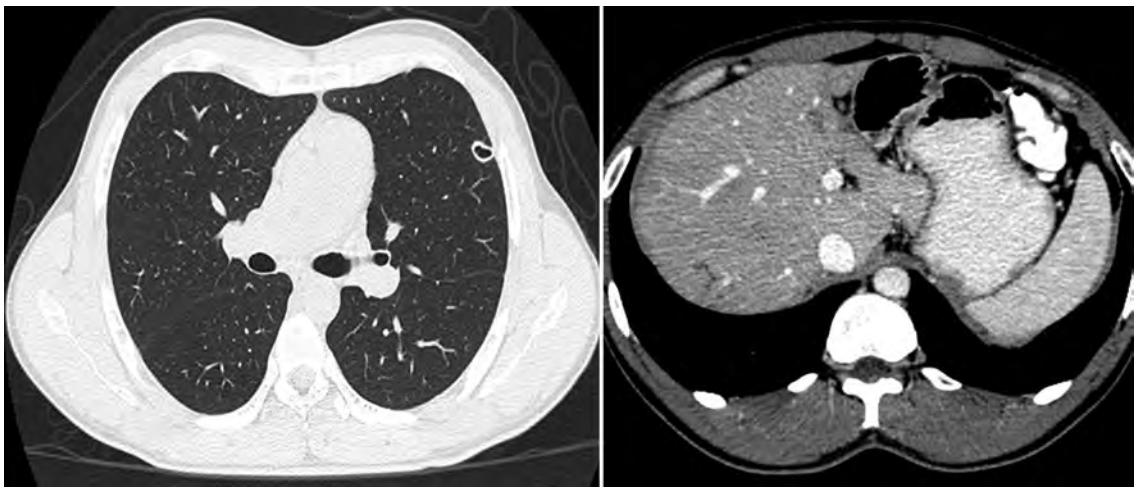


Fig. 3: Follow-up CT scans showing resolving lesions

Acknowledgments

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CASE REPORT

An Unusual Presentation of IgM Myeloma

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Abstract

Immunoglobulin M (IgM) paraproteinemia is usually associated with either lymphoplasmacytic lymphoma (LPL) or Waldenström's macroglobulinemia (WM). Manifestations due to IgM paraprotein include hyperviscosity, acquired coagulopathy, cryoglobulinemia, vasculitis, and cold antibody-mediated autoimmune hemolytic anemia. These manifestations are seen in variable percentage of patients with LPL/WM. IgM myeloma constitutes only 0.5–1% of all myeloma cases. We describe a middle-aged female who presented with 5C's: *c*ryoglobulinemia, *c*oagulopathy (acquired von Willebrand disease), *c*old autoimmune hemolytic anemia, *c*lot (thrombosis due to vasculitis), and *c*loudy vision (hyperviscosity syndrome) attributable to IgM paraprotein, but was diagnosed later with IgM myeloma. IgM is an important differential diagnosis of WM. The current case highlights such diagnostic challenges and their therapeutic considerations.

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Introduction

Multiple myeloma (MM) usually presents with end-organ damage, including CRAB features (hypercalcemia, renal failure, anemia, and bony lesion). Paraprotein subtypes in MM are IgG (52%) > IgA (21%) > light chains only (16%) > IgD (2%)/biclonal (2%). IgM myeloma constitutes only 0.5–1% of all myeloma cases.[1,2] We present a patient who presented with hyperviscosity syndrome (HVS) and other clinical manifestations due to IgM paraprotein, and was later diagnosed as IgM MM. Treatment with plasma exchange (PLEX) and anti-MM regimen reversed all her clinical and laboratory abnormalities. Diagnostic and therapeutic challenges are further discussed.

Case Description

A 35-year-old female complained of headache and bilateral visual blurring for 1 month, which was associated with heavy menstrual bleeding. She also had bluish discoloration of her fingers and toes after cold exposure for the past 2 months. Examination revealed pallor, facial puffiness, and ecchymotic spots over both legs. Fundoscopy showed bilateral grade IV papilledema. During blood sampling, her venous blood clotted immediately. Blood investigations (obtained using warm water bath) were: hemoglobin (Hb) 6 gm/dL, white cell counts 4.0×10^9/L, platelets 100×10^9/L, and corrected reticulocyte count 6%. Peripheral smear showed macrocytosis, red cell agglutination, and polychromasia. Erythrocyte sedimentation rate was 56 mm/hour. Biochemistry revealed indirect hyperbilirubinemia (total bilirubin 3.0 mg/dL and indirect fraction 2.1 mg/dL) and an elevated lactate dehydrogenase (400 U/L, normal < 250 U/L). Monospecific Coomb's test was positive for C3d, indicating cold autoimmune hemolytic anemia (cAIHA). Due to rapid clotting of blood samples, serum cryoglobulin was obtained, which was positive. Further work-up for cAIHA revealed an M band (1.48 gm/dL), IgM lambda subtype. Serum free light chain ratio was 0.13 (0.64–1.25). Serum IgM levels were 32.86 gm/L. Bone marrow aspirate revealed 30–40% plasma cells (PCs). On immunohistochemistry, PCs were positive for CD138 and CD38, and negative for CD20 and CD56 (Fig. 1). Fluorescent *in situ* hybridization (FISH) panel for MM was negative for t(4,14), t(11,14), t(14,20), t(6,16), deletion 13q, deletion 17p, and gain 1q. Lytic lesions were identified in few dorsal vertebrae on positron emission tomography-computed tomography (PET-CT) scan. MYD88 L265P mutation was negative on bone marrow aspirate. The diagnosis of IgM myeloma was considered.

The patient was worked up for the etiology of papilledema. Contrast-enhanced magnetic resonance imaging (MRI) of brain showed leptomeningeal enhancement and sluggish blood flow in the venous sinusoids. Computed tomography (CT) scan of chest and neck vessels revealed partially recanalized thrombus in the superior vena cava (SVC). Analysis of the cerebrospinal fluid including flow cytometry was negative for PC. An opinion from interventional radiology was sought for SVC stenting. Since the SVC was recanalized, stenting was not pursued. Papilledema was attributed to HVS due to IgM paraprotein.

Due to abnormal menstrual bleeding and ecchymotic patches, a coagulation profile was obtained. Her activated partial thromboplastin time (APTT) was prolonged, which corrected after 1:1 mixing with pooled plasma. Lupus anticoagulant was negative. Serum fibrinogen levels and assays for factors VIII, IX, and X were normal. Von Willebrand antigen: Activity ratio was 0.47 (35.8:17), suggesting type-2 von Willebrand disease (vWD), likely acquired von Willebrand disease (avWD). Further subclassification of type-2 vWD was not possible due to lack of laboratory facilities.

Due to grade IV papilledema, urgent PLEX using albumin was initiated. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) protocol was concurrently administered. PLEX had frequent interruptions because of membrane filter clogging as a result of cryoglobulins. Predilution and use of warm hemofiltration fluid during PLEX allowed seamless procedure. After five cycles of PLEX, her vision and headache improved significantly, and papilledema improved from grade IV to grade I. IgM levels reduced to 22.2 gm/L after two cycles and to 20.0 gm/L after five cycles of PLEX. The patient's bleeding stopped, and there was normalization of von Willebrand factor (vWF) antigen: Activity ratio (0.98). The patient was continued on CyBorD regimen. However, the patient failed to achieve partial response after four cycles of CyBorD, and she was switched to carfilzomib, lenalidomide and dexamethasone (KRD). The patient achieved stringent complete remission after four cycles of KRD, but progressed rapidly after 2 months. She was treated with BPD (bendamustine, pomalidomide, and dexamethasone) regimen, with which, she achieved a complete response. She underwent autologous stem cell transplant (ASCT) after high-dose melphalan (200 mg/m^2).

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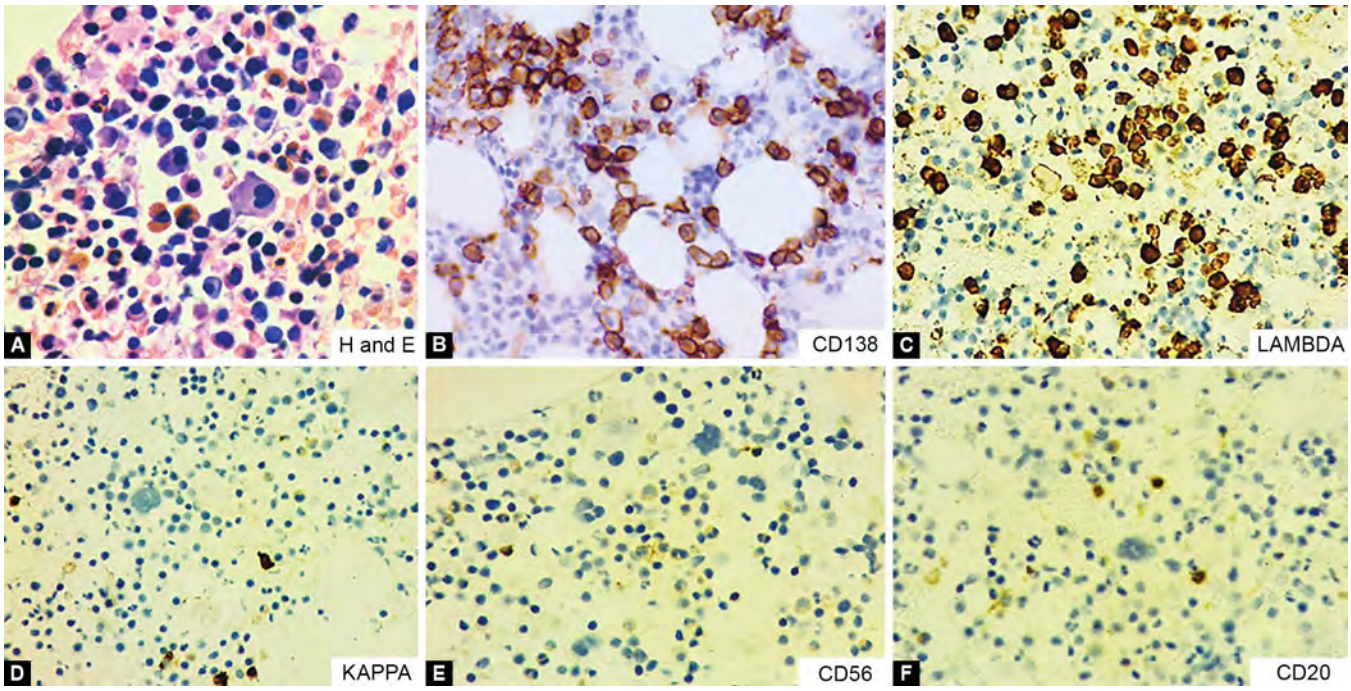

Figs 1A to F: Microphotograph of the bone marrow biopsy (1,000×) showing: (A) Interstitial as well as clusters of PCs (hematoxylin and eosin stain). (B) On immunohistochemistry, these cells were positive for CD138; (C) Lambda light chain; and (D to F) Negative for kappa light chain, CD56 and CD20

However, the patient died during ASCT due to severe sepsis.

Discussion

Hyperviscosity syndrome is defined as a triad of neurological symptoms, vision loss, and mucosal bleeding.[3] Pathologically, increased blood cells or serum proteins and altered blood cells shape could cause raised serum viscosity.[4] Hypergammaglobulinemia is the most common cause of HVS.[3] Plasma cell dyscrasias (PCD) are associated with elevated levels of monoclonal (M) proteins in the serum and/or urine.[2] Serum viscosity in these patients is a composite variable of concentration and physicochemical properties of the underlying M protein. HVS occurs at serum viscosity greater than 4 centipoises (cP) which is usually reached at M > 3 gm/dL (IgM), 4 gm/dL (IgG), and 6 gm/dL (IgA).[5] Larger size and predominant intravascular distribution of IgM are responsible for a stronger association of HVS with IgM paraproteinemia, generally Waldenström's macroglobulinemia (WM).[5,6] Up to 40% of WM patients present with HVS.[5,6] HVS is rare in MM (2–6%).[5,7]

Pathophysiology of avWD in PCD is multifactorial and includes enhanced vWF clearance resulting from autoantibodies (inhibitor) to vWF, adsorption of vWF to PC, loss of vWF multimers due to shear stress from increased serum viscosity (IgM disorders), and binding of vWF to nonspecific antibodies.[8] In the International Society of Thrombosis and Hemostasis (ISTH) database, about 48% cases of avWD had an underlying lymphoproliferative disorder, most commonly monoclonal gammopathy of undetermined significance (MGUS) (23%), followed by MM (9%), WM (9%), non-Hodgkin lymphoma (NHL) (4%), and chronic lymphocytic leukemia (CLL) (3%).[9] Around 2–4% of avWD was attributed to lymphoplasmacytic lymphoma (LPL), and 13% of LPL cases had associated avWD.[10,11] The prevalence of avWD in WM and MM each has been reported as 15%.[12,13] Majority of MM with avWD had IgG subtype, or rarely IgA subtype.[13,14] Association of avWD with IgM MM is extremely uncommon. In our case, avWD resolved after five sessions of PLEX and anti-MM therapy, implicating a direct causal association of IgM paraprotein in its pathophysiology.

Cryoglobulins are immune complexes that precipitate at cold temperatures and dissolve after rewarming. The immune complexes are monoclonal (type-1 cryoglobulins) in PCD.[15] Overall, about 6–10% of patients with cryoglobulins are diagnosed with MM.[16] Among MM patients, cryoglobulins are usually associated with IgG paraprotein and less commonly with IgM and IgA subtypes. In a series of 7 patients with type-1 cryoglobulinemia and MM, 6 had IgG MM and only 1 had IgM MM.[17] Our patient had type-1 cryoglobulinemia associated with IgM lambda, which caused blood clotting during venous sampling, clogging of plasma filters during PLEX, and possibly SVC thrombosis due to vasculitis. Use of preheated syringes and warm water bath for sample transport allowed us to perform laboratory studies.[18] Predilution and the use of warm hemofiltration fluid allowed for smooth PLEX in our patient as previously reported.[19,20]

Cold AIHA is a hemolytic anemia manifesting during cold temperatures due to binding of autoantibodies, usually IgM to the red cells, resulting in predominantly intravascular hemolysis as a result of complement activation.[21] cAIHA could be primary (also known as cold agglutinin disease), due to low-grade monoclonal lymphoproliferative disorder in bone marrow, LPL, marginal zone lymphoma (MZL), or secondary, due to aggressive malignancy (other than LPL/MZL) and infections.[22] cAIHA due to MM is uncommon. In a large multicenter study, out of 232 patients with coronary artery disease (CAD), only one (0.4%) patient was diagnosed with MM.[23] Very few cases of cAIHA with MM have been reported, and none of them have IgM MM.[24–26] Treatment of IgM-associated cAIHA due to B cell or lymphoplasmacytic cell-mediated clonal disease is generally rituximab-based chemoimmunotherapy.[21] However, our patient had PC-mediated cAIHA, which responded to anti-MM therapy.

Immunoglobulin M MM is a rare hematological malignancy presenting like other MM with hypercalcemia, renal failure, anemia, and bone lesion. Rarely, it may present as lymphadenopathy, organomegaly,

and hyperviscosity symptoms.[27] WM is the most important differential of IgM MM and should be ruled out because of therapeutic and prognostic considerations. Distinguishing IgM MM from WM is challenging because of overlapping clinical presentations. WM is characterized by lymphoplasmacytic infiltrate in the bone marrow ($CD20^+$, $CD38^+$, and $CD138^+$), absence of bone lesions and t(11,14) and presence of MYD88 L265P mutation in 90% of cases.[27–29] The presence of lytic bone lesions, clonal PC ($CD20^-$, $CD38^+$, and $CD138^+$), and absence of MYD88 L265P mutation supported the diagnosis of MM in our case.

Conclusion

Immunoglobulin M MM is a rare hematological malignancy that clinically overlaps with WM. Therapeutically, it is crucial to distinguish IgM MM from WM using a combination of immunophenotyping, lytic bone lesions, FISH for *t*(11:14), molecular study for MYD88 L265P mutation and CXCR4 mutation. PLEX is crucial and should be done immediately for patients with papilledema for immediate relief of vision loss.

Conflict of Interest

None.

Funding

None.

Consent

The authors state that a written and informed consent was taken from the patient prior to publication of any material pertaining to her case. The consent was obtained before her death, while she was undergoing her treatment.

Author Contributions

AJ and PG wrote the draft. AJG provided the histopathology images of the patient's bone marrow biopsy. AJ, PG, and SC managed the case. All authors reviewed the final draft before submission.

Artificial Intelligence

The authors of this manuscript state that no AI-based tool was used in drafting this paper.

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CASE REPORT

A Case Series of Dengue Fever with Unusual Presentation and Complications in a Rural Hospital

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Abstract

Background: One of the most dangerous arboviral infections in the world is dengue. There are four significant serotypes for epidemiology. Dengue hemorrhagic fever (DHF) and dengue fever (DF) are the two clinical spectrums indicated by the classification. The majority of cases are stereotyped and take well to fluid resuscitation. Strange clinical manifestations, however, were frequently overlooked and led to mortality. Six of these dengue cases were treated in a rural tertiary care facility for a year, and after receiving problem-based curative therapy, all of the cases recovered fully.

Case description: During the midyear dengue epidemic in 2022, all six patients arrived at the rural tertiary care center located in southern India. There are two females and four males, with a mean age of 30 (range: 19–59). Three DHF, one DF, one dengue shock syndrome (DSS), and two original dengue infections were included in this investigation; most patients experienced significant gastrointestinal bleeding. Additional potentially fatal conditions included myocarditis, unpredictable rapid plasma leak, acute severe hepatitis, severe septic shock, cerebral hemorrhage, diarrhea, and decompensated dengue shock brought on by a third-space fluid leak. In addition to patient-specific proper fluid management, other empirical treatment approaches, such as blood transfusions, were employed. Early identification of the key phase was aided by bedside ultrasound screening. In all six cases, the patients fully recovered.

Conclusion: Even now, treating dengue remains one of the world's most difficult infections. Given the extremely narrow treatment window, the aforementioned atypical presentations and consequences could be lethal if not identified early. These are not uncommon issues that go unreported and are frequently disregarded, so clinicians must be aware of them. To enhance medical research and improve care in rural areas, every patient's clinical management was documented for knowledge sharing.

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Introduction

Dengue is the most common arboviral infection in India. Dengue virus has four related but antigenically distinct serotypes: dengue virus serotype 1 (DENV-1), DENV-2, DENV-3, and DENV-4.[1] The global burden of dengue has increased in recent decades, causing huge impact on both human health and the national economies.[1–3] Dengue infection has a diverse clinical presentation ranging from asymptomatic subclinical infection to severe multi-organ involvement.[3] Although vascular plasma leak is the most common manifestation, dengue can manifest in a multitude of unusual presentations due to organ dysfunction that can carry high mortality.[2,3] Early detection of such manifestations and prompt action could avert the adverse outcome, where clinicians need knowledge and experience. The aim of this case series is to present six such unusual dengue cases.

Case 1 (Myocarditis and Dengue Hemorrhagic Fever Co-occuring with Dengue Virus Serotype 1)

A previously healthy 19-year-old woman complained of having a fever for 2 days along with nausea and body aches. She showed no signs of bleeding, postural problems, or stomach pain. On inspection, she was not pale or icteric, but rather flushed and febrile. She had slight dehydration. The capillary refill time (CRT) was <2 seconds, with blood pressure recorded at 100/70 mm Hg and heart rate at 100 beats per minute. No free fluid was detected in the abdominal examination. There were clear areas of the lungs noted on respiratory system assessment. Examining other systems revealed nothing unusual. Her serotype was determined to be DENV-1 after her NS1 antigen test was positive. She received round-the-clock medical attention for dengue illness. She reported experiencing retrosternal chest pain and excessive fatigue on the 3rd day of the fever. At that time, the electrocardiogram (ECG) showed acute T wave inversion in V2–V5 leads. During that time, her cardiovascular system evaluation was normal. The 2D echo showed diffusely hypokinetic changes of the left ventricle and moderate level of LV function deterioration, while troponin I was negative. Her condition was diagnosed as complex myocarditis related to dengue fever (DF). For 2 days, she received intravenous hydrocortisone at a dosage of 200 mg every 8 hours to reduce myocardial inflammation. On the 4th day after her admission, she complained of stomach pain, and an ultrasound scan revealed free fluid in the hepatorenal pouch. At that time, her heart rate was 70 beats per minute, her blood pressure was 100/70 mm Hg, and her CRT was <2 seconds. She was subsequently admitted to the intensive care unit (ICU) for treatment of dengue hemorrhagic fever (DHF), which had been complicated by myocarditis, under strict observation.

Case 2 (Unpredictable Fast Plasma Leak during the Early Critical Period)

A 28-year-old male presented with a 1-day history of fever, followed by a 3-day frontal headache. He was admitted with symptoms including arthralgia, myalgia, minor postural

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dizziness, and nausea. He reported passing a normal amount of urine. Upon examination, he was hemodynamically stable, with a blood pressure reading of 96/64 mm Hg and no postural decline. The abdomen was supple and nontender. Clinically, there were no signs of plasma leakage. A blood test for dengue NS1 antigen returned positive. On the 3rd day of fever, an abdominal ultrasound revealed a thin rim of free fluid in the hepatorenal pouch, moderate edema of the gallbladder wall, and minor pericholecystic fluid. There were no pleural effusions or ascites noted. Additionally, he did not exhibit any postural decline in blood pressure, tachycardia, or right upper quadrant discomfort. However, his hematocrit had increased from 33 to 38%. Within 6 hours, he had considerable ascites (moderate) and bilateral moderate pleural effusions, as well as decreased urine production. He experienced fluctuating urine output and blood pressure, necessitating multiple boluses of normal saline, Dextran-40, and furosemide to maintain stable vital signs. Sixty percent of his predicted fluid allotment was used in the first 12 hours of the critical phase. His medical condition steadily improved over the next 3 days. However, effusion and ascites were not resolved quickly. His serum albumin level decreased throughout the crucial phase and needed several days to recover. His rehabilitation was uneventful, and he was discharged from the hospital on day 6. He experienced unpredictable fast leakage of plasma into serous cavity during the critical phase.

Case 3 (Occult Undiscovered Decompensated Shock Due to Plasma Leakage)

A previously healthy 49-year-old female was admitted with a history of a febrile illness accompanied by arthralgia and myalgia lasting 4 days. On admission, her NS1 antigen test was positive. She appeared ill, complaining of postural dizziness and abdominal pain.

During the examination, she appeared dehydrated, with bluish cold peripheries, central cyanosis, and collapsed superficial veins. Her supine blood pressure was recorded at 90/80 mm Hg, and her standing blood pressure could not be measured due to severe postural symptoms. The CRT was prolonged, and her respiratory rate was 24 breaths per minute. Lung examination revealed clear sounds, and there was no clinical evidence of free fluid in the abdomen or pleura. Notably, she had not passed urine for the previous 12 hours.

She was clinically diagnosed with DHF and decompensated shock. Consequently, she was admitted to the ICU, where critical phase management was initiated. An initial ultrasound scan of the abdomen did not reveal free fluid in the peritoneal cavity, despite the patient possibly being in the peak phase of plasma leakage. However, 12 hours after admission, a repeat ultrasound scan showed a thin rim of free fluid in the hepatorenal pouch. She was subsequently resuscitated with boluses of crystalloids and colloids. After gaining warm peripheries over the course of roughly 8 hours, she gradually became hemodynamically stable. Her symptoms subsided in the following 2 days as long as fluid control and monitoring were maintained. During the later stage of the leak, she had the least amount of measurable free fluid in her abdomen, despite going into decompensated shock owing to DHF.

Case 4 (Intracerebral Hemorrhage in Dengue Hemorrhagic Fever Dengue Virus Serotype 2)

A 21-year-old male patient was hospitalized at our center 5 days ago with arthralgia and myalgia as part of a febrile illness. The patient experienced a fainting attack with postural dizziness that affected his forehead while traveling to the hospital. He experienced postictal tiredness shortly after being admitted, and he experienced a 5-minute-long generalized tonic–clonic seizure. Upon examination, he showed signs of conjunctival hemorrhages but was not pale. The fall had left him with a bruise across his forehead. He had no clinical signs of plasma leakage and was hemodynamically stable, with a blood pressure of 126/90 mm Hg and a pulse rate of 92 beats per minute. An abdominal ultrasound revealed a small ring of free fluid. Dengue tests indicated positive results for IgM, NS1 antigen, and IgG. The dengue serotype was identified as DENV-2. Based on these findings, a diagnosis of DHF entering a critical phase was made. Strict monitoring commenced, along with the appropriate administration of intravenous and oral fluids. In the meantime, no lateralizing neurological abnormalities were discovered, and the patient was determined to be arousable but sleepy. There was no abnormality in either optic fundus. A noncontrast computed tomography (CT) scan of the brain showed little midline shift, bilateral frontal lobe hyperdense regions, and mild cerebral edema, all of which were suggestive of intracranial hemorrhages. His clotting characteristics were within the typical ranges. To maintain a platelet count >50 $\times$ 10^6/L, he had a platelet transfusion. The careful administration of antiepileptic drugs, intravenous antibiotics, and adequate intravenous fluids was observed. He was initially given phenytoin sodium intravenously but eventually switched to oral phenytoin. Intravenous dexamethasone and mannitol were used to treat cerebral edema. Intravenous tranexamic acid was given to him in order to stop the bleeding from continuing. It was a quiet critical phase. After taking oral antiepileptics for 5 days, his headache and fatigue subsided.

Case 5 (Symptomatic Compensated Shock and Dysentery in Dengue Hemorrhagic Fever)

A 36-year-old man who had been well before now appeared with a 4-day history of fever and widespread malaise. His primary complaints were of the same length: diarrhea and vomiting. At presentation, he did not show any signs of bleeding symptoms, postural problems, or stomach pain. He was found to be febrile and not pallid or icteric upon inspection. With a CRT of 2 seconds, his heart rate was 110 beats per minute, and his blood pressure was recorded at 120/100 mm Hg. Bilateral pleural effusion was seen during the evaluation of the respiratory system, and shifting dullness was found during the abdominal examination. The evaluation of the other systems revealed normal findings. An ultrasound examination of the abdomen indicated a moderate amount of free fluid. Urine and blood samples were collected for analysis. His serotype was determined to be DENV-2, and his NS1 antigen tested positive. The patient was immediately admitted to the intensive care unit and treated for compensatory shock caused by DHF. Total leukocyte count (2.1×10^3 cells/mm^3), platelet count (15×10^9/L), serum glutamic-oxaloacetic transaminase (SGOT) (IU/L) 87, serum glutamic-pyruvic transaminase (SGPT) (IU/L) 59, prothrombin time (seconds) 13.8 with international normalized ratio (INR) 1, and hematocrit (57%), according to preliminary studies. He recovered with careful fluid management. As a result, this patient presented at the height of the critical period with a clinical picture of dysentery related to DHF.

Case 6 (Hepatitis and Acute Gastrointestinal Hemorrhage in Dengue Fever)

A 32-year-old male patient, previously healthy, was admitted with a 10-day history of intermittent fever and three episodes of

hematemesis (vomiting blood) and melena (black, tarry stools). Upon examination, his lungs were normal, but he presented with low blood pressure (90/60 mm Hg) and a pulse rate of 88 beats per minute. His CRT was <2 seconds. There was no visible free fluid in the abdomen, which felt soft and mushy. The remainder of the physical examination was unremarkable. At admission, serology results for dengue showed positive IgM and IgG antibodies. He also exhibited elevated liver enzymes (ALT 560 U/L and AST 840 U/L) and a high INR of 2.1. His complete blood count revealed a hemoglobin level of 11.5 gm/dL and a platelet count of 144 × 10^9/L. DHF was ruled out after an abdominal ultrasound showed no signs of leakage. As a result, the patient was treated as though he had primary DF with bleeding symptoms. To stop the bleeding, tranexamic acid and vitamin K were administered intravenously. Omeprazole was infused intravenously for a full day before being switched to twice-daily intravenous boluses. As his liver transaminases were elevated, he was put on an intravenous N-acetylcysteine infusion. After a few days, his symptoms settled with symptomatic treatment.

Discussion and Conclusion

These six confirmed dengue cases in our case series, all of which occurred in a rural center and had a wide range of atypical manifestations that could be fatal, are summarized. During 2022, each of these patients is seen. Out of the total patients in these cases, three had DHF and there were five males and one female. Two of the six patients experienced significant gastrointestinal bleeding, while the other patient first thought they had dengue shock syndrome (DSS) but instead experienced severe septic shock. The emphasized other atypical signs are decompensated shock, intracerebral hemorrhage (ICH), myocardial inflammation, abnormal plasma leak, liver failure, and occult blood loss. All lives were spared because of the early identification of these symptoms and the proper therapeutic judgments made regarding blood transfusions, antibiotics, and other empirical treatments. Most of these dengue infection symptoms are either not associated with the disease, are not well understood, or are not reported. The majority of these dengue infection symptoms are either not causally related to DF or are underreported or misdiagnosed. Thus, beyond the most prevalent stable form of plasma leak in DHF, controlling dengue requires alertness and preparation.

DHF and its symptoms can lead to catastrophic events such as liver failure. Some of the complications include issues with muscles such as myositis, and even severe kidney damage and cardiac conditions,[3–6] In addition, some patients may also suffer from intracranial bleeding and other harmful forms of life-threatening bleeding.[7] There is also the possibility of endocrine complications, like the triggering of diabetic metabolic ketoacidosis.[8] Among the life-threatening complications of DF and DHF, Guillain–Barré syndrome and encephalopathy are the most well-known.[9] Reducing morbidity and mortality in such circumstances requires early identification and prompt application of suitable therapeutic techniques. Over time, a deeper comprehension of the mechanics of the disease has improved the prognosis, although prompt identification and treatment remain difficult. It is still hard to achieve appropriate diagnosis and treatment, even with an improved understanding of the disease over time.

This case series includes cases of DF, DHF, and primary dengue infection, all of which have peculiar symptoms. Earlier dengue infection and DF without leakage were associated with some potentially lethal sequelae.

While Case 6 had DF, Cases 1, 4, and 5 patients experienced DHF. While the others experienced the previously listed problems, some showed signs of bleeding. A wide range of clinical manifestations, from an infection with no symptoms to a straightforward, nondifferentiated fever to DHF with multiple organ failure, can be seen in dengue patients. Enhanced capillary permeability and fluid extravasation are key characteristics of DHF during the critical phase. Pleural effusion, ascites, and signs of hemoconcentration, such as elevated hematocrit levels, are indicators of the beginning of this phase.[3,10] The critical phase typically lasts 24–48 hours, marked by a progressive increase and subsequent decrease in plasma leak rate.[3,11] However, there are cases where this typical pattern is not observed, such as in the young man in Case 2 who experienced an unpredictable plasma leak leading to rapid development of pleural effusions and ascites within the first 12 hours. Early detection and regular monitoring of these unpredictable cases are crucial for appropriate treatment. The same patient required some time to absorb the fluid after it was leaking into the pleural and peritoneal areas and had hypoalbuminemia. Case 3 details a female patient who showed signs of decompensated shock. Her hematocrit was high, indicating hemoconcentration. However, upon clinical and ultrasonographic presentation, she lacked objective evidence of plasma leakage into serous cavities. This demonstrates that even while plasma leak is said to be limited to the pericardial, pleural, and peritoneal cavities, significant amounts of fluid can nevertheless leak into third spaces at unidentified spots. When there is evidence of intravascular volume depletion and hemoconcentration, the treating physician should diagnose DHF without waiting for an observable fluid leak. On the other hand, routine ultrasound scanning has improved the early identification of complications. Nonetheless, regular ultrasound examinations have improved the early identification of plasma leaks. A well-established characteristic of both DHF and DF is liver dysfunction. Individuals suffering from DF who report experiencing nausea, vomiting, anorexia, and abdominal pain should notify their doctor about the potential involvement of their liver.[12] The etiopathogenesis of DF's liver dysfunction is still unknown. Various mechanisms have been proposed to explain liver dysfunction, including direct effects of the virus or host immune response on liver cells, circulatory compromise, metabolic acidosis, and/or hypoxia caused by hypotension or localized vascular leakage inside the liver.[13,14] In Case 6, a patient with nonleaking DF develops coagulopathy, gastrointestinal bleeding, and liver dysfunction. Both cases were effectively treated with intravenous N-acetyl cysteine and proper hydration maintenance. It functions as a vasodilator to enhance oxygen delivery and consumption, scavenges free radicals, and strengthens antioxidant defense.[15] Further research is necessary to validate the effectiveness of NAC, though. Both DF and DHF can cause bleeding symptoms. Despite the name, leaking—rather than hemorrhage—is the primary characteristic that sets DF apart from DHF. It is still unclear what underlying mechanisms cause bleeding during dengue infections. Thrombocytopenia affects all DHF patients as well as the majority of DF patients.[16] A rare but serious side effect of DF is intracranial hemorrhage. Although the exact cause of intracranial bleeding is still unknown, coagulopathy, platelet dysfunction, thrombocytopenia, and vasculopathy may interact to cause it.[17,18] Our patient, who was mentioned in Case 3, had postural symptoms and was at the peak of leakage. His platelet count was 16 × 10^9/μL upon admission. He had a history of head injuries from falls, and shortly after being admitted, the patient experienced a generalized tonic–clonic seizure. Afterward, it was discovered that he had hemorrhages in both frontal lobes. This might have been the result of something spontaneous that led to

the fall, or it could have been traumatizing after the fall.

Since the underlying causes, such as vasculopathy and platelet dysfunction, are typically still present and irreversible during surgery, managing an ICH in a dengue patient is debatable. Studies on the use of surgery for ICH in DF cases have not been conducted.

In DF, low platelets are the primary risk factor for an ICH. Regarding the timing of primary prophylaxis and platelet transfusion, opinions differ. Prophylactic platelet transfusions have been advised in certain studies when the platelet count is extremely low.[19,20] Since the platelet count was extremely low, our patient underwent a platelet transfusion as a secondary preventive measure.

DHF and DF are linked to a variety of cardiac complications. An abnormal ECG was found in 62.5% of 120 adults with DF, according to research by Kularatne et al.[21] Because the majority of cardiac complications are self-limiting and clinically mild, they are often underdiagnosed.[22] Although the exact cause of dengue's myocardial involvement is unknown, it may result from either cytokine-mediated immune damage or direct viral invasion of the myocardium.[23]

In Case 1, the young patient displayed global hypokinesia in the left ventricle on the 2D echo and myocarditis on the ECG. She received careful fluid management, a brief course of steroids, and conservative treatment. Steroids may theoretically aid in lowering myocardial inflammation and enhancing contractility. Her 2-week follow-up echo revealed that her left ventricular systolic function had returned to normal. Case 5 describes how dengue primarily manifests as diarrhea. We should discuss the lessons we've learned from handling challenging dengue cases. Dengue is generally prevalent worldwide, so similar cases or circumstances could be occurring at any given time. Dengue pathology and pathophysiology still require further research, but these clinical observations need an explanation based on pathophysiological principles. To improve the prognosis of dengue, more effective treatment alternatives are required, which could mislead a clinician into believing that the patient has bacillary dysentery.

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CASE REPORT

Interesting Case of Celphos Poisoning with G6PD Deficiency: Is There a Correlation?

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Abstract

Celphos poisoning is one of the common poisonings in agricultural countries such as India, mainly in rural areas. Its clinical manifestations vary depending on the amount of poison consumed and the time since ingestion. It has a very high fatality rate. As of now, there is no specific antidote available for this poisoning. Its management includes intensive monitoring along with immediate initiation of supportive care. It is associated with multisystem involvement with multiorgan failure in severe cases, but hematological complications are not very common. Here, we present a successfully treated case of a young male with accidental consumption of Celphos poison with delayed presentation to a tertiary health care center. His clinical features were suggestive of hemolysis. On further evaluation, he was found to have glucose-6-phosphate dehydrogenase (G6PD) deficiency.

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Introduction

Celphos [aluminum phosphide (ALP)] is a fumigant pesticide regularly used by farmers in agricultural countries for the storage of cereal grains. Despite its highly toxic nature, it is widely used and an easily available pesticide. Its fatality rate varies from 40 to 80% according to previously published data in the literature.[1] It is used in India under the name of Celphos or rice tablets. It comes in tablet form, each tablet weighing 3 gm with a fatal dose of between 150 and 500 µg. After ingestion, it releases phosphine gas which causes noncompetitive inhibition of the electron transport chain in cytochrome oxidase, leading to diffuse cellular hypoxia.[2] Its symptoms vary from nausea, vomiting, palpitations, and abdominal discomfort in mild cases to serious organ failure in moderate and severe poisoning, including hepatic and renal failure with associated multisystem involvement.[3] The time period between consumption and death depends on the severity of poisoning.

Here, we present a case of a successfully treated 35-year-old male patient with Celphos poisoning and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Case Description

A 35-year-old male patient with no significant past history was brought to the hospital with an alleged history of accidental consumption of Celphos (ALP) on his farm in the morning. Within 6 hours, he started developing breathlessness, yellowish discoloration of eyes, and abdominal pain. He was admitted to a Government Hospital, at his local place within 3 hours, received primary treatment and gastric lavage, and then relatives brought him to the tertiary care center on the 3rd day.

On admission, he was afebrile, with normal pulse and blood pressure, respiratory rate was 40/minute, and oxygen saturation was 88% on room air. Icterus and pallor were present. On chest auscultation, bilateral crepitations were present in the bilateral infrascapular regions. On abdominal examination, it was distended and associated with tenderness in the right hypochondriac region. His arterial blood gas (ABG) showed pH—7.425, pCO_2—31.2, pO_2—214, HCO_3—20, SpO_2—89%, lactate—2.7, Na—134, and K—4.3. Due to SpO_2 and PaO_2 dissociation, methemoglobin levels were checked which were 4%. Electrocardiography (ECG) was suggestive of sinus rhythm.

In view of breathlessness, oxygen support was initiated, and all the relevant investigations were sent in which blood investigations showed anemia (hemoglobin 7.8 gm/dL) and raised total leukocyte counts (TLCs) 26440/mm^3, while platelet counts were normal. Renal function test showed creatinine 0.3 mg/dL, urea 59 mg/dL. Liver function test was deranged (total bilirubin 13.100 mg/dL, direct 2.220 mg/dL, SGOT 134 U/L, and SGPT 44 U/L), suggestive of active ongoing hemolysis. Prothrombin time was 13.6 and INR 1.28. Glycosylated hemoglobin was also raised to 8.4%. NTproBNP was also raised to 328 pg/mL. Serum CK-MB was normal. His high-resolution computed tomography (HRCT) of the chest was suggestive of minimal left pleural effusion with basal atelectasis, and also noted a few atelectasis changes in the right middle lobe and lower lobe with mild ground glass opacities. CT abdomen showed fatty infiltration of the liver, mild splenomegaly with minimal perisplenic fat stranding. His 2D echo was normal with a left ventricular ejection fraction of 60%.

Serial investigations monitoring was done (refer to Table 1).

Based on investigation and examination, he was started on intravenous antibiotics (meropenem), hepatoprotective drugs (ursodeoxycholic acid), antioxidants such as *N*-acetyl cysteine (NAC) infusion and glutathione, antipyretics, analgesics, multivitamins (vitamin C, pyridoxine), and intravenous fluid. Electrolyte imbalance was corrected accordingly. His urine was reddish—cola-colored. His urine routine showed raised glucose and red blood cells (RBCs) (250/µL). In view of suspected hemolysis, serum lactate dehydrogenase (LDH) was sent, which came back elevated at 2475 U/L. Peripheral smear showed predominantly macrocytic hypochromic RBCs with no hemoparasite. His G6PD level was 4.20, suggestive of G6PD deficiency. Coombs test was negative. This was a rare case of Celphos poisoning which presented as hyperbilirubinemia and methemoglobinemia with hemolysis. The patient gradually improved with supportive care and was discharged in a stable condition.

Discussion

Glucose-6-phosphate dehydrogenase deficiency is a genetic disorder that affects RBCs, causing their premature destruction. G6PD is an X-linked enzyme that acts as a catalyst in the hexose monophosphate (HMP) shunt pathway. In the HMP pathway, 6-phosphogluconolactone is produced from glucose-6-phosphate with the help of G6PD enzyme, generating nicotinamide adenine dinucleotide phosphate (NADPH).

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Table 1: Serial investigations monitoring

Day of stay	1	2	3	4	5	7	9
WBC	26,440	27,760	18,630	12,870	9,760	5,720	5,250
Hb	7.8	7.1	6.9	8.3	7.8	8.0	8.1
Blood transfusion	–	1 PRC	1 PRC	–	–	–	–
Platelets	2,41,000	2,15,000	1,60,000	1,37,000	1,36,000	2,09,000	3,29,000
Bilirubin	13.1	–	5	3.35	2.0	1.1	0.89
Direct	2.2	–	1.16	0.96	0.81	0.63	0.52
Indirect	10.8	–	3.84	2.39	1.19	0.47	0.37
SGOT	134	–	88	36	21	22	17
SGPT	44	–	34	31	25	25	21
ALP	112	–	73	69	64	–	72
Prothrombin time	13.6	–	12.3	–	–	–	–
INR	1.28	–	1.16	–	–	–	–
LDH	–	–	2,476	–	–	–	–

This NADPH is required to maintain reduced glutathione, which protects RBCs from oxidative damage. The most common clinical feature of this disorder is drug-induced hemolytic anemia, especially in adults.[4]

Many patients with G6PD deficiency are asymptomatic in the steady state. However, after exposure to trigger factors such as various medications, poisons, infections, fava beans, and metabolic abnormalities, hemolysis occurs, causing anemia, hematuria, and hemoglobinuria.[5]

In case of Celphos poisoning, hemolysis is a rare complication. In healthy individuals, after *in vitro* incubation of erythrocytes with phosphine gas, no hemolysis was found.[6] The icterus in Celphos poisoning may be due to reduced liver perfusion, causing direct damage or due to indirect hyperbilirubinemia, as in this case, caused by hemolysis.[7] On the other hand, Celphos may act as a trigger factor for hemolysis in G6PD-deficient individuals.

As we know, Celphos poisoning is usually fatal in most cases due to the lack of a specific antidote. In our case, the patient survived; he presented 3 days after ingestion with minimal left-sided pleural effusion, mild splenomegaly, indirect hyperbilirubinemia, mild methemoglobinemia, and reddish cola-colored urine due to hemolysis, and was incidentally found to have G6PD deficiency.

After reviewing the literature, only four cases of G6PD deficiency with Celphos poisoning were reported,[5,8–10] and surprisingly, all the patients survived. This suggests that G6PD deficiency might have a protective action against Celphos poisoning to confer a protective effect, potentially mitigating complications. This effect is also known as the paradoxical protective effect. In individuals with G6PD deficiency, the increased oxidative stress from ALP poisoning might paradoxically lead to hemolysis (RBC destruction), which could limit the systemic distribution of toxic by-products of ALP, potentially mitigating the severity of the poisoning.

Conclusion

As there is no specific antidote for Celphos, there are high mortality rates among patients. All possible alternative measures should be explored to save them.

The above case indicates that a strong suspicion of G6PD deficiency should be considered in case of hemolysis post-Celphos poisoning. On the other hand, since all the reported cases of G6PD deficiency with Celphos poisoning survived unexpectedly, further research should be conducted to explore the potential for reducing fatality in Celphos poisoning by discovering agents that can temporarily induce G6PD deficiency.

The possible potential protective mechanisms include:

- Reduced activation of toxic phosphine intermediates due to lower cellular activity.
- Chronic adaptation to oxidative stress, enhancing alternative antioxidant defenses.
- Lower metabolic activity, reducing the impact of phosphine gas.
- Attenuated inflammatory response due to altered reactive oxygen species (ROS).
- Altered or reduced cardiotoxic effects, particularly in myocardial cells.

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CASE REPORT

Takayasu Arteritis with Fistulizing Crohn's Disease: A Rare Presentation

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Abstract

Crohn's disease (CD) is a chronic, recurrent, transmural inflammatory disease with lesions anywhere in the gastrointestinal (GI) tract. Takayasu arteritis (TA) is an idiopathic, chronic, granulomatous inflammatory panarteritis that involves the aorta and its branches, known as "pulseless disease."

Crohn's disease and TA are both associated, as both are granulomatous disorders, and multiple cases of simultaneous occurrence of both diseases have been reported.

Here we are reporting a rare case of simultaneous CD and TA in a young female who had a large enteroenteric fistula between the colon and jejunum and total occlusion of both subclavian arteries with reformed collaterals. The patient was managed with IV antibiotic, IV fluid, and steroid. This unique presentation underscores the importance of considering a potential association between the two conditions in patients presenting with GI symptoms and vascular symptoms.

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Introduction

Crohn's disease (CD) is characterized by chronic, relapsing, transmural inflammation, and skip lesions that can occur in any part of the gastrointestinal (GI) tract, which causes long-standing abdominal pain, loose stools, intestinal obstruction, and lesions around the anus.[1]

Inflammatory bowel disease (IBD) can be associated with different types of vasculitis, among which large vessel vasculitis is likely to be the most common, but it is also associated with cutaneous vasculitis and antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis.[2]

Takayasu arteritis (TA) is a rare, idiopathic, and chronic inflammatory condition characterized by granulomatous inflammation affecting the aorta and its primary branches. It generally manifests in individuals below 40 years. A notable clinical feature is the absence of pulses in the upper limbs, leading to its other name, "pulseless disease."[3]

The pathogenesis of TA and CD remains unclear, but there is a plausible commonality in their pathogenic mechanisms. Both diseases involve granulomatous inflammation, which suggests a shared underlying pathophysiological process characterized by cell-mediated injury. This similarity implies that their cooccurrence is likely more than coincidental.[4,5]

Here we present a case of simultaneous CD and TA in a young female. The patient had an enterocolic fistula. Previously, only two cases of a similar combination have been reported from India.[6,7] Our case is unique, as there was a large fistulous communication between the colon and jejunum.

Case Description

A 35-year-old female presented with acute abdominal pain, vomiting, constipation, and fever for the last 4 days. On general physical examination, peripheral pulses (radial and brachial) of both upper limbs were not palpable, while the pulses of the lower limbs (femoral, popliteal, and dorsalis pedis) were palpable. Upper limb blood pressure was nonrecordable, while lower limb blood pressure was 110/76 mm Hg. On investigations, the patient was diagnosed with subacute intestinal obstruction. The patient also had a history of similar episodes of abdominal pain for the last 6 years, which were managed at a primary health center with intravenous fluids and antibiotics. About 8 years ago, the patient also had a history of episodic bloody diarrhea with pus discharge, which lasted for 2 years.

The laboratory results showed TLC 19470/µL, Hb 9.6 gm/dL, platelet count 2.5 lakh/µL, and ESR 80 mm/hour. Computed tomography (CT) aortography revealed total occlusion of both distal subclavian arteries with reformed collaterals from branches of the proximal subclavian artery and internal mammary artery on both sides (Fig. 1). Echocardiography was normal.

On colonoscopy, there was an ulcerated stricture at 20 cm from the anal verge through which the scope was easily negotiable. At 28 cm, there was a pseudopolyp with multiple longitudinal mucosal ulcers in the descending colon. A fistulous track was seen in the transverse colon, which appeared to be connected to the small bowel. There was complete loss of haustration in the transverse colon (Figs 2A to C). Multiple biopsies were taken, which revealed noncaseating granulomas with lymphoplasmacytic inflammation, focal cryptitis, and crypt abscesses (Fig. 3).

Contrast-enhanced CT abdomen and enterography with rectal contrast was done to delineate the fistula, which showed communication between the transverse colon and proximal jejunal loops. It also revealed edematous thickening in the entire colon with significant mucosal enhancement and loss of haustrations. A small collection was seen containing an air-fluid level, showing peripheral enhancement along the greater curvature in the left hypochondriac region (Figs 4A to D).

According to the above findings, the patient was diagnosed with Crohn's disease along with TA. The patient was managed conservatively with intravenous antibiotics,

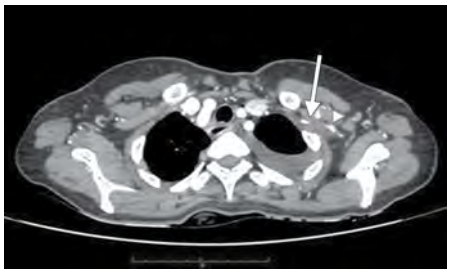

Fig. 1: Axial CECT chest showing circumferential wall thickening and critical narrowing of the left subclavian artery (white arrow) with distal reconstitution by the collateral flow and thin caliber of the left axillary artery (arrow head)

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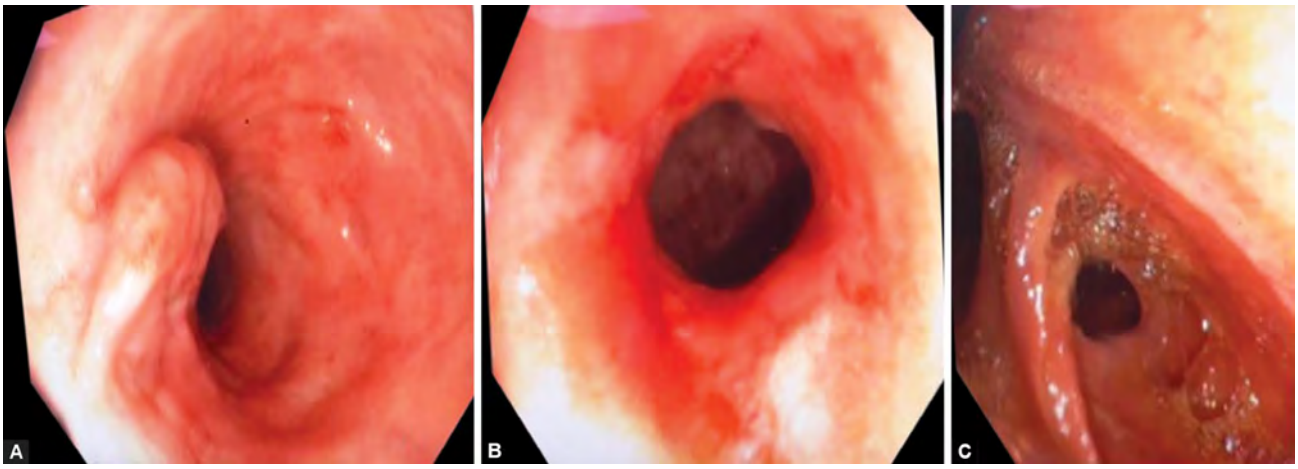


Figs 2A to C: Colonoscopy image revealing: (A) Pseudopolyp at 28 cm from anal verge; (B) Ulcerated structure at 20 cm from anal verge; (C) Fistulous opening in transverse colon

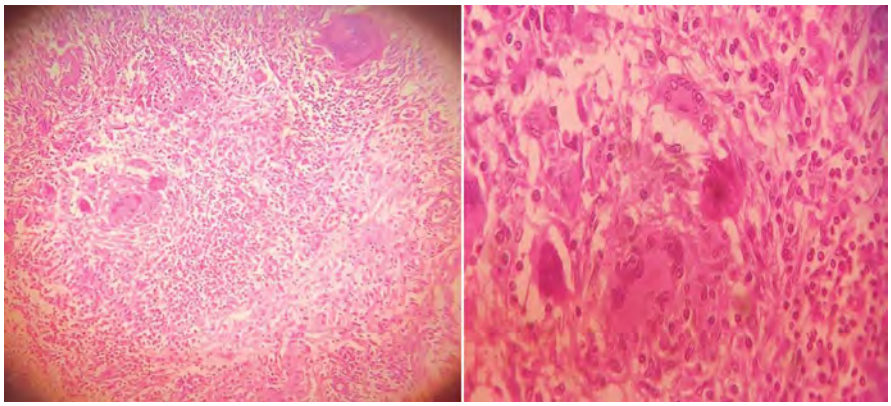
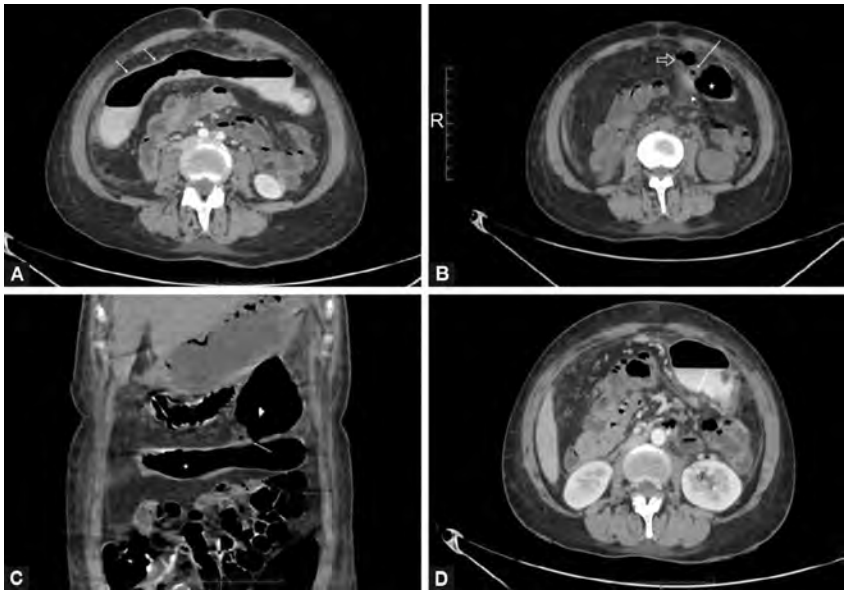


Fig. 3: Biopsy specimen showing predominantly lymphoplasmacytic inflammation with neutrophilic infiltration and granuloma formation



Figs 4A to D: (A) Axial CECT abdomen showing diffuse wall thickening of the transverse colon with complete loss of haustral pattern giving lead-pipe appearance (white arrows); (B) Axial CECT abdomen showing a small air foci within the fistulous tract (solid arrow) between the transverse colon (star) and proximal small bowel in left upper abdomen (open arrow); (C) Coronal section showing approx. 3.5 mm wide fistulous communication (white arrow) between the transverse colon (star) and proximal small bowel loop (arrow head); (D) Axial CECT abdomen with rectal contrast shows a small bowel loop with air contrast level which is filled secondary to the aforementioned enters-colic fistula

fluids, and steroids. The patient improved after 5 days of supportive treatment and was discharged on oral antibiotics and steroids.

Discussion

Crohn's disease is a chronic recurring IBD, which leads to a transmural granulomatous inflammation of any part of the GI tract, most commonly the ileum, colon, or both.[8] The incidence of internal fistulas is 5–10% in CD patients, which can be enteroenteric, enterovaginal, and enterovesical fistulas.[9]

Takayasu arteritis is an uncommon, idiopathic, chronic inflammatory condition marked by granulomatous arteritis affecting the aorta and its major branches. It presents before the age of 40 years.[10]

In TA, the inflammation can affect the whole length of the aorta. Any branch of the aorta can be involved in this disease, but the most common are the subclavian and common carotid arteries. The pattern and severity of the disease can vary depending on geographic location, but stenotic lesions are predominant, present in over 90% of patients, while aneurysms are present in around 25% of cases.[11]

It has been noted that IBD is commonly associated with various types of vasculitis more than expected, with TA being the most frequent subtype.[12] This association tends to occur more frequently in patients of young age compared to those with TA alone, and it is notably more prevalent among female patients. In most cases, IBD precedes the onset of TA, although there are reports where the sequence is reversed or both conditions are diagnosed simultaneously.[12]

Several case reports with simultaneous occurrence of TA and CD have been reported, despite theoretical estimates suggesting this coexistence might only happen in 1 in

10 billion individuals. Both conditions are granulomatous disorders, suggesting a potential pathophysiological link between them.[13]

Yassinger et al. in 1976 reported the first case of IBD and TA in a 15-year-old patient.[14] After that, Kusunoki et al. published about 37 patients in which both CD and TA were present; in 78% of cases, the diagnosis of CD preceded or occurred simultaneously with the diagnosis of TA.[13] Steroids (prednisolone + other immunosuppressants) were given to 33 patients, and among them, four patients required surgery.[13]

Reny et al. reported 44 patients with TA, of which 9% (four patients) were also affected by CD. These patients were younger and had more systemic symptoms than the patients with TA alone.[15]

There are two cases of CD and TA reported from India. Shrinivas et al. reported a 15-year-old girl with the rare coexistence of TA and IBD.[6] Suyamburajan et al. reported simultaneous TA and CD in a patient who had presented with heart failure and severe aortic regurgitation, followed by bloody diarrhea.[7]

While the exact causes of both diseases are still unclear, several contributing factors have been identified, such as genetic predisposition, infectious agents, distinct inflammatory patterns, and immune system imbalances. T cell-mediated immune responses seem to play a central role by triggering the release of pro-inflammatory cytokines like TNF-α, IL-1, and IL-12. Specifically, TNF-α significantly contributes to granuloma development, which is why anti-TNF-α monoclonal antibodies can be a potential treatment modality for both granulomatous conditions.[16,17]

Minami et al. reported nine patients (eight of whom were women) with both IBD and TA who did not respond to standard treatment but showed symptom improvement and reduced steroid use after receiving anti-TNF-α therapy.[18]

In conclusion, the coexistence of Crohn's disease and TA in a single patient presents unique diagnostic and therapeutic challenges due to the overlapping symptoms and inflammatory pathways involved. Our case is particularly noteworthy due to the presence of a large fistulous communication between the colon and jejunum, a rare and complex manifestation of Crohn's disease. This unique presentation underscores the importance of considering a potential association between the two conditions in patients who present with GI and vascular symptoms.

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CASE REPORT

A Novel Mutation of Fanconi–Bickel Syndrome: A Case Report

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Abstract

A 19-year-old girl from a consanguineous marriage showed signs of delayed motor developmental milestones since infancy, a protuberant abdomen, and failure to thrive. She suffered from cor pulmonale as a result of restrictive lung disease, pulmonary hypertension, and chronic interstitial lung disease. Diagnosed with resistant rickets elsewhere, she was on treatment with Joulie's solution. Physical examination revealed an undernourished state and features of rickets. Laboratory results were suggestive of proximal renal tubular acidosis (RTA), dyslipidemia, postprandial hyperglycemia, and elevated alkaline phosphatase. Skeletal X-rays confirmed rickets, and an abdominal ultrasound showed hepatomegaly.

Whole-exome sequencing identified a homozygous missense variant in the *SLC2A2* gene (p.Glu486Gly), confirming Fanconi–Bickel syndrome (FBS). Management included phosphorus, bicarbonate, vitamin D supplementation, dietary changes, and conservative care. Follow-up showed improvement in height.

Fanconi and Bickel (1949) initially reported the rare disorder known as FBS, which is attributed to mutations in the glucose transporter 2 (GLUT2) transporter gene. Due to its autosomal recessive inheritance, genetic counseling and prenatal diagnosis are essential. To the best of our knowledge, this is the first reported case in the world of a novel genetic mutation causing FBS.

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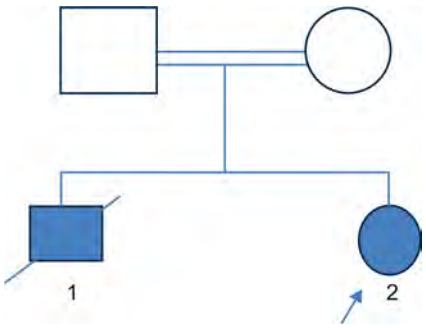
Case Description

A 19-year-old girl, the second child born to third-degree consanguineous marriage (first cousins) from Karnataka, was transitioned to adult nephrology care from the pediatric unit. She had a protuberant abdomen, delayed developmental milestones since infancy, and failure to thrive.

At the age of 3 years, she sustained a fracture of the left humerus due to trivial trauma. She was diagnosed with resistant rickets and was treated with Joulie's solution. She was diagnosed with cor pulmonale, pulmonary hypertension, and chronic interstitial lung disease at the age of 10 years. Pulmonary function test was suggestive of restrictive lung disease. Her elder brother had similar complaints, was bedridden, and expired at the age of 3 years.



Pedigree chart

On examination, she had frontal bossing, occluded teeth, grade III clubbing, Harrison's sulcus, pectus carinatum, rachitic rosary, malunified fracture of left humerus, widening of the wrist joint, and bow leg deformity. She was undernourished with a height of 100 cm (<3rd percentile), weight of 20 kg (<3rd percentile), and body mass index (BMI) of 20 kg/m^2. Systemic examination revealed hepatomegaly.

Laboratory tests revealed hyperchloremia (Cl—109 mEq/L), normal anion gap metabolic acidosis (pH—7.3, serum bicarbonate—11 mEq/L), and albumin (1+) and glucosuria on the urine dipstick. A 24-hour urine protein excretion was 424 mg. She had dyslipidemia and postprandial hyperglycemia. She had normal liver function test (LFT); however, alkaline phosphatase was elevated (2063 U/L, normal range 117–390 U/L) (Table 1—laboratory investigations).

The skeletal X-ray (Figs 1 and 2) showed features typical of rickets. Computed tomography (CT) of the chest showed interstitial lung disease (Figs 3A and B). The ultrasound of the abdomen confirmed hepatomegaly (Fig. 4). The two-dimensional (2D) echo (Fig. 5) was suggestive of dilated right atrium, right ventricle, pulmonary hypertension, and dilated left ventricle with an ejection fraction of 45%.

Whole-exome sequencing was conducted in response to characteristics that point to renal tubular acidosis (RTA). In exon 11 of the *SLC2A2* gene (chr3: g.170998021T>C; depth: 75×), a homozygous missense variant was found that causes glycine to be substituted for glutamic acid at codon 486 (p.Glu486Gly; ENST00000314251.8). The SLC2A2 protein's protein kinase domain contains the observed variant (PF00069). Mutations in the *SLC2A2* gene (OMIM*138160) that is homozygous or compound heterozygous cause Fanconi–

Table 1: Laboratory parameters

Laboratory parameters	*Values*
Hemoglobin (g/dL)	13
Total count (cells/mm^3)	6450
Platelet count (cells/mm^3)	337000
Serum creatinine (mg/dL)	0.29
Blood urea (mg/dL)	12
Serum sodium (mEq/L)	133
Serum potassium (mEq/L)	3.8
Serum chloride (mEq/L)	109
Serum calcium (mg/dL)	8.5
Serum phosphorus (mg/dL)	2.0
Alkaline phosphatase (U/L)	2063
Serum uric acid (mg/dL)	7.1
Direct bilirubin (mg/dL)	0.1
Indirect bilirubin (mg/dL)	0.2
SGOT (U/L)	116
SGPT (U/L)	32
Total protein (g/dL)	7.4
Serum albumin (g/dL)	4.8
Serum magnesium (mg/dL)	2.1
Vitamin D (ng/mL)	25

SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase

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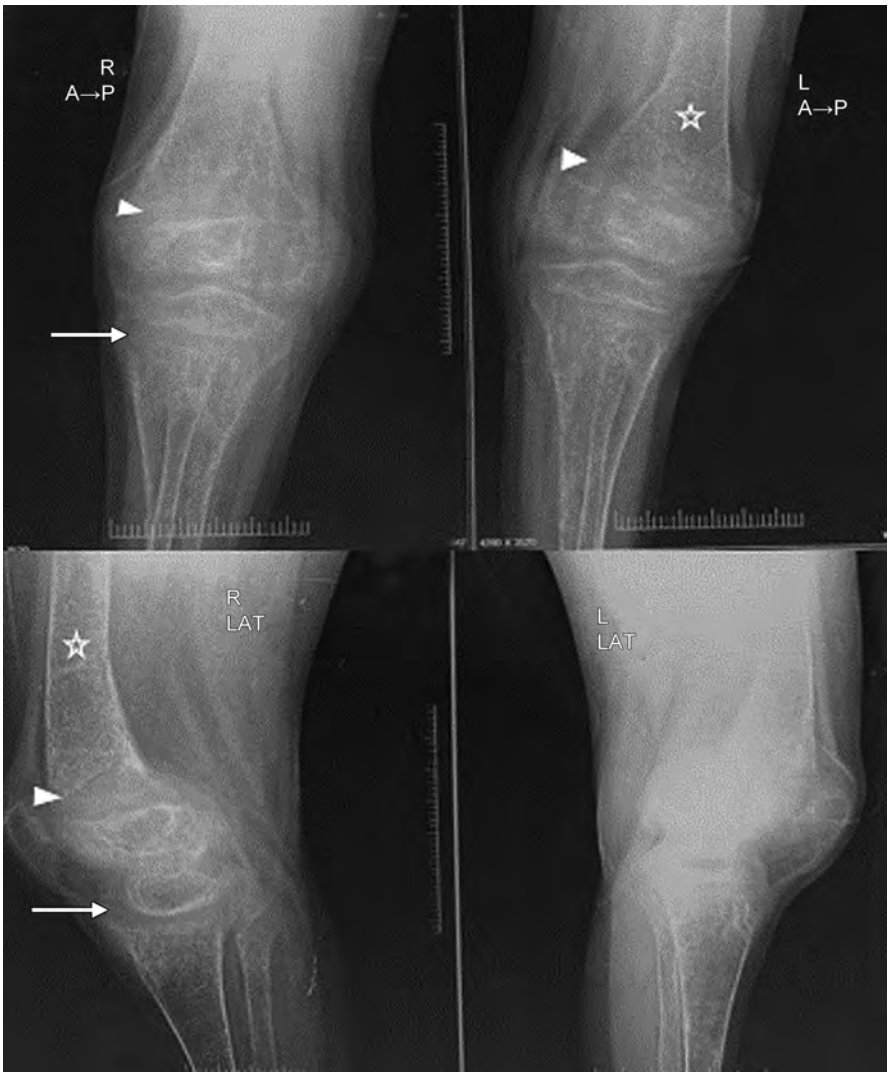
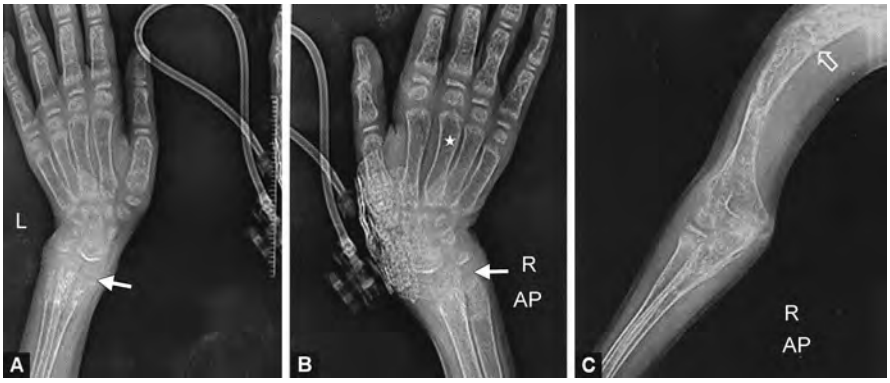


Fig. 1: Anteroposterior and lateral views of bilateral knee joints depict widened lucent band of physis (arrows). There are also absent zones of provisional calcification with mild fraying and cupping of distal femoral epiphysis (arrowheads). Similar fraying and cupping are also seen along bilateral proximal tibial metaphysis. Note the reduced bone density with coarsened trabeculae (stars)



Figs 2A to C: (A and B) Anteroposterior views of bilateral wrists also show widened lucent band of physis with fraying and cupping of distal radial and ulnar metaphysis (solid arrows). Reduced bone density and coarsened trabeculae (star) are also seen; (C) Oblique view of right elbow shows old pathological fracture of humerus with resultant bowing (open arrow)

Bickel syndrome (FBS) (OMIM#227810). After the diagnosis of FBS, the family was advised conservative management and was continued on phosphorus, bicarbonate, and vitamin D supplements. Uncooked corn starch was advised, and lactose was eliminated from the diet. Follow-up after 4 months showed an improvement in weight by 1.5 kg (Fig. 6).

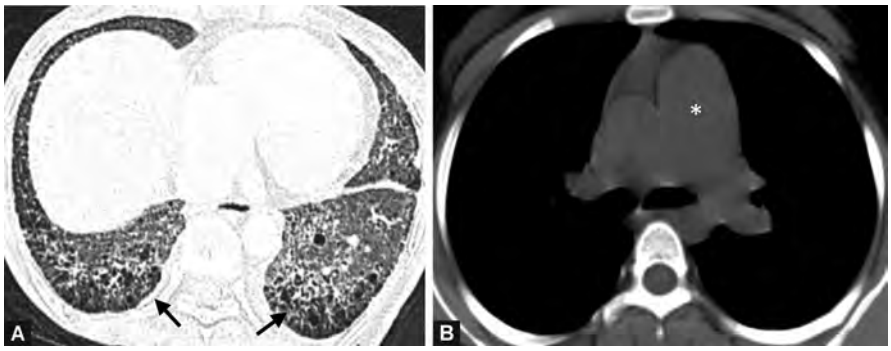
Discussion

Fanconi and Bickel first discovered FBS, a rare genetic illness that affects how carbohydrates are metabolized, in 1949.[1] FBS is a rare disorder of carbohydrate metabolism caused by pathogenic mutations in the glucose transporter 2 (GLUT2) transporter gene, *SLC2A2*. It was formerly known as glycogen storage disease type XI. In 1997, Santer et al. first proposed that FBS could be caused by a genetic defect in GLUT2.

Glucose transporter 2 is a part of a monosaccharide transporter family that moves sugars without requiring energy. After eating, this transporter transfers glucose and galactose into the hepatocytes, and when fasting, it exports free glucose out of the hepatocytes. Hyperglycemia and hypergalactosemia following meals in people with FBS are caused by the liver's decreased absorption of these sugars, which may be made worse by an inadequate insulin response to elevated blood glucose levels. When peripheral glucose stores are exhausted, impaired glucose export from hepatocytes causes fasting hypoglycemia.[2] The inability of glucose to be exported through the basolateral membranes of renal tubular cells causes glycosuria in patients with FBS.

Clinical symptoms of FBS patients usually involve an enlarged liver from glycogen accumulation, intolerance to glucose and galactose, hypoglycemia during fasting, tubular nephropathy, and severe growth retardation.[3] Individuals with a delayed diagnosis frequently experience truncal obesity, delayed puberty and growth, dental caries, hypophosphatemic rickets-related bone problems, and a cherubic facial appearance.

Fanconi–Bickel syndrome does not have a specific treatment. Reducing RTA and treating it with vitamin D, calcium, phosphorus, and bicarbonate supplements, as well as preserving water and electrolyte balance, are all part of managing renal Fanconi syndrome. It is advised to eat small, frequent meals of uncooked cornstarch.[4] Although the prognosis for FBS is usually favorable in terms of survival, those who are affected usually have small stature.



Figs 3A and B: Computed tomography of the chest axial lung window (A) and soft-tissue window (B) reveal coarse reticulations with diffuse interlobular septal thickening and honeycombing in bilateral basal segments (solid arrows) along with dilated pulmonary artery (asterisk) suggestive of fibrotic interstitial lung disease with pulmonary arterial hypertension

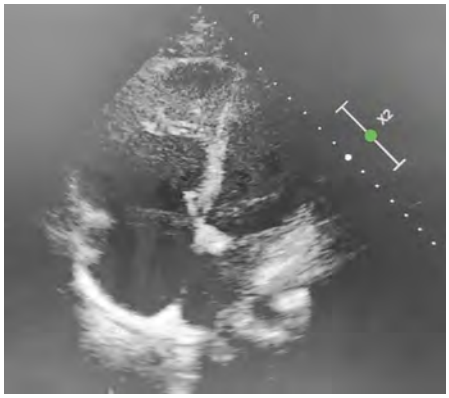


Fig. 5: Two-dimensional echo apical four-chamber view—dilated right atrium and right ventricle

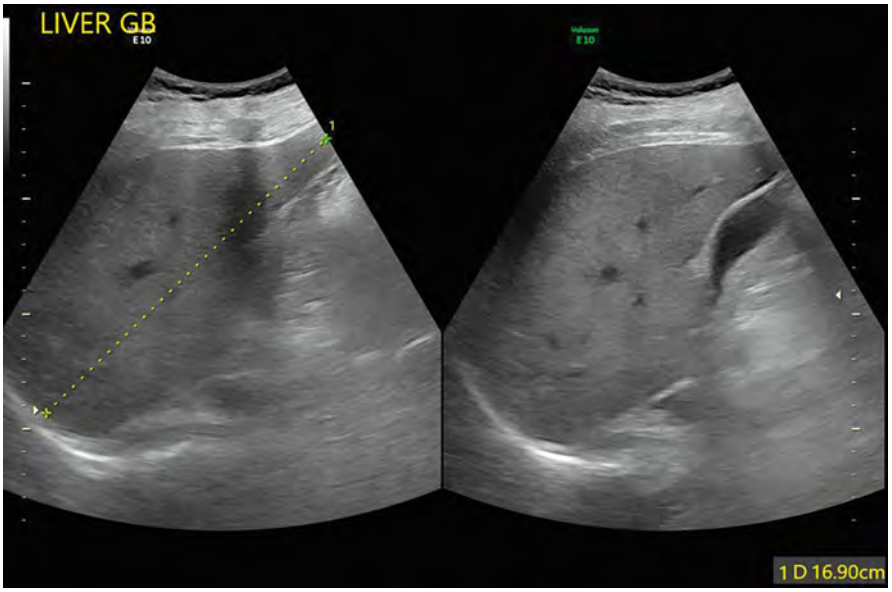


Fig. 4: Ultrasonography of the abdomen reveals enlarged liver ~16.9 cm with normal echotexture suggestive of hepatomegaly

Fig. 6: Patient after treatment

Only a small number of cases from India to worldwide have been reported to have FBS,[5–9] all of which involved hepatomegaly and renal dysfunction in children in consanguineous families. There is no common mutation in India, as each case has shown distinct mutations.[6–9]

Worldwide, this is the first case with a novel mutation in exon 11.[10] Also, this is the first case from India reported in an adult patient with genetic confirmation. Genetic counseling is necessary because FBS is an autosomal recessive condition with a 25% chance of recurrence in siblings. For their next pregnancy, couples may be offered prenatal diagnosis via mutation analysis on chorionic villus sampling at 11 weeks of pregnancy.

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CASE REPORT

Klebsiella pneumoniae Induced Leukocytoclastic Vasculitis

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Abstract

Leukocytoclastic vasculitis (LCV) is an immune-mediated single-organ vasculitis. It is a self-limiting disorder. Common triggers are drugs, infections, malignancy, or underlying autoimmune conditions. Here we discuss the case of an obese, middle-aged hypertensive female who presented with painful right lower limb swelling and productive cough for the last 5 days. She underwent medical and surgical management and was treated as a case of cellulitis with bilateral pneumonia. During the treatment course, she developed a nonblanchable petechial rash, which initially was attributed to the antimicrobial agent (piperacillin-tazobactam), but the culture report of the purulent sputum provoked the broadening of the differential diagnoses to include alternate causes for the rash, which proved to be a diagnostic dilemma.

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Introduction

Leukocytoclastic vasculitis (LCV) is a small vessel vasculitis. It is localized and rarely has any systemic manifestations. *Klebsiella pneumoniae*-induced LCV is an immune-mediated small vessel vasculitis caused secondary to either bacteremia or a localized infection. When suspecting LCV secondary to infection, the source of infection needs to be identified and treated with an appropriate antimicrobial agent. Usually, clearing of infection results in rash resolution, but some resistant cases might require immunosuppressive therapy.

Case Description

A 58-year-old hypertensive female presented with complaints of painful right lower limb swelling and erythema for 7 days along with a single large blister formation over the dorsum of the right foot. She had a recent travel history with a significant history of walking wearing tight footwear, following which she developed the blister. Possibly, repetitive trauma led to the formation of a blister, which had ruptured 3 days back. It was associated with purulent discharge from the ulcer site. Since the last 5 days, she had developed intermittent high-grade fever along with a productive cough. The expectoration was copious in amount and was purulent with a yellowish tinge. There was no past history of any drug allergy. On examination, she was febrile, had sinus tachycardia, her blood pressure was 148/96 mm Hg, and her respiratory rate was 22 breaths per minute. On local examination, her right lower limb had irregular patchy areas of erythema below the knee. She had varicosities on her bilateral lower limbs with pitting edema. She had an open wound of 3 × 3 cm with purulent discharge on the dorsum of her right foot with unhealthy rounded margins, with slough and pus flakes at the base of the ulcer. Areas of skin color change along with peeling of the normal skin were seen around the ulcer margins (Figs 1 and 2). On systemic examination, there were fine crepitations on auscultation in the basal lung fields. Cardiovascular, gastrointestinal, and neurological system examination was unremarkable.

Her initial investigations revealed microcytic hypochromic anemia with neutrophilic leukocytosis—hemoglobin 10.3 gm/dL, total leukocyte count 12.6 thousand/mm^3, and C-reactive protein of 201 mg/L. Her liver and kidney function tests were unremarkable. Glycated hemoglobin level was 6%. Chest X-ray was suggestive of bilateral lower zone lobar consolidation with effusion. She was started on broad-spectrum IV antibiotic cover of piperacillin-tazobactam. Wound debridement was done under all aseptic conditions, and purulent discharge was drained and sent for microscopy and culture. Regular wound cleaning and dressing was advised further.

On day 3 of admission, she developed a nonitchy, nonpainful petechial rash above the upper end of the dressing material, which was nonblanching and nontender to touch. Possibility of drug-induced rash was kept in mind, although the point against it was that the rash was nonpruritic and limited only to the right lower limb. On complete hemogram, there was no eosinophilia, and her serum immunoglobulin E (IgE) level was normal.

Over the next 2 days, the rash coalesced to form dense nonblanching, nonpalpable areas of purpura and ecchymoses (Fig. 3). A possibility of vasculitic rash was considered more favorable, likely of infective or autoimmune etiology, and the patient was continued on the same antibiotics. A skin biopsy was planned and done on the 5th day of admission as the lesion was progressing further and its appearance intensified with an angry red color. A trial of low-dose steroids was kept in mind but deferred until the biopsy report. Bilateral lower limb arterial and venous Doppler and a two-dimensional (2D) echocardiography scan were done to rule out infective or embolic phenomena of cardiovascular origin, which revealed no significant abnormality. Differential diagnoses were broadened to include antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis or immunoglobulin A (IgA) vasculitis, and a workup was sent for serum complement levels, IgA, antinuclear antibodies *via* immunofluorescence and quantitative analysis, c-ANCA, and p-ANCA, all of which returned normal. The skin punch biopsy of size 0.4 × 0.3 × 0.2 cm on histopathological examination showed an inflammatory infiltrate

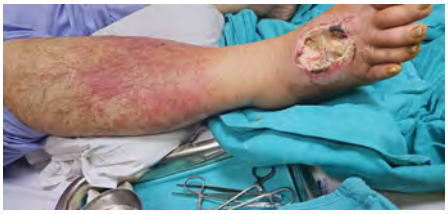

Fig. 1: Shows the anterior–posterior view of the right lower limb, depicting the dorsum of the foot with a debrided ulcer wound 5 days after admission and debridement. The wound measures approximately 3 × 3 cm, with unhealthy rounded margins, and slough and pus flakes at the base. Surrounding the ulcer, areas of skin discoloration, and peeling of normal skin are visible. Furthermore, dense nonblanching, nonpalpable ecchymoses with irregular margins, and patchy involvement are observed extending 3–4 cm above the ankle joint and involving the lower three-fourths of the calf circumferentially

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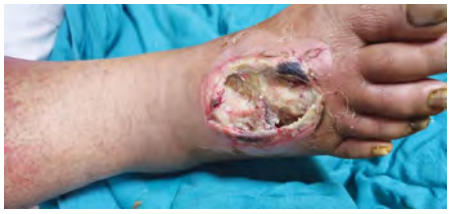

Fig. 2: Showing the debrided ulcer wound after 5 days in close detail

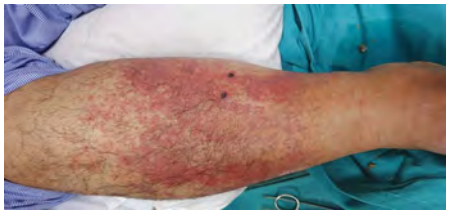

Fig. 3: Depicts the rash on day 7 at the peak of progression, showcasing an erythematous, nonblanching, and nonpalpable rash surrounding the affected area. On the medial side of the mid-calf, two dark circular lesions, approximately 2 cm apart, indicate the site of a skin biopsy

composed of neutrophils, lymphocytes, eosinophils, and histiocytes with destruction of the vessel wall without fibrinoid necrosis. Immunofluorescence did not reveal any deposits. Diagnosis suggested was of small vessel LCV.

On day 6 of hospitalization, the sputum culture reports returned positive for *K. pneumoniae* sensitive to piperacillin-tazobactam. The wound pus, blood, and urine cultures were sterile.

A diagnosis of infection-induced LCV was made over drug-induced vasculitis, points being in favor that on day 8 of treatment with the same antimicrobial agent, the patient's rash started resolving and had completely resolved by day 12. The patient was afebrile, repeated chest X-rays showed signs of resolution, and her leukocyte counts normalized. The patient was advised regular dressing and IV antibiotics and was discharged with advice for close follow-up. She made a full recovery in due course of time, which was supportive of LCV secondary to *Klebsiella* more than anything else.

Discussion

Leukocytoclastic vasculitis is a single-organ, small vessel vasculitis. It is defined as a vasculitis of an artery, arterioles, capillaries, or vein of any size without any feature of systemic vasculitis. LCV can be idiopathic or associated with infections, drugs, malignancy, and autoimmune disorders.[1]

Cellulitis is the inflammation of the subcutaneous tissue. Risk factors for lower limb cellulitis cases are aging, obesity, venous insufficiency, edema, skin surface disrupted by trauma, ulceration, or inflammatory diseases. It involves the lower extremities in about 70–80% of cases.[2]

Glycemic control also plays an important role in the pathophysiology of cellulitis. A study from the American Diabetes Association showed a 12% increase in the risk of cellulitis with every 1% increase in HbA1c.[3] Her prediabetic status and multiple abovementioned risk factors such as obesity, vascular insufficiency, edema, and local trauma may have contributed to her developing cellulitis of the right lower limb.

Almost all drug classes have been implicated in the etiology of LCV [antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapeutic agents, antihypertensives, and antiepileptics]. Infections, malignancy, systemic diseases [systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's], ANCA-associated vasculitis, cryoglobulinemic vasculitis, and IgA-associated vasculitis are also to be ruled out. Extensive workup is required to rule out signs of any systemic involvement.[4,5] Investigations in cases of a suspected case of vasculitic rash include a mandatory skin biopsy in all adult patients. Most cases of LCV present with nonpalpable, nonblanching petechiae or purpura, which can coalesce, ulcerate, or form hemorrhagic bullae. Diagnosis relies on identifying the etiology and the skin biopsy findings.[5]

Drug-induced vasculitis has been considered a separate entity in the Chapel Hill classification of vasculitis (2012).[6] Out of all drug-induced vasculitis, drug-induced LCV is the most common type. According to a large retrospective study from North America, 31% of all cases of cutaneous small vessel LCV are drug-induced. Some of these have also been reported to cause ANCA-associated and sporadic IgA-associated vasculitis. Pathogenesis of drug-induced vasculitis involves immune complex-mediated endothelial injury as drug form haptens and induces immune response. The mean time of onset of drug-induced vasculitis is 14 days.[7]

Infection-induced vasculitis is the most common cause of secondary vasculitis, and it involves both immune and nonimmune mechanisms of vessel invasion and necrosis.

Evaluation of cause and targeted treatment is the cornerstone of management. LCV has been associated with bacteria, parasites, viruses, and fungi. The most common bacteria involved are *Staphylococcus*, *Salmonella*, *Mycoplasma*, and *Mycobacterium*. Viruses causing LCV include hepatitis B, C, Epstein–Barr virus, Coxsackie virus, and human immunodeficiency virus. *K. pneumoniae* lower respiratory tract infection and bacteremia have both been reported to have caused LCV.[8,9]

Differentiating between LCV caused by drug use or infection is a clinical challenge, as the histopathological findings remain the same for both. In this case, the onset of illness and the appearance of the rash was the clinching point in the diagnosis. The patient had developed complaints of fever 5 days prior to admission while the rash over the right lower limb appeared on day 3 of admission or 3 days after antimicrobial initiation; however, the rash started resolving on day 8 of treatment despite being on the same antimicrobial agent. As discussed earlier, there is a lag period of about 5–7 days for the inciting agent to enter the body and form immunogenic haptens, which are then responsible for the inflammatory reaction seen in all forms of immune-mediated vasculitis. While comparing the two main differentials at hand, the conclusion that the immune reaction triggered due to infection was the primary inciting event in causing the rash, rather than the short duration of use of the antimicrobial agent, was more acceptable. Secondly, there is a paucity of corroborative data implicating piperacillin-tazobactam in cases with LCV.

Treatment in a case of infection-induced LCV usually involves specific antimicrobial therapy. Risks regarding flare-up of infection with the use of immunosuppressive therapy need to be kept in mind during treatment and used accordingly when required in resistant cases. Prognosis is usually favorable, with 90% of cases achieving resolution within weeks to months, while only 10% progress to chronic disease averaging 2–4 years.[10]

Conclusion

This case presents the critical importance of thorough clinical evaluation in differentiating the etiology of LCV. The patient's development of a purpuric rash during treatment for *K. pneumoniae* infection initially raised concerns about drug-induced vasculitis due to piperacillin-tazobactam. However, the timing of rash onset, clinical progression, and lack of substantial evidence implicating the antibiotic pointed to the infection as the primary trigger. This case highlights the necessity of identifying the underlying cause of LCV, as targeted treatment of the inciting event, rather than the vasculitis itself, is key to achieving favorable patient outcomes.

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CASE REPORT

Rhabdomyolysis Related to High-dose Atorvastatin: A Case Report

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Abstract

The extreme form of statin-related muscle involvement leading to rhabdomyolysis is not uncommon. We, in this case report, present a patient with rhabdomyolysis following high-dose atorvastatin treatment. The patient was a 60-year-old female with a background of coronary artery disease and acute coronary syndrome, who was subjected to percutaneous coronary intervention and stenting 2 months back and was then put on high-intensity statin (atorvastatin 80 mg daily) and other guideline-recommended drugs. She presented with severe generalized body aches, fatigue, and marked weakness in the proximal muscles of her limbs and acute renal shutdown. She was diagnosed to be a case of statin-induced rhabdomyolysis on the basis of an extremely high creatine phosphokinase level of 36,210 units/L. Despite fluid and electrolyte management and alternate-day hemodialysis, the patient's renal parameters did not improve, and she succumbed on day 15 of hospitalization.

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Introduction

Statin-associated muscle symptoms (SAMSs) have been downplayed in many mega-statin trials. A large number of authors have attributed the symptoms to the so-called "Nocebo effect"[1,2] and emphasized the role of counseling to encourage continuation of statin therapy instead of withdrawing the drugs.[2,3] However, more serious and life-threatening adverse effects of statin therapy, e.g., rhabdomyolysis leading to acute kidney injury (AKI) and hepatocellular damage and resultant death, have been sporadically reported as isolated case reports in the literature as collected in MEDLINE.[4] Analysis in this review of Mendes et al.[4] showed that the incidence of rhabdomyolysis could be 0.3–13.5 cases per 10,00,000 cases of statin prescriptions, and overall mortality related to rhabdomyolysis could be to the tune of 15%. Here, we report the case of a 60-year-old female patient with recent acute coronary syndrome (ACS), status post-percutaneous intervention (PCI), on high-intensity statin (HIS), developing rhabdomyolysis and AKI leading to renal shutdown and death.

Case Description

A 60-year-old female presented with rest angina 2 months back and was diagnosed as a case of coronary artery disease (CAD), acute anterior non-ST elevation myocardial infarction (NSTEMI). She had no history of any form of atherosclerotic cardiovascular disease (ASCVD) prior to her hospitalization for ACS. Her coronary angiogram revealed single-vessel disease with 99% proximal critical stenosis in the left anterior descending (LAD) artery. She was subjected to PCI and stenting with a drug-eluting stent to LAD with good results. Postprocedure, she was put on ticagrelor 90 mg twice daily, aspirin 75 mg once daily, atorvastatin 80 mg daily, and metoprolol 50 mg once daily. The total duration of her high-dose statin intake was for a period of approximately 60 days prior to hospitalization for the present illness, and she was on no other antilipid drugs such as ezetimibe or fibrates. Neither she was on any other drugs, e.g., amiodarone, calcium channel blockers, or macrolide antibiotics, which are known to interfere with P450 CYP 3A4 enzyme system, which has the potential to induce myopathy with concomitant statin use. In addition to her present problem, she also had gallstone disease (GSD) presenting as chronic cholecystitis with off-and-on episodes of acute-on-chronic cholecystitis, and she was under the follow-up care of a surgical gastroenterologist. She had no prior history of either renal or neurological problems, and her renal parameters were absolutely normal prior to PCI.

Presently, she was hospitalized with nausea and repeated vomiting, abdominal discomfort, and marked generalized body aches, more marked in the proximal muscles of the upper and lower limbs, with extreme weakness in the said parts. An initial provisional diagnosis of acute on chronic cholecystitis was made in view of her background disease and gastrointestinal symptoms, and her muscle symptoms were attributed to an associated metabolic problem. She was investigated accordingly. However, her abdominal ultrasound did not reveal any evidence of the acute phase of the chronic GSD. In view of her muscle symptoms in the background of HIS, including other routine investigations, serum samples were sent for creatine phosphokinase (CPK) and lactic dehydrogenase (LDH) levels, and urine analysis was made for hematuria and myoglobin.

General physical examination revealed a body weight of 62 kg, a height of 158 cm, and a body mass index of 24.89. She was hemodynamically stable, but was mildly febrile (temperature 100°F) and mildly icteric as well. Her pulse rate was 100/minute regular, BP was 120/80 mm Hg. She had no evidence of lymphadenopathy or skin rash. Cardiovascular system examination was essentially normal, and she was not in heart failure. On palpation of the abdomen, there was mild epigastric tenderness, but no significant organomegaly was observed. Examination of the respiratory system did not contribute anything. Central nervous system examination did not show any cranial nerve dysfunction, neither was there any generalized sensory deficit. However, there was marked tenderness, especially in the proximal muscles of both upper and lower limbs, with a muscle power of grade I.

Laboratory parameters and results of specialized investigations are noted below:

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Sr. no.	Parameters	Baseline	7th day	13th day
1.	Urine for myoglobin	Negative	Negative	
2.	Urine for occult blood	Positive	Positive	
3.	Hb (gm/dL)	10.4	9.0	
4.	Total leukocyte count/cm^2	7,700	30,000	19,900
5.	ESR (mm/hr)	82		86
6.	C-reactive protein (mg/L)	56	67	
7.	Serum LDH (IU/L)	1,487 (R 105–333)		
8.	CPK (U/L)	31,646 (R 30–135)	36,210	
9.	Blood urea (mg/dL)	79 (R 6–24)	260	
10.	Serum creatinine (mg/dL)	4.7 (R 0.59–1.04)	6.79 (on dialysis)	
11.	Serum sodium (mEq/L)	128 (R 135–145)	130	132
12.	Serum potassium (mEq/L)	5.0 (R 3.5–5.5)	6.2	6.0
13.	Liver function tests (at baseline)	Serum total bilirubin (mg/DL)—1.1 (R < 1.0), SGOT/SGPT (U/L)—672/875 (R 8–45 for SGOT and 7–56 for SGPT), and SAP (IU/L)—241 (R 44–147)		
14.	Lipid profile (baseline) (mg%)	Total cholesterol 146, triglyceride 150, HDL-C 42, and LDL-C 62		

Other Investigation Findings

- Abdominal ultrasound: Evidence of GSD with chronic cholecystitis and medical renal disease.
- Cerebrospinal fluid: Analysis was essentially normal.
- Lower limb motor nerve study: Evidence of left peroneal axonal neuropathy.
- MRI of lumbosacral spine and screening of whole spine: Ligamentum flavum hypertrophy at the level of L4 to S1, multiple age-related lumbosacral disc desiccation changes as well as cervical degenerative changes.
- Electrocardiogram (ECG) and 2DE: Echocardiogram were normal. Her pre-PCI finding of anterior NSTEMI had normalized.

Clinical Course

The patient was given intensive supportive care, but she developed progressive worsening of renal function, leading to anuria. She was put on varying periods of hemodialysis on alternate days. Her muscle power also did not show signs of improvement despite complete withdrawal of statin, though muscle tenderness improved to some extent. On the 14th day of hospitalization, she developed repeated asystole, and an attempt was made to address the problem with temporary pacing. The terminal event was drug nonresponsive hypotension and shock, and she finally succumbed on the 15th day.

Discussion

The patient had symptomatic rhabdomyolysis as evident from her symptoms, physical findings, and serum levels of extremely high CPK. She had the classic triad of rhabdomyolysis, i.e., muscle pain and tenderness, muscle weakness and fatigue, and urinary findings. Dark or tea-colored urine is supposed to be a part of the triad.[4] However, this patient had microscopic hematuria. Her acute renal shutdown probably precluded eliciting such a finding. Only 12.5% of the series reported by Mendes et al.[4] had such presentation as part of the triad.

Obviously, the rhabdomyolysis in the present case can be attributed to HIS. The patient was on 80 mg of atorvastatin which has been guideline-recommended dosage in post-ACS patients.[5,6] Rhabdomyolysis unrelated to statin has been reported in personnel exposed to extreme muscular stress and strain. They include high endurance athletes, defense members, old and frail individuals, alcoholics, and sedentary inactive people suddenly going for high-intensity exercise. On the contrary, the risk of rhabdomyolysis and other adverse events with statin use can get exacerbated by several factors, including compromised hepatic and renal function, hypothyroidism, diabetes mellitus, or concomitant use of drugs as mentioned earlier.[7] Rhabdomyolysis in this case could not be attributed to any of the described causes.

Myotoxicity in the form of rhabdomyolysis is a serious complication of statin therapy. This has been reported with all statins, especially with HIS doses.[4,7,8] Occasional Indian reports are there in the literature.[9,10] These sporadic individual case reports make it difficult to assess the different risk factors predisposing to such fatal complications. The US Food and Drug Administration MEDWATCH reporting system listed 3,339 cases of statin-associated rhabdomyolysis in a period of 13 years between January 1990 and May 2002, indicating that the problem may not be that uncommon.[7] Mendes et al.[4] from their review of MEDLINE to other sources gathered 644 case reports, from which only 112 were picked up for analysis because they met the entry criteria. The group was divided into three categories, i.e., mild, moderate, and marked according to CPK levels, the last category having a CPK level of >50 times the upper limit normal (ULN) which was so in 58% of the group. While more than 60% had muscle weakness and tenderness, other symptoms included inability to walk, flaccid muscles, and gastrointestinal symptoms. There were a total of 17 deaths (15%) in this series. Majority were on simvastatin and atorvastatin, but some were on other statins as well. The most interesting finding in the whole group was that >90% were receiving a combination of statins and fibrates which made the group vulnerable to myotoxicity.

High-dose statin is a standard of care recommendation for patients of established ASCVD in general and ACS patients in particular, in different guidelines.[5,6] However, caution should be exercised while prescribing very high doses of statins to the group with earlier noted risk factors, and a high index of suspicion should be in the mind of physicians with minimal SAMS. Symptomatic cases must be carefully followed up and investigated to rule out myotoxicity instead of labeling them as cases with "nocebo effect" to prevent serious complications such as rhabdomyolysis.

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CASE REPORT

Trapped in the Vasculature: Delving into Intravascular B-cell Lymphoma

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Abstract

Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive variant of diffuse large B-cell lymphoma (DLBCL) in which neoplastic lymphoid cells proliferate within the lumen of small blood vessels involving any organ. The rarity and intravascular involvement of this lymphoma make this diagnosis difficult. Only 5% of these cases show atypical cells in peripheral blood. Some cases may present with hemophagocytic syndrome. Here, we report a case of IVLBCL diagnosed in a 65-year-old male who presented with vague symptoms of fever and fatigue. Peripheral blood smear showed approximately 5% atypical blast-like cells, which led to bone marrow examination. Flow cytometry immunophenotyping was done on aspirate followed by immunohistochemistry on trephine biopsy, and a diagnosis of IVLBCL was made (IVLBCL). Radiological evaluation was done by positron emission tomography (PET) scan, and cerebrospinal fluid (CSF) examination was done as part of the workup. Six cycles of R-CHOP chemotherapy were given with intrathecal methotrexate, and minimal residual disease (MRD) assessment was done twice. No recurrence of the disease was seen till 1-year follow-up post diagnosis. The case emphasizes that IVLBCL, being rare and aggressive, requires complete diagnostic workup in terms of laboratory and radiological studies, which play an important role in differential diagnosis and deciding the prognosis.

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Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive subtype of diffuse large B-cell lymphoma (DLBCL) with a peculiar characteristic of proliferating neoplastic lymphoid cells within the lumen of small blood vessels without any obvious extravascular tumor mass and with or without a few circulating lymphoma cells.[1,2] This unusual presentation makes it more difficult to diagnose with a single diagnostic tool and needs strong clinical suspicion for choosing right investigations. Some of the common organs involved are skin, central nervous system (CNS), and bone marrow.[1–3] Geographically, IVLBCL is divided into "classical" and "Asian" variant seen in Western and Asian countries, respectively. Bone marrow involvement is more frequent in Asian variant, while cutaneous and CNS involvement is more common in Western countries. Cutaneous variants show better prognosis over others due to easy visibility of the disease and early diagnosis.

Case reports and case series on IVLBCL are the only source of information about this disease and contribute to knowledge about different clinical presentations, role of supportive investigations, and the effect of timely or delayed diagnosis and treatment.

We are describing here a case of IVLBCL, from its clinical presentation, diagnostic workup, and treatment and follow-up.

Case Description

A 65-year-old male presented with fever and fatigue. No comorbidities were present. No lymphadenopathy or any organomegaly was found on general physical examination. Routine investigations were done, and here are some positive findings. Serum LDH (lactate dehydrogenase) was elevated (710 U/L), and serum ALP (alkaline phosphatase) was raised (172 U/L). As part of investigations, complete blood count (CBC) was done, which showed pancytopenia. Hemoglobin was 7.2 gm/dL, total WBC count was 2,300/mm^3 and platelets were 55,000/L. Peripheral smear examination revealed few atypical or blast-like cells, approximately 5%, and few dysplastic neutrophils. These cells were large, having a high N:C ratio and fine nuclear chromatin with one to two prominent nucleoli suspicious of myelodysplastic syndrome with excess blasts or acute leukemia.

Bone marrow aspirates revealed adequate cellularity and 25–28% atypical medium to large cells with one to two prominent nucleoli and moderate amount of basophilic cytoplasm. Flow cytometry immunophenotyping showed a cluster of 18% cells with moderate to high side scatter and bright CD45 positive, just above lymphocyte cluster on CD45/side scatter plot. Additional CD markers were added to assess lymphoma involvement. These atypical cells had shown positivity for CD19 (moderate), CD20 (bright), CD5 (moderate), CD38 (moderate), cytoplasmic CD79α (moderate), kappa (moderate) and were negative for CD23, CD200, CD10, FMC7, CD11c, CD25, CD103, cytoplasmic CD3, cytoplasmic MPO, CD34, TDT, CD3, CD4, CD8 (Figs 1 and 2).

On the basis of expression of above markers and no lymphadenopathy or organomegaly on general physical examination, diagnosis of CD5 positive CD10 negative mature B-cell neoplasm was made with possibilities of blastoid variant of mantle cell lymphoma or CD5 positive DLBCL. A heparinized sample was sent for cytogenetic evaluation for mantle cell lymphoma; t(11;14) was negative. Bone marrow biopsy showed the presence of atypical lymphoid cells within the marrow vascular spaces (Fig. 3A). They had a high N:C ratio and nuclear hyperchromasia; focal extravasation is seen. The remaining marrow showed trilineage hematopoiesis. Immunohistochemistry (IHC) was done, which showed CD20 positivity in an intravascular pattern. Further evaluation showed positive expression of BCL2, MUM1, and negative for BCL6, CD10, CD30, cyclin D1, SOX 11, and CD3. Ki-67 was 30–40% (Figs 3B to D).

The final diagnosis of intravascular large B-cell non-Hodgkin lymphoma was made. Meanwhile, positron emission tomography (PET) scan was done, and it showed mild hepatosplenomegaly with mild increase in activity in the spleen. Cerebrospinal fluid (CSF) analysis showed no cells and normal biochemical findings. Once the diagnosis was made, six cycles of R-CHOP

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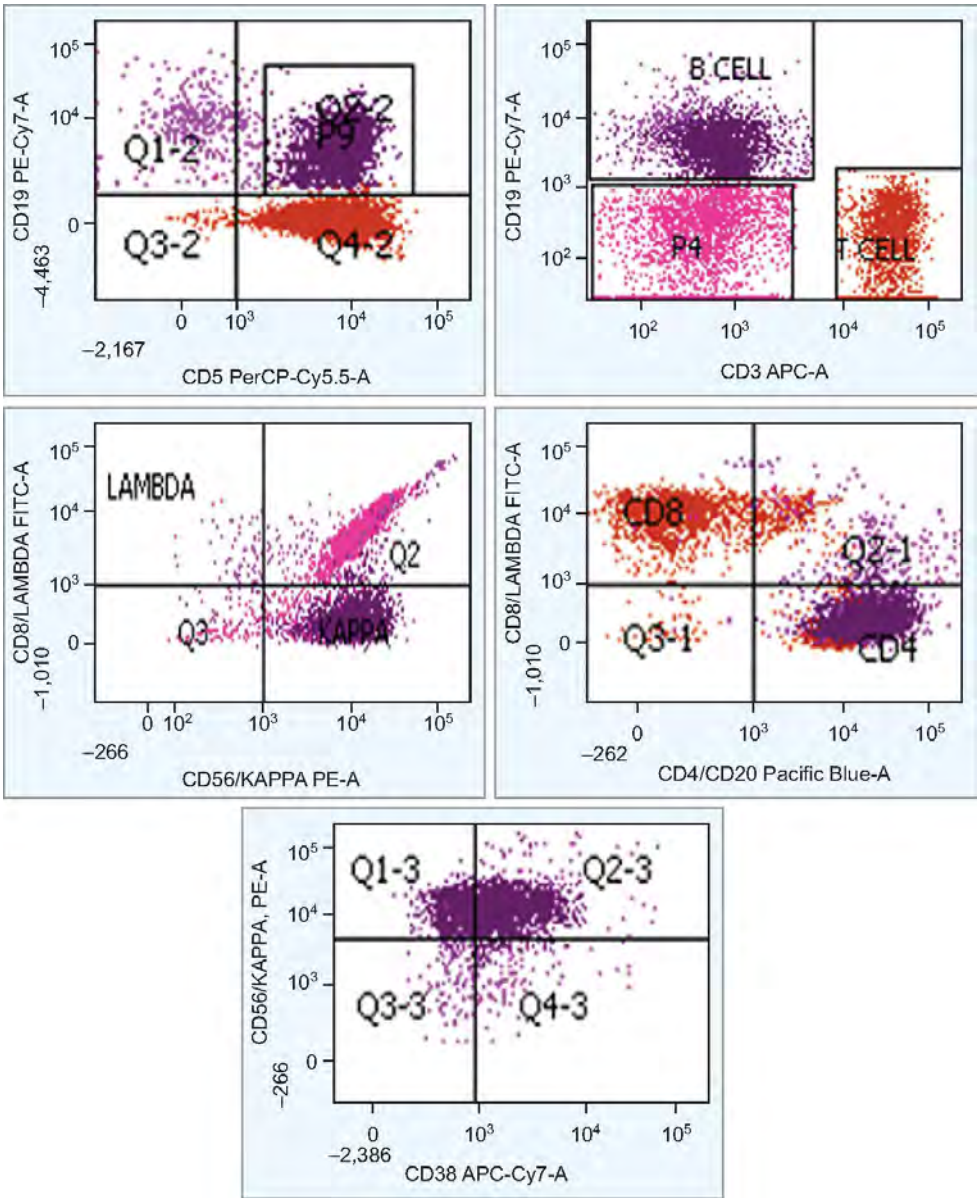


Fig. 1: Neoplastic lymphoid cells (purple color) are positive for CD19, CD20, CD5, CD38 and are kappa restricted. Normal B cells seen in pink and T cells are in red color

(rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) with intrathecal methotrexate were given. Follow-up CBC and peripheral blood smear (PBS) examination showed disappearance of lymphoid cells in peripheral blood. Post six cycles of chemotherapy, a repeat bone marrow examination with minimal residual disease (MRD) studies by immunophenotyping was negative for MRD. Repeat PET scan was also reported as complete metabolic response.

Discussion

Intravascular large B-cell lymphoma is one of the aggressive and rare forms of DLBCL, most commonly seen in the elderly.[4] The annual incidence of the disease is even <0.5 cases per 10,00,000.[1] A rarer variety of intravascular large cell lymphomas of natural killer (NK)/T-cell origin also exists.[5] The most peculiar feature of this disease is the heterogeneity in its clinical presentation, which in turn depends on the organ involved.[1–4,6] IVLBCL can be divided into "classical variant," which is seen in Western countries, and "Asian" variant.[1,4] Where CNS and cutaneous involvement is more common in the Western world, bone marrow is seen more frequently involved in Asians,[1,2,4] which is primarily involved in our case. Other common presentations are hepatosplenomegaly and hemophagocytic syndrome.[1] The exact reason for intravascular restriction of these malignant cells is not known.[4,7]

Laboratory Evaluation

Routine laboratory investigations frequently show pancytopenia, raised LDH and beta-2 microglobulin, and abnormal liver functions as seen in our case.[1,7] The final diagnosis is made on biopsy of the organ involved, which is suggested by most evident symptom of presentation, which was bone marrow in our case, and it presented as pancytopenia with a few abnormal cells on peripheral smear. Although it was an intravascular and a hematolymphoid neoplasm, the presence of neoplastic cells in peripheral blood is rare—5–9% cases.2,4 This could also be a reason for less availability of data on flow cytometry immunophenotyping.

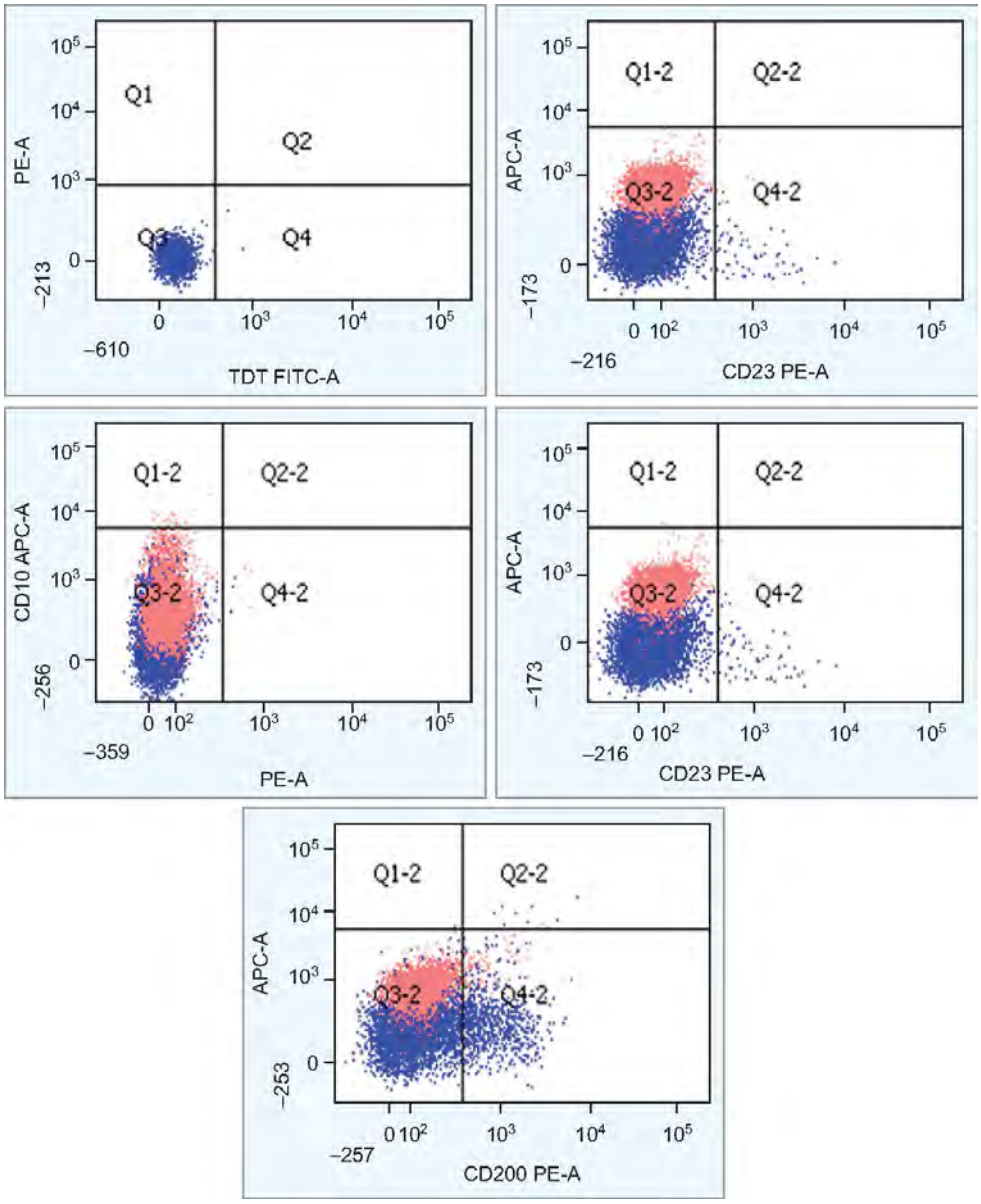


Fig. 2: Neoplastic lymphoid cells (blue) showing negative expression for CD23, CD200, CD10, and TDT. T cells are seen in orange color

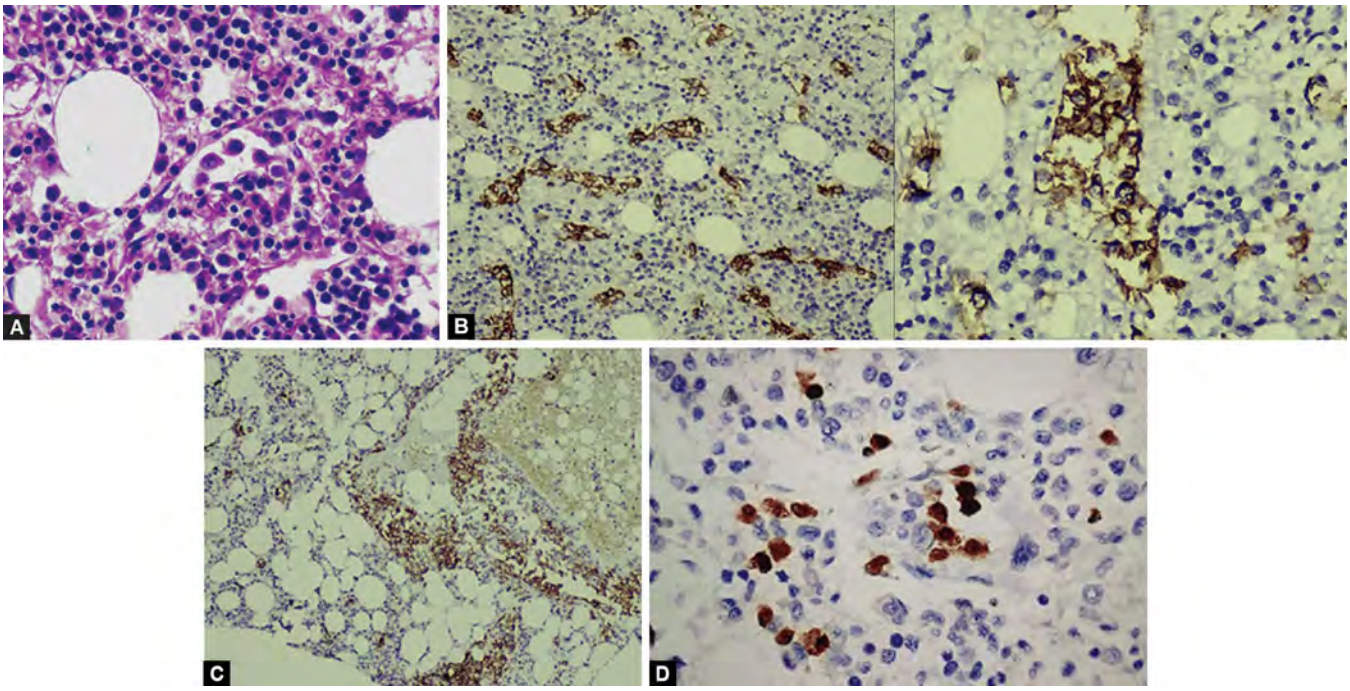
CD20 is expressed frequently by these lymphoma cells; hence, it forms the basis for current chemotherapy. In rare incidences, cases negative for CD20 are diagnosed by positivity of other B-cell markers such as CD79α and/or Pax-5.[8]

As per the Hans algorithm, 75–80% cases of nongerminal center phenotype show positive expression of Irf/Mum1.[8] Positivity of CD10, BCL-2, and BCL-6 is seen in 13–22%, >90% and 25–60%, respectively.[6,8] Anti-Ki 67 is always helpful in assessing proliferation index.[3] Murase et al. mentioned CD5 positivity in 38% of the cases, higher frequency of bone marrow/peripheral blood involvement, and presence of hepatosplenomegaly in CD5 positive CD10 negative cases.[8] These findings were found consistent with our case. Some of the possible differential diagnoses of CD5 negative intravascular lymphoma may include marginal zone lymphoma (MZL), splenic diffuse red pulp small B-cell lymphoma (SDRPL), and hairy cell leukemia (HCL), but possibilities reduce in cases of CD5 positivity.[7,8]

Therapy

The aggressive nature of the disease with or without CNS involvement mandates effective chemotherapy. Several studies in the past have shown benefit with anthracycline-based therapy like CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone). Addition of rituximab to intensify the regimen as R-CHOP with intrathecal methotrexate has shown improved outcome with increased overall survival (OS) and higher complete remission up to 80%. Hence, it is considered standard treatment.[1–4,7] CNS prophylaxis with intrathecal methotrexate should be considered as CNS relapse is seen commonly.[1]

Though autologous hematopoietic stem cell transplantation (auto-HSCT) is still a point of contention[7] but patients who received auto-HSCT as consolidation have shown increased survival rate with 3-year OS of 91–100% in one series.[1]



Figs 3A to D: (A) H&E image showing intravascular neoplastic lymphoid cells; (B) CD20 highlighting neoplastic lymphoid cells [(a) Scanner view; (b) High power view); (C) BCL2 positive expression in neoplastic lymphoid cells; (D) Ki67 expression in neoplastic lymphoid cells

Conclusion

Intravascular large B-cell lymphoma is a rare and aggressive form of DLBCL, with a high degree of variability in clinical presentation as well as organ involved. Where biopsy and IHC studies conclude the case, different laboratory investigations including blood, serum, and radiological imaging studies play an important role in ruling out other differential diagnoses. A good PBS examination and flow cytometry immunophenotyping are useful in picking up cases despite few abnormal cells in peripheral blood. Treatment with R-CHOP halts disease progression and may achieve complete remission. Intrathecal methotrexate prevents CNS involvement.

References

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