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Case Reports

Contents

CASE REPORT

Respiratory Bronchiolitis-associated Interstitial Lung Disease in a Nonsmoker with Biomass Fuel Exposure

Ambika Sharma[1*], Mahendra K Bainara[2], Govind S Rajawat[3], Suresh Bishnoi[4]

Received: 27 September 2024; *Accepted:* 17 June 2025

Abstract

A 40-year-old nonsmoking female with a history of biomass fuel exposure presented with a persistent dry cough and progressive dyspnea, ultimately diagnosed as respiratory bronchiolitis-associated interstitial lung disease (RBILD) through transbronchial cryobiopsy. This case highlights the rare occurrence of RBILD in nonsmokers and emphasizes the diagnostic value of cryobiopsy in unexplained interstitial lung disease. Multidisciplinary collaboration was essential for accurate diagnosis and management.

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Introduction

Respiratory bronchiolitis-associated interstitial lung disease (RBILD) is a rare form of interstitial lung disease primarily associated with heavy smoking. It is characterized by the presence of pigmented macrophages within the bronchioles, peribronchiolar inflammation, and varying degrees of fibrosis in the surrounding lung parenchyma. However, the condition is exceptionally rare in nonsmokers, making its diagnosis in such individuals particularly challenging.[1]

We present the case of a 40-year-old female, a nonsmoker, who presented with a 4-year history of a dry cough and a 2-year history of progressive dyspnea on exertion. Her condition was eventually diagnosed as RBILD, an extremely rare occurrence in nonsmokers.

Case Description

The patient, a homemaker, reported a persistent and progressive dry cough over the past 4 years, with no postural, diurnal, or seasonal variation. She also had dyspnea on exertion for the last 2 years, which progressively worsened from climbing upstairs to feel breathless on walking for a few minutes on level ground [modified Medical Research Council (mMRC) grade I to grade III], over the last 6 months. There were no associated symptoms such as hemoptysis, wheezing, chest pain, fever, loss of weight, or appetite. There were no complaints of joint pain or swelling, skin rash, visual disturbances, or difficulty in swallowing. No signs and symptoms suggestive of Raynaud's phenomenon or any other connective tissue diseases. She did not report any history of tuberculosis, coronavirus disease (COVID-19), diabetes, hypertension, or other significant medical conditions in the past.

The patient had been using inhalers for the past 4 years with no relief. She had a history of biomass fuel exposure, using a chulha (traditional stove) for cooking for approximately 25 years, often for more than 6 hours/day. She lived in a pucca house and belonged to a lower-middle-class family. She was married and had three children. There was no significant obstetric and gynecological history. None of her family members had a similar illness or any other significant illness.

Clinical Examination

On examination, the patient was conscious, cooperative, and well-oriented. Her vital signs were as follows: pulse rate of 100 beats/min, respiratory rate of 24 breaths/min, blood pressure of 110/70 mm Hg, and body temperature of 98°F. Her oxygen saturation on a pulse oximeter (SpO_2) was 88% on room air at rest. Physical examination revealed the presence of clubbing but no pallor, icterus, cyanosis, lymphadenopathy, or edema. There was the use of accessory muscles of respiration.

Auscultation revealed bilateral fine end-inspiratory crepitations throughout the chest. Cardiovascular examination showed normal heart sounds (S1 and S2) without any murmurs. The central nervous system and gastrointestinal system examinations were within normal limits.

Investigations

Routine laboratory tests are described in Table 1. Screening tests for connective tissue disease were negative (Table 2). The test for hypersensitivity pneumonitis panel was negative. Ultrasonography of the whole abdomen was normal with no hepatosplenomegaly. ECG revealed sinus tachycardia. Two-dimensional (2D) echocardiography showed mild tricuspid regurgitation and a normal left ventricular ejection fraction. Induced sputum for acid-fast bacilli smear and GeneXpert test for mycobacteria were negative.

Radiology

Chest X-ray (PA view) revealed bilateral reticulonodular opacities (Fig. 1).

Table 1: Laboratory parameters

Test	*Results*
Hemoglobin	11.2 gm/dL
Total leukocyte count	7000/mm^3
Neutrophils	70%
Random blood sugar	Within normal limits
Liver and kidney function test	Within normal limits
Erythrocyte sedimentation rate	30 mm/hr
Human immunodeficiency virus (HIV)	Nonreactive
Urine routine microscopy	Within normal limits
Serum calcium	Within normal limits
Serum angiotensin-converting enzyme (S. ACE)	Within normal limits
Mantoux test	7 × 8 mm induration
Prothrombin time, partial thromboplastin time, and international normalized ratio (INR)	Within normal limits
RTPCR for COVID-19	Negative

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Computed tomography (CT) chest (Fig. 2) showed inter- and intralobular smooth septal thickening with minimal ground-glass haziness, traction bronchiectasis, and subpleural honeycombing, showing bilateral upper and lower lobe predominance, suggestive of interstitial lung disease. Additionally, there were small pneumatoceles in the right lung field, ill-defined centrilobular ground-glass density nodules in the bilateral lower lobes, likely representing bronchiolitis. Findings were suggestive of usual interstitial pneumonitis with a bronchiolitis pattern.

Bronchoscopy and Biopsy

In view of no definite diagnosis on clinical and radiological basis, bronchoscopy and transbronchial cryobiopsy were performed. Through an ultrathin bronchoscope working channel, a 1.1 mm cryoprobe was advanced in the lateral segment of the right middle lobe. Cryobiopsy was taken after freezing for 4 seconds. Postprocedure bleeding was managed with the instillation of cold saline and wedging the scope in the segment. The biopsy was sent for histopathological study.

Histopathological examination (HPE) was suggestive of RBILD (Fig. 3).

Table 2: Connective tissue disease profile test

Test	*Results*
Rheumatoid factor	Negative
Antinuclear antibody (ANA)	Negative
Antidouble-stranded DNA (Anti-dsDNA)	Negative
Anticitrullinated protein	Negative
Anti-SSA	Negative
Anti-SSB	Negative
Scl 70	Negative
RNP/Sm	Negative
Anti-Jo1 Ab	Negative
PL-7	Negative
EJ/OJ/Ku	Negative
MI-2	Negative
MDA-5	Negative
U2 snRNP	Negative
Anti-Pm/ Scl Ab	Negative
TIF1 Gamma	Negative
Anti-U1-RNP Ab	Negative

Management and Follow-up

Patient was advised to avoid biomass fuel exposure, which she followed. A course of prednisolone started with 30 mg/day, which was gradually tapered over a 3-month period. The patient has shown gradual improvement in her symptoms over a 3-month follow-up. Her dyspnea has improved from mMRC grade III to II. She does not require oxygen support, and her room air saturation is 94% at rest. Six-minute walk distance improved to 300 meters. Forced vital capacity improved from 58 to 63%. Patient is currently under follow-up.

Discussion

Respiratory bronchiolitis-associated interstitial lung disease is a rare form of interstitial lung disease predominantly found in smokers. Approximately 0.2 to 0.3% of patients were found to have RBILD in studies from India.[2,3] This case highlights the significant role of biomass fuel exposure as a potential risk factor for the development of interstitial lung diseases such as RBILD, even in nonsmokers. The patient's history of prolonged exposure

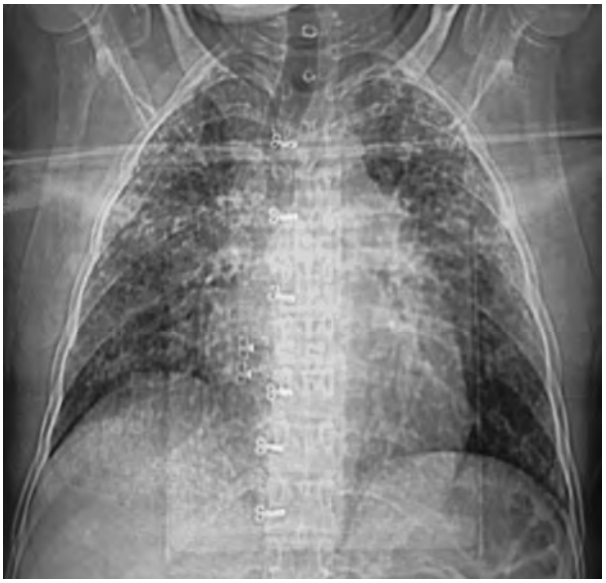
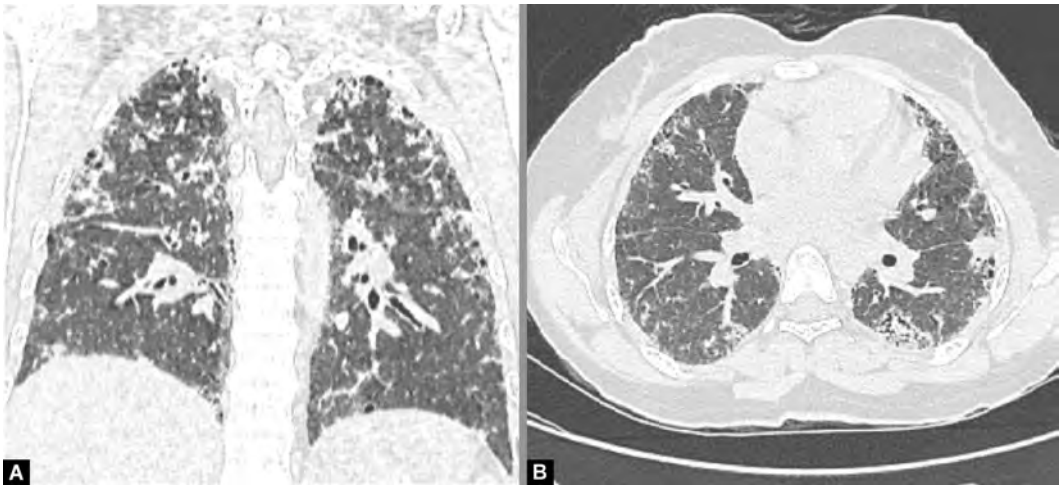
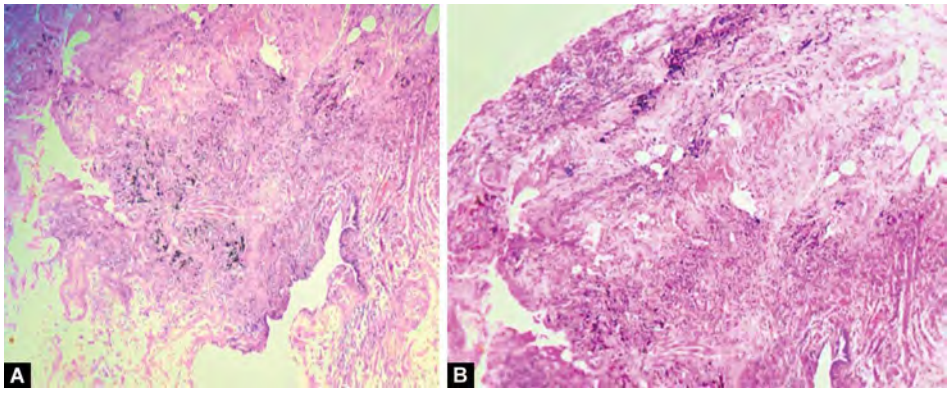


Fig. 1: Chest X-ray (scout image) view shows bilateral reticulonodular opacities more in the upper and mid zones, and cardiomegaly



Figs 2A and B: High-resolution computed tomography of the chest (lung window): (A) Coronal section; and (B) Axial section showing Inter- and intralobular smooth septal thickening is noted in both lung fields with minimal ground glass haziness, traction bronchiectasis, and subpleural honeycombing, showing bilateral upper and lower lobe predominance, suggestive of interstitial lung disease



Figs 3A and B: Histopathological image of lung biopsy: (A) 4× image showing terminal bronchiole in the lower field, right side lined by columnar epithelium. Underlying tissue shows edema and fibrosis. The middle and upper field shows carbon pigment deposition and interstitial fibrosis; (B) 10× image showing complete obliteration of alveoli by interstitial fibrosis, collagen deposition, and carbon pigment in the lung parenchyma. Overall histomorphology suggestive of respiratory bronchiolitis-associated interstitial lung disease

Table 3: Literature review on RBILD in nonsmokers

Study (Author and Year)	*Case description (Nonsmokers)*	*Exposures*	*Diagnostic methods*	*Findings*
Woo OH et al. (2007)[4]	Nonsmoker with significant exposure to second-hand smoke	Second-hand smoke	VATS biopsy, radiologic findings	RBILD pattern confirmed pathologically
Fraig et al. (2002)[1]	Two nonsmokers: (1) Exposed to diesel fumes and fiberglass; (2) Exposed to second-hand smoke	Diesel fumes, fiberglass, second-hand smoke	Retrospective review	Environmental exposures contribute to RBILD
Moon J et al. (1999)[5]	Nonsmoker with occupational exposure to solder flux fumes	Solder flux fumes	Pathological review of 10 cases	All cases were smokers except one nonsmoker
Johnson et al. (2003)[6]	35-year-old nonsmoking woman exposed to biomass smoke from indoor cooking	Biomass smoke	Imaging, transbronchial biopsy	RBILD diagnosed via biopsy, chronic cough, dyspnea
Mehta et al. (2011)[7]	42-year-old nonsmoking man with significant occupational exposure to metal dust	Metal dust	Lung biopsy, CT scan	Typical RBILD findings: progressive dyspnea, chronic cough
Flower M (2017)[8]	33-year-old male vaping for 3 months	E-cigarette	VATS biopsy, radiologic findings	RBILD pattern confirmed pathologically

to chulha smoke for cooking large meals for a family of 20 people over many years is likely a contributing factor.

Upon a detailed review of the literature, only a few documented cases have been identified, as outlined in Table 3. These cases suggest that environmental exposures, such as inhalation of biomass smoke or occupational hazards, might play a significant role in the pathogenesis of RBILD in nonsmokers.[1,4–8]

The pathogenesis of RBILD in nonsmokers is not fully understood. It is hypothesized that prolonged exposure to environmental pollutants, such as biomass smoke or occupational dust, might trigger a similar inflammatory response as seen in smokers. This results in the accumulation of pigmented macrophages and the subsequent development of interstitial lung disease. However, why only certain individuals develop RBILD remains unclear, suggesting potential genetic or immunological predispositions.[6]

This case also brings importance in view of its radiological picture not matching with typical RBILD. High-resolution computed tomography (HRCT) chest in RBILD usually presents with bilateral centrilobular ground-glass nodules, but in this case, it resembled the usual interstitial pneumonia (UIP) pattern. It was similar to a study done by Moon et al., who, in a review of 168 lung biopsies performed for suspicion of idiopathic pulmonary fibrosis, found 10 were RBILD.[5]

Additionally, this case emphasizes the importance of transbronchial cryobiopsy in the diagnosis of undiagnosed interstitial lung diseases. The collaboration of a multidisciplinary team (MDD) was crucial in reaching the correct diagnosis in this complex case.

Conclusion

This case underscores the need for awareness of RBILD as a potential diagnosis in patients with a history of biomass fuel exposure, even in the absence of smoking. Early recognition and diagnosis using tools such as transbronchial cryobiopsy can aid in the management of such rare conditions.

Acknowledgments

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CASE REPORT

Guillain–Barré Syndrome and Viral Thyroiditis—Coexisting Together or Viral Thyroiditis as a Cause of Guillain–Barré Syndrome: An Unsolved Enigma!

Vikram A Londhey[1*], Mrinal S Shelke[2], Aditya P Patil[3]

Received: 04 August 2025; *Accepted:* 26 August 2025

Abstract

Hyperthyroidism can sometimes mimic Guillain–Barré syndrome (GBS). Polyneuropathy, paraplegia, and thyrotoxic periodic paralysis presenting as hypokalemia can be the presentation of hyperthyroidism. This case highlights the similar presentation of two clinical conditions that can occur simultaneously, or one of them may precipitate the other. A high index of suspicion is essential for the diagnosis.

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Introduction

Guillain–Barré syndrome (GBS) is an acute polyradiculoneuropathy which is autoimmune in nature, clinically presenting as ascending symmetrical limb weakness, areflexia, and autonomic dysfunction. Mimics of GBS are hypokalemia, acute transverse myelitis, botulism, tick paralysis, myasthenia gravis, thyrotoxic periodic paralysis (TPP), thyroid storm, etc. Many bacterial infections and viral infections are known to be preceding GBS. We present a case of GBS in a patient who had a history of fever and thyroid swelling in the neck, which was diagnosed as thyroiditis that had possibly precipitated GBS.

Case History

A 22-year-old female patient presented with weakness of both lower limbs for 1 day, which progressed to involve the upper limbs in the next 48 hours. There was no history of diarrhea or vomiting. There was no history of cranial nerve involvement, bladder or bowel involvement, or sensory involvement. There was no history of trauma, recent vaccination, or toxin exposure. On inquiry, she gave a history of fever 4 weeks back. The fever was not associated with chills, rash, burning micturition, or diarrhea. The fever was associated with mild myalgias but no joint pains, sore throat, headache, or conjunctival suffusion. On examination, there was sinus tachycardia with a pulse rate of 110/minute. Blood pressure was normal. The patient had normal higher mental functions such as cognition, speech, and memory. Cranial nerves were normal on examination. There was hypotonia, flaccidity, and areflexia in all four limbs with a power of 2/5 in lower limbs at all the joints and 3/5 in upper limbs at all the joints. Plantar response was flexor; sensory and cerebellar examinations were normal. She had a thyroid swelling which was moving on deglutition and tender to touch. Her serum potassium was 4.2 mEq/L, which was normal and ruled out hypokalemia. Her nerve conduction study revealed acute demyelinating polyneuropathy with absent H reflexes. Thus, the diagnosis of GBS was made based on the clinical findings and nerve conduction velocity (NCV). The patient was treated with intravenous immunoglobulin (IVIG) for 5 days and showed a good response and complete recovery of muscle power. In view of persistent tachycardia, goiter, fine tremors in the outstretched hands with warm and moist palms which pointed toward hyperthyroidism, her thyroid function tests were advised. Her free T3 was 6.4 pg/mL (normal 2.3–4.2 pg/mL) and free T4 was 2.1 ng/dL (normal 0.8–1.8 ng/dL) were elevated with thyroid-stimulating hormone (TSH) of 0.005 mIU/L (normal 0.4–4.0 mIU/L). Anti-TPO, anti-TRAb, and thyroglobulin antibodies were negative. Ultrasound (USG) of the thyroid was suggestive of thyroiditis. In view of the history of fever and negative thyroid antibodies, it was suspected that the patient probably had viral thyroiditis as the thyroid gland was painful. This viral thyroiditis had possibly given rise to GBS. The patient was treated with propranolol 10 mg thrice a day and carbimazole 10 mg thrice a day. After 1 month of follow-up, the heart rate had settled and there was no residual muscle weakness in any of the four limbs. The thyroid functions had also normalized and the dose of propranolol was reduced to 10 mg once a day (long-acting preparation).

Discussion

Polyneuropathy and paraplegia have been described in severe hyperthyroidism by Charcot in 1888.[1] TPP with thyroid storm as a first presentation of Graves' disease has been reported by Banavathu et al.[2] Potassium ion channel defect is proposed as a mechanism of TPP, which causes severe hypokalemia due to transcellular shift of potassium ion, which in turn is due to adrenergic drive seen in hyperthyroidism. Thus, TPP mimics GBS. Increase in the thyroid hormone levels increase the risk of frequency and severity of GBS.[3] The plasma membrane of the neurons and the thyroid cells is rich in gangliosides.[4] These gangliosides can cause autoantibodies, which can lead to GBS. Environmental factors such as bacteria and viruses are attributed to the development of autoimmune diseases.[5] The most common environmental factors are infective agents such as bacteria, for example, *Campylobacter jejuni* and *Mycoplasma pneumoniae* and viruses such as Epstein–Barr virus (EBV), cytomegalovirus (CMV), Zika virus, Herpes zoster, hepatitis B, and human immunodeficiency virus (HIV). The antibodies to these infective agents have affinity for GM1 and GT1A gangliosides,

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which are located in paranodal areas and nodes of Ranvier in peripheral nerves. Molecular mimicry and cytokine stimulation are the probable mechanisms involved in the pathogenesis of GBS.[6] In a case report by Ali et al., quadriplegic patient presenting as thyroid storm where GBS was a close differential has been reported. In this case reported by Ali et al., nerve conduction study was normal, and hence, IVIG was not given. The patient recovered after normalization of the thyroid functions.[7]

In our patient, potassium was normal; hence, the possibility of TPP is ruled out. The NCV was very classical of GBS and so was the response to IVIG therapy. Antithyroid antibodies were negative. The clinically tender thyroid gland with the USG of the thyroid suggestive of thyroiditis and the thyroid function tests suggestive of hyperthyroidism raise a strong suspicion of viral thyroiditis, which could have triggered GBS. The limitation in our case is that we could not identify which virus was the causative agent of viral thyroiditis. Both the diseases were diagnosed and treated appropriately. Hence, it remains an unsolved enigma whether viral thyroiditis precipitated GBS or whether the two entities coexisted.

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CASE REPORT

Gerstmann Syndrome: A Rare Clinical Presentation of Focal Hyperglycemic Seizures

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Abstract

Hyperglycemic hyperosmolar nonketotic syndrome (HHNS) is a complication of type 2 diabetes mellitus that can progress to coma and death if left untreated. Focal hyperglycemic seizures are still an uncommon but noteworthy association of HHNS and most commonly involve the occipital and parietal lobes. Gerstmann syndrome, also called angular gyrus syndrome, consists of a tetrad of finger agnosia, acalculia, left-right disorientation, and agraphia that is usually accompanied by aphasia and most commonly presents in parietal lobe pathology. Here we report a case of a 50-year-old right-handed male with complaints of focal right-sided upper limb and facial seizures and findings of acalculia, finger agnosia, left-right disorientation, semantic aphasia, and loss of comprehension. Laboratory reports suggested HHNS seizures that presented clinically as Gerstmann syndrome. Magnetic resonance imaging (MRI) of the brain revealed dominant (left in our case) parietal lobe pathology. Although it is understood that HHNS is linked with focal neurological deficits, the exact mechanism by which this happens is still unknown, and Gerstmann syndrome associated with hyperglycemic seizures is still underreported, necessitating additional research.

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Introduction

Focal hyperglycemic seizures are an acute and rare complication of hyperglycemic hyperosmolar nonketotic syndrome (HHNS), which itself is a hyperglycemic emergency.[1] HHNS usually affects people in their 50s and 60s and makes up about 1% of all hospital admissions for diabetes-related conditions every year.[1] This clinical state of HHNS is defined by elevated blood glucose and serum osmolality, dehydration in the absence of serum, and urinary ketones.[2] In 1924, an Austrian neuroscientist, Josef Gerstmann, first identified the Gerstmann syndrome in a 52-year-old female case.[3] It is an uncommon neurological condition characterized by a constellation of symptoms, including finger agnosia, acalculia, left-right disorientation, and agraphia.[4] Although the etiology is widely varied, ranging from ischemic stroke and cortical atrophy to tumors, multiple sclerosis, etc., almost all of them include an insult to the brain that affects the dominant parietal lobe.[5] The four characteristics might each have a specific anatomic localization in the parietal lobe that is adjacent to or overlapping with one another.[6] Here we present a case of focal hyperglycemic seizures that presented with Gerstmann syndrome symptoms and semantic aphasia.

Case Description

A 50-year-old right-handed male with a 15-year history of diabetes mellitus, on insulin therapy but noncompliant, presented with approximately 10 episodes of facial twitching and right upper limb jerks, likely focal convulsions, each lasting 30–60 seconds over the past 4 days. He denied complaints of headache, fever, persistent weakness in any limb, trauma, or head injury, and had no history of addictions or substance abuse. On general examination, he was vitally stable. A neurological examination done after the resolution of the seizure episode revealed semantic aphasia, acalculia, finger agnosia, and left-right disorientation, consistent with Gerstmann syndrome. An electroencephalogram (EEG) showed an abnormal ictal period, while laboratory investigations and imaging studies, including magnetic resonance imaging (MRI) of the brain and computed tomography (CT) of the head, suggested focal seizures associated with the HHNS. The findings are summarized in Table 1. Apart from the abnormalities highlighted in the table, all other metabolic parameters were within normal limits.

The patient was managed with intravenous (IV) fluid hydration to correct the hyperosmolar state associated with HHNS, alongside midazolam 0.1 mg/kg IV bolus for acute seizure control. During hospitalization, subcutaneous human insulin and glargine were administered according to a sliding scale to stabilize his blood glucose levels. Upon discharge, the patient was transitioned to a fixed insulin schedule. His seizures resolved completely before discharge, and follow-up evaluations revealed improved glycemic control with no recurrence of seizures or other symptoms.

Discussion

As the prevalence of diabetes is increasing, so is the incidence of its associated conditions such as HHNS;[1] however, Gerstmann syndrome is an uncommon clinical entity.[3] HHNS is characterized by dehydration, elevated blood glucose and plasma osmolality, and absent ketosis.[1] Uncertainty exists regarding the precise pathophysiology causing seizures in hyperglycemic hyperosmolar conditions. One of the hypothesized mechanisms is decreased glucose uptake and Krebs cycle activity. This increases alternative glucose metabolism pathways, resulting in the production of succinic acid from GABA, lowering GABA levels, which lowers the seizure threshold.[2] Other potential reasons can be osmotic diuresis, dehydration, hyponatremia, and hyperglycemia-induced damage to the cerebral vasculature, resulting in a transient ischemic attack. Focal hypoxic-ischemic injury results in excitotoxic damage and mitochondrial malfunction during epileptogenic activity, causing Na^+/K^+ ATPase pump failure, cellular enlargement, and cytotoxic edema.[2] The presence of cytotoxic edema in the left parieto-occipital lobe in our case corroborates this hypothesis.

Although Gerstmann syndrome should include finger agnosia, acalculia, left-right disorientation, and agraphia, studies suggest it usually occurs as an incomplete triad and is usually accompanied by aphasia and, less commonly, by apraxia, optic ataxia, cognitive decline, numbness, or weakness.[5] Tekgol Uzuner et al. also suggest that pure Gerstmann syndrome is a rare clinical entity.[3] Ardila hypothesized that it is usually agraphia

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Table 1: Laboratory and imaging findings of the patient

Laboratory investigations / imaging	*Values*	*Reference range*
Blood glucose	459 mg/dL	<140 mg/dL
HbA1c	14.3%	4–6%
Serum osmolality	318.8 mOsm/kg	280–295 mOsm/kg
Urinalysis		
Glucose	+++	Absent
Ketones	Absent	Absent
MRI brain	Multifocal lesion of cytotoxic edema in the cortical region of the left parieto-occipital lobe with restricted diffusion (Fig. 1)	–
CT brain (plain and contrast)	No intracranial pathology	–

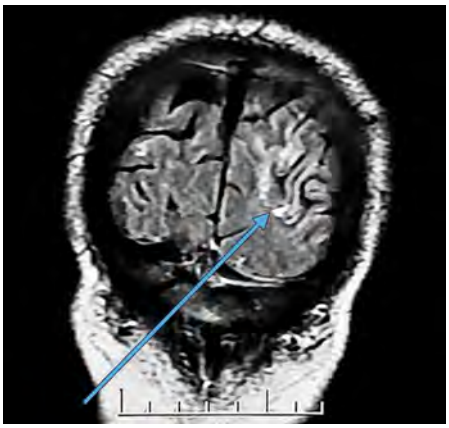

Fig. 1: MRI brain demonstrating ill-defined T2 hyperintense signals in the left parieto-occipital region, suggestive of cytotoxic edema

that is missing from the tetrad and is only present when the pathology extends to the superior parietal lobe area.[6] This theory also holds in our case, wherein three symptoms out of a tetrad, without agraphia, along with semantic aphasia and alexia, are present.

In hyperglycemia-induced seizures, characteristic MRI findings include cortical hyperintensity with restricted diffusion, subcortical T2 hypointensity, and cortical or leptomeningeal postcontrast enhancement, primarily involving the parieto-occipital region. On T2 and fluid-attenuated inversion recovery (FLAIR) imaging, cytotoxic edema, along with hyperperfusion and vasogenic edema, causes cortical hyperintensity and restricted diffusion most commonly in the occipital, followed by parietal, temporal, and frontal lobes.[2] While there is proximity between the areas, all four components have specific anatomic localization in the brain.[6] In our case, multifocal lesions of cortical cytotoxic edema were seen with restricted diffusion in the left parieto-occipital lobe, which explains the right-sided presentation of Gerstmann syndrome with HHNS. Hence, seizures at initial presentation in the clinical setting of uncontrolled hyperglycemia, hyperosmolar state, and absence of ketone bodies should raise the possibility of hyperglycemia-induced seizures.[2]

Although some cases of Gerstmann syndrome can be treated, no definitive treatment exists. Treatment is aimed at removing the cause if it is reversible.[5] HHNS seizures are easily reversible with proper glycemic control, and hence, treatment delay would be unacceptable. In our case, symptom reversal was brought about by controlling blood glucose and continuous RBS monitoring, and it was possible to discharge the patient symptom-free.

Conclusion

Our case highlights the importance of a unique presentation of the hyperglycemic hyperosmolar nonketotic syndrome in the form of Gerstmann syndrome and focal seizures, the cause of which is easily reversible if recognized early and treated promptly; failure of which can lead to drug-refractory seizures and a wide range of other neurological manifestations of increasing severity.

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CASE REPORT

Neuroendocrine Tumor of Unknown Primary Origin with Liver Metastasis Leading to Nonislet Cell Tumor Hypoglycemia

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Abstract

We describe a case of a 32-year-old nondiabetic lady who presented to our hospital with episodes of recurrent hypoglycemia. Investigations revealed suppressed insulin-like growth factor-1 (IGF-1) and elevated IGF-2 to IGF-1 ratio in the absence of hyperinsulinemia, which favored a diagnosis of nonislet cell tumor hypoglycemia (NICTH). Imaging revealed multiple lesions in the liver and a mesenteric nodal mass. Liver biopsy was suggestive of metastatic well-differentiated neuroendocrine tumor (NET) [World Health Organization (WHO) grade 3]. Our patient had a fairly aggressive progression of disease. She was given chemotherapy for the tumor, but the anatomic site of the primary malignancy could not be determined despite extensive imaging and diagnostic workup. This case highlights NICTH, which is a rarely encountered but life-threatening cause of hypoglycemia, and underlines the importance of tumor localization for effective treatment.

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Introduction

Recurrent hypoglycemia in a nondiabetic individual is relatively rare and may occur due to drugs, sepsis, or endocrine abnormalities. Tumor-induced hypoglycemia is an uncommon cause. The tumors that present with hypoglycemia are most commonly pancreatic beta cell tumors, that is, insulinomas.[1] Nonislet cell tumor hypoglycemia (NICTH) is an even rarer clinical entity, with incidence estimated at one per million people per year.[2] It is mediated by the secretion of insulin-like growth factor-2 (IGF-2) or big IGF-2 (its high molecular weight precursor) and not by tumor insulin secretion. Diagnosis is made by a suppressed insulin, C-peptide, and an elevated IGF-2/IGF-1 ratio.[3,4] The most common cancers causing NICTH are tumors of the GI tract, liver, lungs, adrenal, ovary, and mesenchymal tumors.[5]

Neuroendocrine tumors (NETs) are rare neoplasms that originate from neuroendocrine cells. They can occur in various organs but are most commonly seen in the gastrointestinal tract, pancreas, and lungs. NET of unknown origin refers to cases where metastatic NETs are detected but the primary tumor site remains unidentified. It accounts for 10–15% of all NET cases.[6] NETs can be classified as functional NETs that produce hormones leading to specific syndromes or nonfunctional NETs that do not secrete hormones or cause clinical symptoms. Hypoglycemia is a common presentation of pancreatic NET (incidence 1–4 cases per million per year). Other types of NETs are less frequently associated with hypoglycemia.[6] Here we describe a case of NICTH due to a NET of unknown primary origin with metastasis in the liver.

Case Description

A 32-year-old lady presented to our hospital with complaints of multiple episodes of alteration in mental status in the form of confusion and drowsiness associated with diaphoresis and abdominal pain for the past 1 month. The patient reported multiple emergency visits in which she had documented blood glucose <45 mg/dL. These episodes immediately subsided after food intake and dextrose infusion. She was a known case of primary hypothyroidism, for which she was taking Tab. thyroxine 75 mcg once a day. There was no history of diabetes mellitus, alcohol abuse, use of insulin, oral hypoglycemic agents, or similar complaints in the family. There was no history of fever, loss of appetite, loss of weight, alteration of bowel habits, jaundice, nausea, or vomiting. On presentation, the patient was conscious, oriented to time, place, and person, had stable vitals, and random capillary glucose was 98 mg/dL. Systemic examination revealed nontender hepatomegaly 3 cm below the right costal margin in the midclavicular line. She was admitted for evaluation.

Her initial biochemical and hematological investigations (hemogram, kidney function, liver function tests, and serum electrolytes) were within normal limits. Urine routine examination did not show glycosuria. During a spontaneous hypoglycemic episode, plasma glucose level was found to be 21 mg/dL. This episode was managed by infusion of dextrose, which led to resolution of the neuroglycopenic symptoms. The details of further workup for hypoglycemia are mentioned in Table 1.

Serum insulin and C-peptide during an episode of hypoglycemia were found to be low. Serum IGF-1 was suppressed, but IGF-2 was in the normal range. IGF-2/IGF-1 ratio was 14.4, highly suggestive of NICTH. Sulfonylurea screen was negative. Tumor markers like S. AFP, CEA, CA19-9, and CA 125 were normal. Thyroid functions and serum cortisol levels were within normal limits. Chest X-ray was also normal. Abdominal and pelvic ultrasound revealed hepatomegaly with multiple round to oval target-like lesions in hepatic parenchyma and a right adnexal follicular cyst. These findings were confirmed on CECT abdomen, which also showed multiple hypodense lesions showing peripheral enhancement, largest measuring 4.3 x 3.4 cm in segment 8 of the liver, with few showing targetoid appearance. Enlarged para-aortic, retrocaval, peripancreatic, and mesenteric lymph nodes were also present. The pancreas was completely normal. Differential diagnosis of multifocal

Table 1: Workup for hypoglycemia

Test	*Value*	*Normal range*
HbA1c	4.7	<5.7
8 AM cortisol	9.52	6–18 µg/dL
S. insulin	1.85	2.6–25 µg U/mL
S. C-peptide	0.29	0.2–4 ng/mL
IGF-1	49.9	71–234 ng/mL
IGF-2	720	322–853 ng/mL
S. growth hormone	2.2	<5 ng/mL

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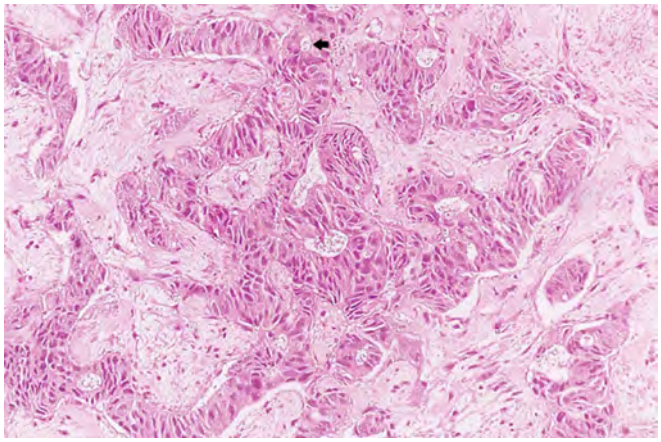

Fig. 1: Tumor cells arranged in a trabecular pattern with focal pseudo-glandular arrangement (arrow) in a desmoplastic stroma (H&E × 200)

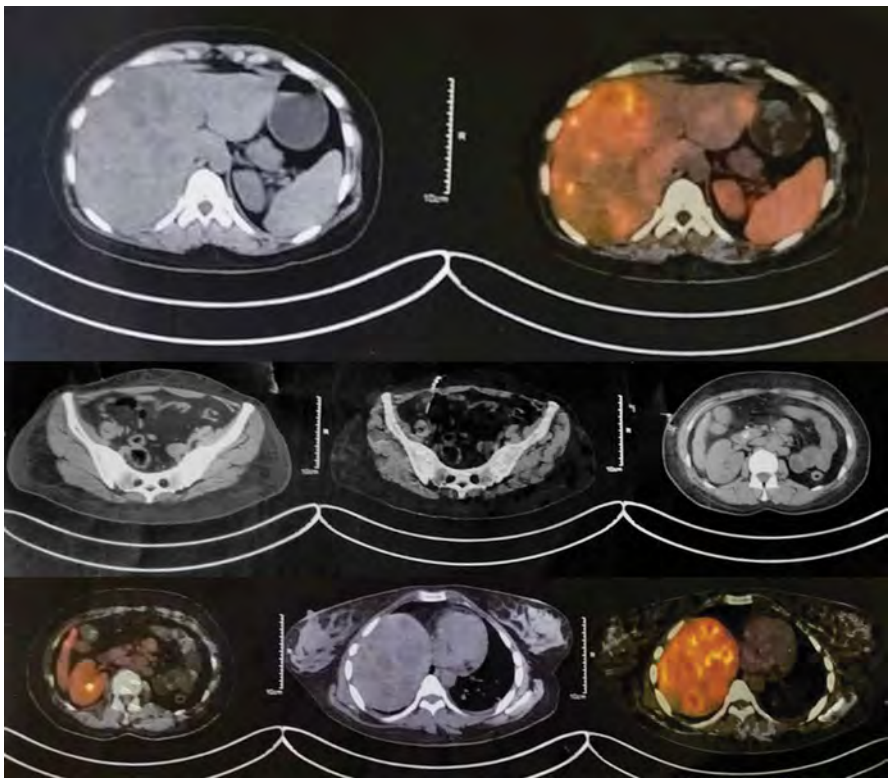

Fig. 3: Gallium-68 DOTANOC PET CT scan showing multiple tracer-avid hypodense lesions in both lobes of the liver (largest in segment 8) and subcentimetric paraaortic and common iliac nodes

hepatocellular carcinoma and hypovascular metastasis was considered.

These hepatic lesions were biopsied, which revealed metastatic well-differentiated NET (WHO grade 3). Immunohistochemistry for CEA, EMA, CK 19, pancytokeratin, chromogranin, and synaptophysin was positive, and CK 7, CK 20, CD56, PR, and Glypican 3 was negative. Tumor cells showed p53 and retained expression of RB with Ki 67 proliferation index of 45–50% (Figs 1 and 2).

A Gallium-68 DOTANOC positron emission tomography/computed tomography (68Ga-DOTANOC PET/CT) was done to search for primary malignancy (Fig. 3). It was suggestive of metastatic disease without any obvious primary lesion. It also showed a nontracer-avid mesenteric nodal mass arising from the root of the mesentery (1.7 x 1.7 cm).

During hospital stay, the patient's neuroglycopenic symptoms progressed acutely, and she started having hypoglycemic seizures. On confirmation of the diagnosis of tumor-induced hypoglycemia, the patient was given glucocorticoids (oral dexamethasone). However, the symptoms became refractory to clinical treatment. Diagnosis remained elusive even after liver biopsy, as detailed

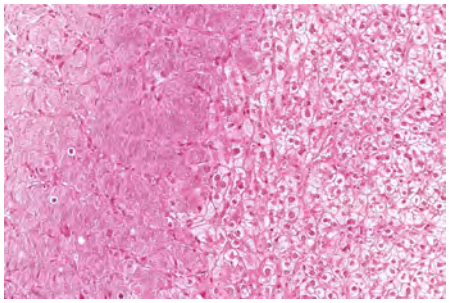

Fig. 2: Abrupt interface of tumor (left) with surrounding liver parenchyma (right). Closely packed tumor cells with high N/C ratio (H&E × 200)

imaging could not localize the primary tumor. Imaging did, however, reveal metastasis of a NET in the liver. The patient was initiated on chemotherapy as per the CAP-TEM protocol (capecitabine, temozolomide). The patient deteriorated and subsequently succumbed to the disease within 6 months of diagnosis.

Discussion

Tumor-induced hypoglycemia developing in nonpancreatic tumors is known as NICTH. NICTH is a dangerous paraneoplastic syndrome, which is underdiagnosed and underreported. De Groot et al. reported that nonislet cell tumors mainly arise in solid tumors of mesenchymal or epithelial origin. Hypoglycemia was associated with only 1% of nonpancreatic NETs, and of these cases, all had a known primary origin.[7] In our case, the patient presented with recurrent episodic hypoglycemia and was asymptomatic before that. Some case reports document an interval as long as 19 and 30 years after diagnosis.[8,9]

Literature review revealed very few cases of NICTH associated with NETs. Zweibach et al. described a 34-year-old lady with a metastatic NET (metastasis to bone and brain) causing NICTH with the primary in the abdomen. Hypoglycemia was not the presenting symptom; rather, it occurred 3 years after diagnosis.[10] In contrast, we report a case of a 32-year-old lady with a metastatic NET to the liver where the patient presented with recurrent episodic hypoglycemia.

In NICTH, investigations usually reveal decreased serum insulin, C-peptide, and IGF-1; however, levels of total IGF-2 may be normal or high. The ratio of IGF-2/IGF-1 was >11 (normal 3:1),[11] which is diagnostic of NICTH. Low GH levels favor a diagnosis of NICTH. An increased fraction of free IGF-1 negatively feedbacks, resulting in low GH.[12] This plays a role in resource-poor settings where testing for IGF-2 is not easily available. A previous case series from Japan described

hypokalemia in 53% of patients.[13] Our case demonstrated a normal GH level and normal serum potassium.

Ga-68 DOTANOC PET/CT is the functional imaging of choice as it can detect very small lesions.[14] Studies show it has helped in the detection of undiagnosed primary tumors in patients with metastatic NETs in about 59% of patients.[15] In our case, it helped reveal metastatic lesions and a suspicious mesenteric mass or lymph node, which was 1.7 x 1.7 cm but was not amenable for biopsy. Surgical excision of the tumor is the best modality for treatment of NICTH. When resection is not feasible, debulking or embolization may be done.[12] Adjuvant therapy includes glucocorticoids, which reduce levels of IGF-2.[16]

In selected cases, surgical exploration may be warranted when all available diagnostic tools have failed. When the primary site is unidentifiable, an open exploration or laparoscopy can be considered, but the supporting evidence is limited.[17,18] According to a past study, even then the primary site was not found in about 13% of cases.[19] In our case, surgical exploration could not be performed due to the aggressive progression of the disease and poor general condition. The refractoriness of hypoglycemia to treatment makes the presented case unusual. It exposes the challenges in treating NICTH due to an unknown primary malignancy, as targeted therapy could not be given.

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CASE REPORT

A Curious Case of Abdominal Pain with Reset Osmostat and Rhabdomyolysis

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Abstract

Acute intermittent porphyria (AIP) is a neurovisceral disease with multisystemic clinical manifestations, which are often nonspecific and highly variable. The triad of convulsions, abdominal pain, and hyponatremia in a young woman points toward acute porphyria. AIP should be suspected in all cases of abdominal pain if it is associated with seizures, hyponatremia, encephalopathy, autonomic hyperactivity, a history of passage of dark urine, or acute flaccid paralysis. Here we describe a case of AIP in a male patient who presented with abdominal pain, seizures, and hyponatremia. He had unusual features, such as rhabdomyolysis, hyponatremia due to reset osmostat, mild elevation of pancreatic and liver enzymes, mild renal dysfunction, and reversible biochemical hyperthyroidism.

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Introduction

Porphyrias are inborn errors of metabolism caused by deficiency of enzymes involved in heme synthesis. Acute intermittent porphyria (AIP) is a neurovisceral disease with variable clinical manifestations, such as abdominal pain, seizures, and acute flaccid paralysis mimicking Guillain–Barré syndrome. AIP is an autosomal dominant disorder caused by deficiency of porphobilinogen deaminase (PBGD) and is more common in females. Symptomatic AIP has a prevalence of 5.9 per million people in Europe. The prevalence of the mutation is 1 carrier per 2,000 persons in the Western population. Over 400 mutations have been reported in the long arm of chromosome 11 at the HMBS gene, which codes for PBGD. The majority of people with this mutation do not develop symptoms, and additional triggers are required to cause symptomatic porphyria. In AIP, neurological symptoms occur due to accumulation of PBG and aminolevulinic acid (ALA) and depletion of heme groups and hemoproteins in different tissues. Common symptoms are abdominal pain, tachycardia, dark urine, peripheral neuropathy, constipation, nausea, vomiting, mental changes, hypertension, back pain, sensory neuropathy, postural hypotension, convulsions, chest pain, and coma. The color of freshly voided urine is unremarkable, as ALA and PBG are colorless. When urine is exposed to light at ambient temperature, it turns dark amber or port wine–reddish color due to formation of porphobilin. The triad of convulsions, abdominal pain, and hyponatremia in a young woman raises the possibility of acute porphyria.[1] AIP should be suspected in all cases of abdominal pain if it's associated with seizures, hyponatremia, encephalopathy, autonomic hyperactivity, history of passage of dark urine or acute flaccid paralysis.[2] Molecular diagnosis is very useful in diagnosis and genetic counselling.[3]

Case Description

A 27-year-old man was brought to the emergency department after experiencing an episode of generalized tonic–clonic seizure. There was no history of fever, headache, or diarrhea. He reported persistent diffuse abdominal pain for the past 3 days and had a few episodes of vomiting. On examination, he was conscious, alert, and oriented. He had a soft abdomen with normal bowel sounds. His blood pressure and pulse were variable, with episodes of hypertension and tachycardia. His motor system was normal, with normal deep tendon reflexes. Sensory system examination showed normal sensation over the limbs and trunk. There were no focal neurological deficits or meningeal signs. Abdominal ultrasound and computed tomography (CT) abdomen were done as per surgical consultation due to persistent severe abdominal pain and were normal.

He had a history of respiratory failure following coronavirus disease 2019 (COVID-19) infection while in Dubai and was on assisted ventilation for a few days. He had hyponatremia and one episode of convulsion during hospitalization at that time.

He had a history of recurrent abdominal pain and was evaluated at multiple hospitals with investigations like gastroduodenoscopy, which were normal. His episodes of abdominal pain were often precipitated by alcohol intake. Prior to the present episode, he had an alcoholic binge. There was no illicit drug use prior to the present episode. His CT head was normal. His routine investigations showed severe hyponatremia (116.6 mEq/L) (Tables 1 and 2). Peripheral blood smear did not show any basophilic stippling. He was treated with intravenous levetiracetam and was started on 3% saline.

Investigations to find the cause of hyponatremia revealed hypoosmolar hyponatremia with normal fractional excretion of uric acid (FEUA), elevated fractional excretion of sodium (FENa), high urinary Na and Cl, with a urine osmolality of 414 mOsm/kg, suggestive of reset osmostat. His Furst ratio was 1.42. His serum uric acid was high, and serum creatinine was marginally elevated. Rhabdomyolysis was considered, and creatinine phosphokinase (CPK) was sent and found to be high (7,830 U/L). Urine myoglobin was negative.

In view of the triad of abdominal pain, convulsion, and hyponatremia, urine was sent for porphobilinogen assay on the day of admission and was reported as positive. It was repeated after 2 days and was consistently positive. He was advised 24-hour urine porphobilinogen and ALA assay. Owing to financial restraints, only 24-hour urine ALA was done, and it was elevated. His urine was kept in sunlight for color change, which turned amber.

During the hospital course, he had persistent hiccups, vomiting, and abdominal pain and was treated symptomatically. He had constipation during the hospital stay, which required an enema for bowel evacuation. He had insomnia and was treated with lorazepam. Water restriction did not improve his serum sodium, and there was only marginal elevation of serum sodium with daily 400 mL 3% saline. In view of rising CPK (Table 3), he was given normal saline, which caused a rapid fall in his serum sodium to 106 mEq/L, ruling out a renal salt-wasting syndrome.

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Table 1: Blood investigations

Investigations	*Results*	*Normal value*
Hemoglobin	12.2 gm%	12–16 gm%
Total count	9550 cells/mm^3	4000–11000 cells/mm^3
Neutrophils	75%	40–70%
Lymphocytes	24%	20–40%
Eosinophils	1%	2–6%
Platelet count	2.25 L/mm^3	1.5–3.5 L
ESR	4 mm/hour	<20 mm/hour
CRP	0.49 mg/L	<6 mg/L
Sodium	116.4 mEq/L	136–145 mEq/L
Potassium	3.6 mEq/L	3.5–5.5 mEq/L
Serum osmolality	258 mOsm/kg	275–295 mOsm/kg
RBS	127 mg%	80–140 mg%
Urea	30 mg%	20–40 mg%
Creatinine	1.44 mg%	0.8–1.2 mg%
Uric acid	15.48 mg%	3.5–7.2 mg%
Calcium	8.9 mg%	8.8–10.6 mg%
Phosphorus	2.49 mg%	2.5–4.5 mg%
Magnesium	2.48 mg%	1.8–2.6 mg%
Amylase	93 U/L	22–80U/L
Lipase	68 U/L	0–60 U/L
Total bilirubin	1.14 mg%	0.3–1.2 mg%
Direct bilirubin	0.33 mg%	<0.2 mg%
SGOT	125 U/L	<50 U/L
SGPT	149 U/L	<50 U/L
Alkaline phosphatase	103 U/L	30–120 U/L
Total protein	6.9 gm%	6.6–8.3 gm%
Albumin	4.1 gm%	3.5–5.2 gm%

Table 2: Urine investigations

Investigations	*Results*	*Normal values*
Urine sodium	157 mEq/L	
Urine creatinine	43.7 mg/dL	
Urine uric acid	28.9 mg/dL	
Urine osmolality	414.3 mOsm/kg	50–1200 mOsm/kg
FENa	4.44%	1–2%
FEUA	6.15%	4–11%

FENa, fractional excretion of sodium; FEUA, fractional excretion of uric acid

Table 3: CPK levels during hospital stay

Date	*1/9/23*	*2/9/23*	*3/9/23*	*4/9/23*	*6/9/23*
CPK Normal—(46–171 U/L)	7830 U/L	23400 U/L	60000 U/L	46430 U/L	6310 U/L

Table 4: Hormonal assay

TSH	0.029 mIU/mL	0.35–5.5 mIU/mL
FT3	3.38 pg/mL	2.5–3.9 pg/mL
FT4	1.2 ng/dL	0.6–1.1 ng/dL
Cortisol (8 AM)	21.10 µg/mL	5–23 µg/mL

As his serum sodium was not improving with 3% saline, he was started on tolvaptan, which increased his Na levels. At discharge, his serum Na was 123 mEq/L and 2 weeks after discharge it was 133 mEq/L, with a normal FEUA. His initial thyroid function test was suggestive of primary hyperthyroidism (Table 4), which on follow-up became normal.

Discussion

In a series of 101 patients with acute hepatic porphyria, 96% were diagnosed between the ages of 15 and 40, with a higher prevalence among women. Abdominal pain was the most frequent symptom.[4] The signs and symptoms, in decreasing order of prevalence, included abdominal pain, tachycardia, dark urine, motor neuropathy, constipation, vomiting, mental changes, hypertension, and absent reflexes. Other less common symptoms include back pain, sensory neuropathy, postural hypotension, convulsions, chest pain, and coma. Precipitating factors were hormones, drugs, infection, starvation, stress, and alcohol.[5]

Abdominal pain is reported in 74–100% of patients, lasting from several hours to days. It is typically severe and may be localized to the epigastrium, right iliac fossa, lower abdomen, or may be generalized. While autonomic neuropathy is considered the main cause, intestinal vasoconstriction and ischemia have also been implicated. In addition, ALA exerts a direct spasmodic effect on the gut.

Neurological manifestations generally appear 3–21 days after the onset of abdominal pain. Patients may present with low back pain, limb pain, or headache.[6] Porphyric neuropathy is usually motor-predominant, though some individuals exhibit sensory loss in the so-called "old bath costume distribution." Seizures occur in up to 20% of cases, while severe hyponatremia—often due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH)—as well as acute encephalopathy, delirium, hallucinations, and psychosis are seen in about 10%. The structural similarity between ALA and GABA allows ALA to interact with GABA receptors, thereby provoking seizures.

Hyponatremia is reported in as many as 53% of acute attacks.[7] Its causes include hypovolemia, SIADH, and cerebral or renal salt wasting (CSWS). Both SIADH and CSWS are characterized by normal or elevated urinary sodium together with an increased fractional excretion of uric acid (FEUA), whereas in the "reset osmostat," a variant of SIADH, FEUA remains within the normal range. In our patient, persistently normal FEUA with elevated fractional excretion of sodium (FENa) was consistent with reset osmostat. Administration of high-dose dextrose may further contribute to hyponatremia.

Laboratory evaluation often shows minor elevation of liver enzymes.[8] Elevation of transaminases occurs in 13% of cases. ALA is nephrotoxic and can lead to chronic tubulointerstitial nephropathy or focal

cortical atrophy. Porphyria-associated kidney disease (PAKD) is seen in more than half of patients with symptomatic AIP, and approximately 60% of those with PAKD also develop hypertension.[9] Elevated serum amylase and lipase levels, along with acute pancreatitis, have been reported in AIP.[10] Transient hyperthyroidism has also been described in many symptomatic cases.[11] During acute attacks, an increase in thyroxine-binding globulin may occur, leading to hyperthyroid manifestations.

In AIP, most patients experience only one or a few attacks, whereas about 3–8%—predominantly women—develop recurrent episodes, defined as more than three attacks per year, which may continue for several years. Long-term complications of AIP include chronic kidney disease, hypertension, and hepatocellular carcinoma (HCC). The renal involvement is usually a tubulointerstitial nephropathy, thought to result from the toxic effects of porphyrin precursors. The risk of HCC is markedly increased—by approximately 60–70-fold compared with the general population.[12] Notably, HCC in AIP often occurs without underlying cirrhosis and is usually associated with normal alpha-fetoprotein levels.

Management of AIP involves addressing acute attacks, preventing recurrence, ongoing monitoring, and treating long-term complications. Intravenous hemin as hematin or heme arginate is the only specific treatment available for acute attacks. Carbohydrate loading (300–500 gm/day) is a suitable therapy in those with mild symptoms. Cimetidine is effective for acute porphyric crisis and long-term management. It has been suggested that rhabdomyolysis-induced heme release prevents severe neurological manifestation in AIP. Weekly, biweekly, or monthly IV hemin infusion reduces the frequency of attacks. Monthly subcutaneous injections of givosiran [small interfering RNA (siRNA) directed against delta-aminolevulinic acid synthase I] markedly reduce attack rates, and liver transplantation is curative.[12] Seizures can be treated with diazepam, levetiracetam, gabapentin, magnesium, or propofol.

Our case had many peculiarities. AIP usually occurs in females, in contrast to our patient. Hyponatremia is common in AIP, but it is usually hypovolemic or due to SIADH. In our patient, it was due to reset osmostat. Our patient had rhabdomyolysis, which could be due to hyponatremia or due to ALA itself. He had mild elevation of serum lipase and amylase levels without any other evidence of pancreatitis. He had reversible biochemical hyperthyroidism. Diagnosis of AIP is very important, as most drugs used in the treatment of abdominal pain and seizures can worsen the clinical condition.

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CASE REPORT

A Rare Case of Primary Hypertrophic Osteoarthropathy Secondary to *SLCO2A1* Gene Mutation

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Abstract

Hypertrophic osteoarthropathy (HOA), also known as pachydermoperiostosis is an unusual cause of digital clubbing. It is a rare osteo-arthro-dermopathic syndrome which is associated with clubbing of fingers, thickening of skin in the face and scalp, seborrhea, and subperiosteal new bone genesis. It is divided into two types: Primary (PHOA) and secondary HOA, with the latter being common. PHOA accounts for a very meager portion of HOA cases. PHOA is usually inherited in an autosomal dominant fashion and rarely follows autosomal recessive inheritance pattern. We report a case of a male who presented with a history of progressive and painful enlargement of distal phalanges of hands and feet for 6 years. After all examinations and tests ruled out the secondary causes for HOA, genetic sequencing was performed to confirm the diagnosis of PHOA. Sequencing revealed homozygous nonsense mutation in *SLCO2A1* gene. This mutation is postulated to impair the degradation of prostaglandin E2 (PGE2), leading to its elevated levels. PHOA is an atypical cause of clubbing which usually poses a challenge in diagnosis. This report also underscores the importance of genetic sequencing in appropriate diagnosis and management of the PHOA.

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Introduction

Hypertrophic osteoarthropathy (HOA), also known as pachydermoperiostosis is an uncommon osteo-arthro-dermopathic syndrome. It is divided into two types: Primary hypertrophic osteoarthropathy (PHOA) and secondary HOA. HOA is associated with digital clubbing, periosteal new bone formation of long bones and arthritis. Secondary HOA is most commonly related to lung pathologies, in most cases as a paraneoplastic syndrome. It is also cognate with heart, liver, or intestinal diseases. Primary or idiopathic HOA (PHOA), accounts for a small portion of HOA cases, that is, around 3–5% of all cases.[1,2] When this is distinctly associated with lung diseases, it is coined as hypertrophic pulmonary osteoarthropathy (HPOA).[3] PHOA is most commonly inherited as autosomal dominant, infrequently with an autosomal recessive inheritance pattern. It is postulated to be related to abnormality in prostaglandin E2 (PGE2) metabolism. Here, we present our patient with PHOA associated with mutation in *SLCO2A1* gene.

Case Description

A 37-year-old male presented with history of progressive pain and enlargement of distal phalanges of hands and feet for 6 years. He also reported progressive swelling in both his lower limbs for the past 3 years. He had multiple consultations with various doctors for the same complaints over the years, but with little or no improvement. His past history included duodenojejunostomy for gastric outlet obstruction secondary to peptic ulcer disease. He also had traumatic amputation of distal phalanges of right middle and ring finger following a freak accident while working. He did not reveal any history of connective tissue diseases in the family or similar complaints in the family.

On examination, his vitals were stable. He had pallor, and significant clubbing was seen in both hands and feet (Figs 1 and 2). He also had bipedal pitting edema. Ridges were prominent in the forehead with severe acne and thickening of skin. There were no features of forehead enlargement, separated teeth, or other signs of acromegaly. Musculoskeletal examination revealed tenderness at distal ends of forearm and legs.

Initial laboratory investigations done revealed hemoglobin of 6.5 gm/dL. Iron profile showed low serum ferritin with elevated total iron-binding capacity (TIBC). Peripheral smear showed microcytic hypochromic anemia. Renal function test and serum electrolytes were unremarkable. Liver function test was normal except for elevated alkaline phosphatase (ALP). Serum insulin-like growth factor (IGF)-1 was within normal limits (110 ng/mL). An antinuclear antibody (ANA) test done was negative. Forearm and leg X-rays showed features of new bone formation in the subperiosteum (Fig. 3). Chest X-ray imaging done after the clinical diagnosis of HOA did not reveal any abnormalities. Echocardiogram did not reveal any evidence of structural heart diseases. On further evaluation, colonoscopy and upper gastrointestinal (GI) endoscopy and colonoscopy done to look for gastrointestinal

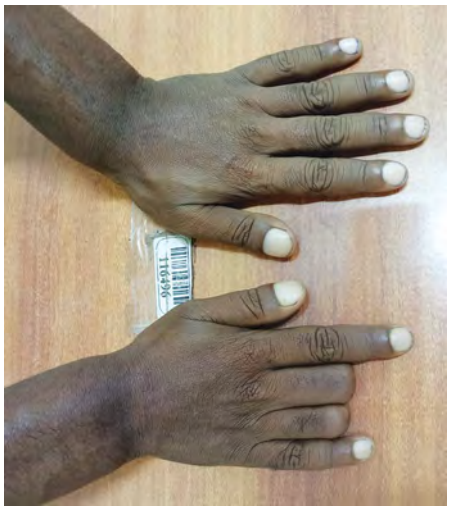

Fig. 1: Digital clubbing seen in the hands

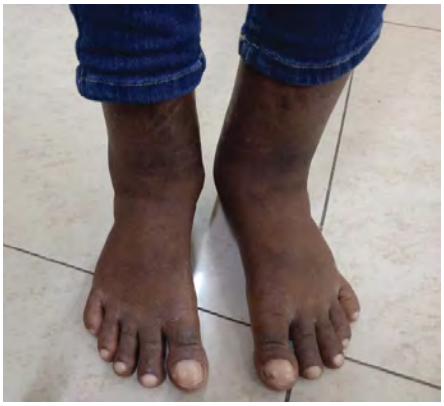

Fig. 2: Digital clubbing seen in the feet

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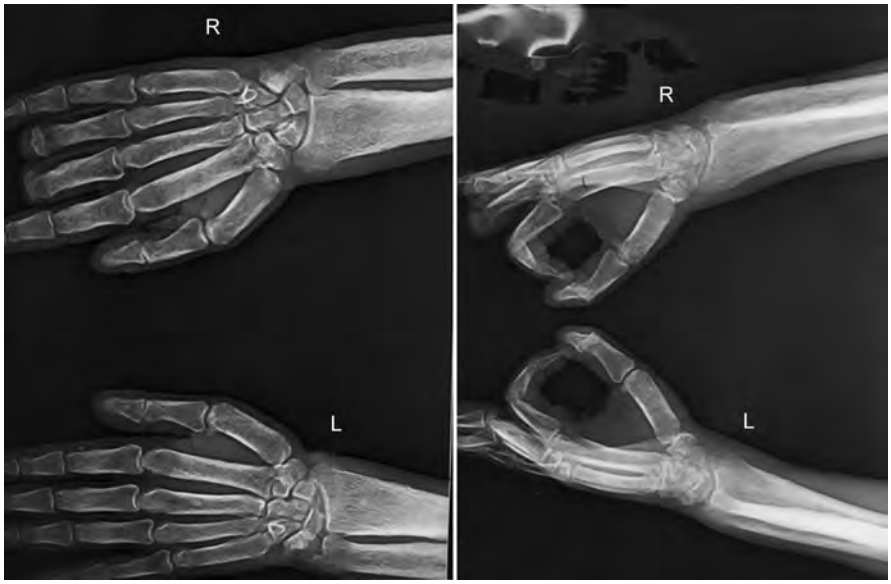

Fig. 3: Anteroposterior and lateral radiographs of both hand and distal forearm were taken. All images revealed smooth, mild periosteal reaction in the distal radius, ulna, and metacarpals

secondary causes of HOA, showed mild, nonspecific inflammatory changes. Contrast-enhanced computed tomography (CECT) thorax done to look for respiratory secondary causes of HOA did not reveal any significant abnormalities.

After secondary causes were ruled out, whole-genome sequencing was carried out to evaluate for primary causes of HOA. A homozygous nonsense variant in exon 8 of the *SLCO2A1* gene on chromosome 3 with autosomal recessive inheritance was identified. The mutation resulted in a stop codon and premature truncation of the protein. Based on clinical, laboratory, and genome sequencing features, the patient was diagnosed with PHOA. The patient was started on sulfasalazine (1500 mg daily in divided doses) and paracetamol (1300 mg daily in divided doses). His anemia was corrected with packed red blood cell (PRBC) transfusion and iron supplementation. Sulfasalazine dose was tapered over 6 months as patient improved symptomatically in terms of reduced polyarthralgia. Isotretinoin (50 mg daily) was used for acne and thickening on skin, which gradually improved. As of December, 2024, 18 months after the diagnosis, the patient is on regular follow-up and reports being happy with his disease activity. He is currently on low dose of sulfasalazine (500 mg daily) for long-term management and continues to do well.

Discussion

Hypertrophic osteoarthropathy usually presents with manifestations of skin and bone. The term was first used in the late 19th century. HOA can either be secondary or primary. The PHOA is familial and is known to follow both autosomal dominant and autosomal recessive inheritance. While accurate prevalence of HOA is not known, one study in the literature reported a prevalence in population of 0.16%. Males are primarily more affected (male-to-female ratio, 7:1).[4] Also, clinical features are seen to be of greater intensity in males.[4]

A wide array of diseases such as lung malignancies, particularly adenocarcinoma, cyanotic heart diseases, cystic fibrosis, and inflammatory bowel disease can beget secondary type of HOA. Although accurate mechanism is not elucidated, possible mechanisms have been postulated. Abnormal levels of PGE2 appear to be the cornerstone in the pathogenesis. Widely accepted postulate is inflammatory mediators activating endothelium and leading to generation of unusually large platelets. Typically, inactivation of the fragmentation of the platelets and mediators of inflammation takes place in the lungs, which is believed to be impeded in HOA.[5,7]

In PHOA, the latest studies have found a relation between mutations in *SLCO2A1* and *HGPD* genes and PHOA. These genes are associated with production of proteins which are involved in modulating pro-inflammatory mediators. When mutations occur in these genes, prostaglandins' usual transport and breakdown are severed, giving rise to accumulation of these compounds, especially PGE2. This accretion contributes significantly in pathogenesis of PHOA. This elevated levels of PGE2 lead to overexpression of vascular endothelial growth factor (VEGF), which in turn has trophic and angiogenic effects, precipitating angiogenesis, new bone formation, and edema.[7,8]

Hypertrophic osteoarthropathy usually affects the bone and skin, but rarely can present with wide cranial sutures, hypertrophic gastropathy, and patent ductus arteriosus. The most frequent clinical sign is clubbing of the fingers. Skin changes manifesting commonly are thickening with discernible skin folds. This is usually seen on the face. Other features are palmoplantar hyperhidrosis, acne, and seborrhea. In some patients, bony pain and arthralgia predominate as presenting complaints.[4]

Clinical manifestations in patients with *SLCO2A1* gene mutations exhibit variable expressivity, which explains the varied onset of the disease. There is no specific diagnostic test for this disorder. X-ray imaging of the tubular bones showing subperiosteal new bone supports the diagnosis. The existence of distinctive facial attributes along with clubbing of fingers and pointers of periostosis in X-ray imaging is the major criteria which advocates the diagnosis.[5] This implies the necessity for thorough exploration for secondary causes. In the absence of secondary causes, it is contemplated as primary. Erythrocyte sedimentation rate (ESR) and ALP are raised in several cases, which becomes practical in disease monitoring and follow-up.[4,5]

There is no definitive treatment established for HOA. Treatment is mainly aimed at alleviating symptoms and is palliative. Few reports in the literature show nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or steroids to be fruitful in palliation of bony pain and arthralgia. Bisphosphonates have also shown to relieve bony pain due to its osteoclast inhibitory action. Nguyen et al. showed sulfasalazine to be effective in relieving symptoms.[9] Other treatment modalities which are used in varying success are colchicine, methotrexate, octreotide, and pamidronate.[9,10] We used sulfasalazine and paracetamol over other drugs as we wanted to avoid worsening of patient's peptic ulcer disease.

Conclusion

Hypertrophic osteoarthropathy is an unusual etiology of digital clubbing. It also necessitates a meticulous search for secondary causes, as this could be the presenting feature of more treacherous disease. In the absence of secondary causes, it is considered primary. Recognition of particular genes through sequencing is pivotal in diagnosing PHOA. Due to its

unusual occurrence, a high degree of clinical intuition is imperative in effectual management of these cases.

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CASE REPORT

Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like Episodes: A Masquerader of Young-onset Stroke

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Abstract

Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, also known as MELAS, is an uncommon genetic disorder of mitochondrial inheritance. It presents as variable neurological and systemic manifestations. Here, we present a case of a young male who was a known case of seizure disorder and multiple neurological deficits. His clinical presentation included progressive hearing loss, diminution of vision, and recurrent headaches with vomiting. Neurological examination showed asymmetric limb weakness. Young-onset stroke was evaluated, and a magnetic resonance imaging (MRI) scan showed bilateral parieto-occipital hyperintensities. Serum lactate levels were high, which increased the suspicion of MELAS. m.3243A>G mutation was detected in mitochondrial DNA, confirming the diagnosis. Treatment involved the adjustment of antiepileptic therapy and the initiation of mitochondrial supplements. Our case emphasizes the heterogeneous clinical presentation and diagnostic challenges of MELAS as an important cause of young-onset stroke, highlighting the importance of early suspicion and confirmatory investigations for personalized management strategies to optimize patient outcomes.

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Introduction

Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) is an uncommon mitochondrial disorder that profoundly affects patients' overall health and quality of life. Stroke-like events, muscle weakness, and increased lactate levels characterize this syndrome, among other clinical manifestations. MELAS typically emerges during childhood or early adulthood and can lead to considerable morbidity due to its progressive course and the severity of its neurological consequences.

The stroke-like episodes are characterized by neurological impairments that show atypical vascular distribution patterns. These episodes may present with temporary hemiparesis, cortical blindness, and fluctuations in consciousness, frequently accompanied by seizures and intense headaches.

The young-onset stroke necessitates looking for the secondary causes, as these present as recurrent stroke episodes. Particularly, common risk factors such as hypertension, diabetes, and high cholesterol are absent in the younger population. MELAS syndrome should be taken into account as a potential diagnosis in younger individuals who experience stroke-like episodes, particularly if other neurological or systemic symptoms are also present. This case report underscores the importance of considering MELAS in the differential diagnosis of stroke in younger patients. It also emphasizes the necessity of a thorough diagnostic evaluation to accurately identify this condition in such cases.

Case Description

A 19-year-old male, with a 5-year history of seizures marked by myoclonic jerks followed by generalized convulsions, came in with weakness in all four limbs. Additionally, he had bilateral sensorineural hearing loss (SNHL) for the past 4 years and progressive vision deterioration over the last 2 years. The patient also reported a 15-day history of headache, worsened by neck movements, with a frontal pattern, photophobia, and vomiting. Throughout this period, the severity of his SNHL and vision loss gradually increased.

The patient's vital signs were stable, and the systemic evaluation showed no significant findings. Neurologically, the examination revealed a normal Glasgow Coma Scale (GCS) score, bilateral SNHL, and reduced visual fields in the left hemifield of both eyes. Additionally, abnormal plantar reflexes were noted, with an extensor response on the right and a flexor response on the left. Additionally, the patient exhibited signs of delayed puberty, including the absence of axillary hair, lack of a mustache, and short stature (height 134 cm, more than two standard deviations below the mean for his age).

The initial diagnostic assessments included:

- NCCT of the head: Identified bilateral calcifications in the basal ganglia and occipital infarcts.
- Hormonal profile: Luteinizing hormone (LH) 1.85 IU/L, follicle-stimulating hormone (FSH) 2.43 IU/L, both within normal limits.
- Thyroid function tests: T3 3.29 nmol/L, T4 0.67 nmol/L, thyroid-stimulating hormone (TSH) 1.54 µIU/mL.
- CSF analysis: Results were normal.
- Fundoscopy: No abnormalities detected.
- Serum lactate: Elevated at 11.6 mmol/L.
- Creatine kinase (CK): 509 U/L
- Lactate dehydrogenase: 290 U/L
- Vitamin D3: 37 ng/mL
- Prolactin: 11.22 ng/mL
- Testosterone: 0.91 ng/mL
- Cortisol: 213 nmol/L
- HbA1c: 4.1%.
- Visual evoked potential (VEP): Indicated dysfunction in the left visual pathway.

Around 2.5 months later, the patient developed left-sided weakness, reduced response, inappropriate dressing behavior, and confusion between left and right sides. Neurological examination revealed muscle wasting in all four limbs, decreased strength on the left side, and cognitive decline. There was no significant family history.

Magnetic Resonance Imaging (MRI) Findings

MRI scans revealed:

- T2-weighted hyperintensities in the bilateral parieto-occipital regions (Fig. 1).

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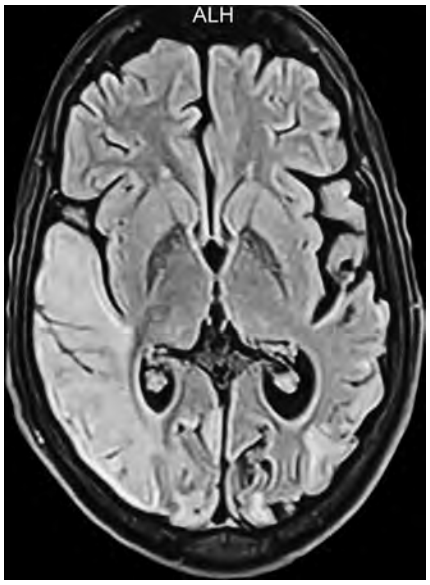

Fig. 1: T2-weighted hyperintensities in bilateral parieto-occipital lobes

- Bilateral basal ganglia showed diffusion restriction.
- Lactic acid peak is present in magnetic resonance spectroscopy.

Muscle biopsy findings were unremarkable.

Genetic analysis for the gene m.3243A>G mutation was present. This analysis confirmed the diagnosis of MELAS syndrome.

The patient was initially prescribed levetiracetam to manage seizures, with gradual discontinuation of valproate. Additionally, the patient began supplementation with benfotiamine (vitamin B1), carnitine, coenzyme Q10, arginine, riboflavin, and biotin. Adjustments to the antiepileptic regimen were made as seizures persisted.

Discussion

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome is one of the most common mitochondrial disorders passed down maternally.[1] The condition is mainly caused by a mutation in mitochondrial DNA, where adenine is replaced by guanine at nucleotide position 3243 (m.3243A>G) within the *MT-TL1* gene. This gene is responsible for encoding the tRNALeu (UUR), which is essential for mitochondrial function.[2,3] The MELAS study group in Japan has established diagnostic guidelines that combine clinical, laboratory, and genetic testing criteria.[4]

Category A: Features Suggestive of Stroke-like Episodes

- Headache with accompanying vomiting.
- Hemiplegia.
- Seizures.
- Acute focal lesions detected on brain imaging.
- Cortical blindness or hemianopia.

Category B: Mitochondrial Dysfunction Signs

- Mitochondrial abnormalities were found in a muscle biopsy.
- Elevated lactic acid in both plasma and cerebrospinal fluid, or reduced mitochondrial enzyme activity.
- Detection of a specific gene mutation.

Definitive Diagnosis

Presence of at least two criteria from category A and two criteria from category B, with a total of four.

Probable Diagnosis of MELAS

- One criterion from category A and two from category B, for a minimum of three.

The diagnosis of MELAS was confirmed in this patient based on the combination of symptoms, including headaches, vomiting, seizures, and elevated lactate levels in the plasma, alongside the identification of the m.3243A>G mutation. This genetic mutation affects the *MT-TL1* gene, which is responsible for encoding the tRNALeu (UUR), a critical component in mitochondrial protein synthesis. As a result, the mutation disrupts normal mitochondrial function, leading to impaired energy production and widespread dysfunction in various organs, contributing to the characteristic features of MELAS syndrome. The energy deficit from mitochondrial dysfunction leads to abnormal mitochondrial growth in blood vessels, causing angiopathy and impaired circulation, which contributes to stroke-like episodes. Additionally, reduced nitric oxide (NO) production, due to lower levels of precursors such as arginine and citrulline, along with oxidative stress, further worsens vascular health and exacerbates symptoms.[5]

Stroke-like episodes are a key feature of MELAS syndrome, affecting 84–99% of patients. These episodes often present with a variety of neurological symptoms, including transient aphasia (temporary loss of language abilities), vision impairment, and motor weakness, typically affecting one side of the body. Severe headaches, changes in mental status such as confusion, and seizures are also common. These episodes, which cause significant disruption to daily life, contribute to progressive neurological deterioration, as repeated events lead to cumulative brain damage and long-term cognitive and motor impairments. Neuroimaging typically shows asymmetric, nonvascular "stroke-like" patterns, mainly in the temporal, parietal, and occipital regions. While MR angiography is often normal, MR spectroscopy usually reveals elevated lactate levels. This case underscores the importance of considering MELAS in younger patients with stroke-like episodes and highlights the need for lactate measurements in diagnosis.

Mitochondrial mutations typically affect all offspring of a female carrier, yet the patient's older siblings were unaffected. This may be due to the patient's heteroplasmic mutation or a *de novo* mutation. The m.3243A>G mutation presents a wide clinical spectrum, from severe MELAS in about 10% of carriers to asymptomatic cases in another 10%. Intermediate phenotypes can manifest between these extremes, involving single-organ disorders such as cardiomyopathy or diabetes, or multiorgan issues with symptoms such as myopathy, diabetes, and hearing loss. Our ability to trace the exact origin of the mutation was limited, as the patient declined genetic testing for the siblings.[6]

Furthermore, this case underscores the importance of early MELAS diagnosis due to the complexities associated with treatment. Valproic acid should be avoided in MELAS patients, as it can impair mitochondrial function, potentially worsening seizure activity.[7,8] Other anticonvulsants that may adversely affect mitochondrial metabolism include gabapentin, vigabatrin, topiramate, zonisamide, ethosuximide, phenytoin, carbamazepine, and phenobarbital.[9] In this case, the patient was initially treated with valproate prior to the definitive diagnosis, which may have contributed to the exacerbation of seizure-like episodes.

By gaining a deeper understanding of these aspects of MELAS syndrome, clinicians can improve their ability to diagnose, manage, and treat affected patients while minimizing the risk of medication-related complications.

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CASE REPORT

Bilateral Parotid Tuberculous Lymphadenitis Mimicking Warthin Tumor in an Elderly Male: A Case Report

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Abstract

Tuberculosis involving the parotid lymph nodes is rare and can clinically and radiologically mimic benign neoplasms such as Warthin tumor, particularly when bilateral. We present the case of a 72-year-old male with bilateral parotid swellings, initially suspected to be Warthin tumors based on magnetic resonance imaging (MRI) findings showing well-defined, cystic lesions with focal solid components and central necrosis. Histopathological examination following ultrasound-guided biopsy revealed caseating granulomas consistent with tuberculous lymphadenitis. This case highlights the importance of including infectious etiologies such as tuberculosis in the differential diagnosis of bilateral parotid lesions, especially in endemic regions.

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Introduction

Bilateral parotid gland swellings in elderly males typically raise suspicion for Warthin tumor, a benign salivary gland neoplasm with a known association with smoking and male sex. However, infectious etiologies, particularly tuberculosis, may mimic this presentation both clinically and radiologically.[1,2] Tuberculous involvement of parotid lymph nodes is uncommon, accounting for less than 1% of extrapulmonary tuberculosis cases, but should be considered in endemic regions or in cases showing atypical clinical courses.[3]

Case Description

A 72-year-old male presented with painless, gradually progressive bilateral parotid swellings of 3 months' duration. There were no associated fever, weight loss, or night sweats. Clinical examination revealed soft, mobile, and nontender swellings over both parotid regions without facial nerve involvement.

Imaging Findings

Magnetic resonance imaging of the head and neck showed bilateral well-marginated lesions within the parotid glands. The lesions were cystic with mild peripheral enhancement. No intraparotid ductal dilation or calcification was noted. Based on these findings, Warthin tumors were considered the primary differential diagnosis (Fig. 1).

Intervention and Diagnosis

Due to the bilateral nature and necrotic features, ultrasound-guided fine-needle aspiration cytology (FNAC) was performed, which showed granulomatous inflammation. Subsequent core needle biopsy revealed caseating granulomas with Langhans giant cells. Ziehl–Neelsen staining demonstrated acid-fast bacilli, confirming tuberculous lymphadenitis.

Further Workup

The patient underwent chest radiography and sputum testing, which were negative for active pulmonary tuberculosis. No evidence of systemic involvement was found. He was initiated on standard antitubercular therapy (ATT) and showed favorable response over subsequent follow-up.

Discussion

Tuberculous lymphadenitis of the parotid gland is a rare and often overlooked form of extrapulmonary tuberculosis, frequently leading to diagnostic challenges due to its ability to mimic benign neoplasms such as Warthin tumor.[1,2] Warthin tumor is the second most common benign salivary gland tumor, predominantly affecting elderly males and smokers, and is characteristically bilateral in a minority of cases. However, bilateral parotid involvement by tuberculosis is exceedingly rare, with only isolated case reports in the literature.[3,4]

Radiologically, both tuberculous lymphadenitis and Warthin tumor may present as well-defined, cystic lesions with or without solid components and central necrosis, making differentiation based solely on imaging difficult.[1] In endemic regions, the possibility of infectious etiologies should be considered when evaluating cystic or necrotic parotid lesions, especially when bilateral or when the clinical course is atypical for neoplasm.[2,3]

Histopathological confirmation remains the gold standard for diagnosis. FNAC and core needle biopsy are essential tools, with the latter providing more definitive evidence through identification of caseating granulomas and Langhans giant cells. Detection of acid-fast bacilli by Ziehl–Neelsen staining or molecular methods confirms the diagnosis of tuberculosis.[4,5] Early tissue diagnosis is critical to avoid unnecessary surgical intervention, as Warthin tumors are typically managed surgically, while tuberculous lymphadenitis responds well to medical therapy alone.[5]

Management with ATT leads to excellent outcomes in most cases, with resolution of the lesions and prevention of complications. Routine evaluation for systemic tuberculosis, including chest radiography and sputum analysis, is important to rule out concurrent pulmonary involvement and to guide comprehensive treatment.[3,5]

In summary, clinicians should maintain a high index of suspicion for tuberculous lymphadenitis in patients presenting with bilateral parotid swellings, particularly in tuberculosis-endemic areas or when the clinical and imaging features are atypical for neoplasm. Timely recognition and appropriate management can prevent unnecessary surgery and ensure optimal patient outcomes.[2,5]

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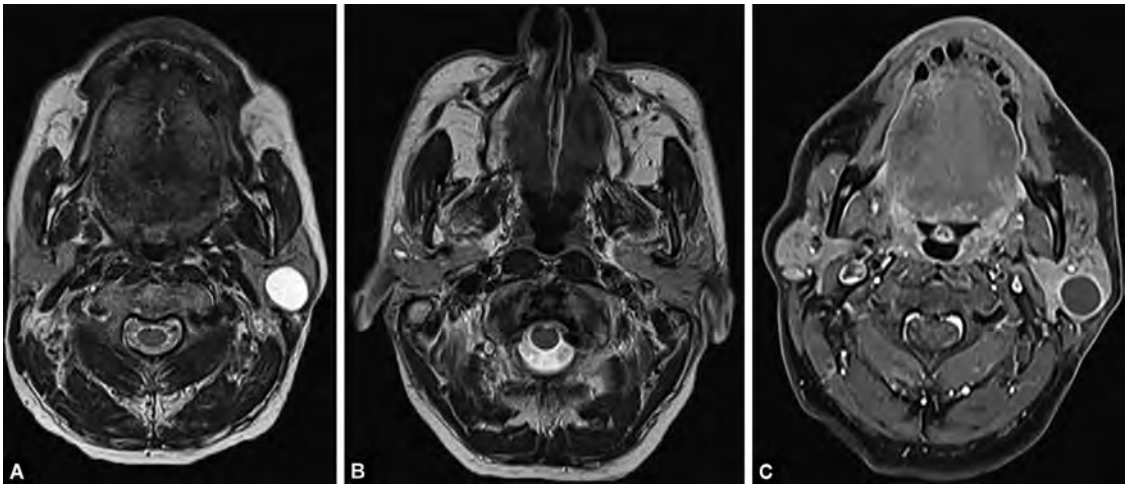

Figs 1A to C: (A) T2-weighted imaging hyperintense cystic lesion in superficial lobe of left parotid gland; (B) Few small T2WI hyperintense cystic lesion in right superficial lobe of parotid gland; (C) Postcontrast image show peripheral rim enhancement of the cystic lesion without solid component

Conclusion

In regions with high tuberculosis prevalence, bilateral parotid swellings with cystic or necrotic imaging patterns should raise suspicion for tuberculous lymphadenitis, even in elderly males where Warthin tumor is a common consideration.[1,2] Biopsy and histopathological confirmation remain indispensable for definitive diagnosis and for avoiding unnecessary surgical intervention.[4,5]

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CASE REPORT

Radiologic Deception: A Case Report of Tuberculosis with Nodular Onset and Cystic Conclusion

Chandrika Sachar[1*], Ankita Garg[2], Sanjeev Jindal[3]

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Abstract

Cystic lung disease is a rare and underrecognized manifestation of pulmonary tuberculosis (TB), often masquerading as other diffuse cystic lung disorders and complicating timely diagnosis. We present the unusual case of a 25-year-old woman who developed progressive dyspnea and pleuritic chest pain shortly after initiating antituberculous therapy. Initial imaging revealed classical miliary nodules without cystic changes. However, within a month of treatment, follow-up high-resolution CT unveiled an unexpected transformation of numerous thin-walled cysts clustered in the upper lobes, accompanied by ground-glass opacities, septal thickening, and a tree-in-bud pattern suggestive of active endobronchial spread. This radiological evolution, occurring posttreatment initiation, points to a dynamic pathophysiological process likely involving immune-mediated airway obstruction, necrosis, and structural remodeling of the parenchyma. This case reveals a rare form of pulmonary TB that mimics other cystic lung diseases. In TB-endemic areas, early recognition of cystic transformation, especially with recurrent pneumothorax or atypical imaging, is vital. Though uncommon, it highlights TB's chameleon-like nature and the value of serial imaging in guiding timely, effective management. Radiologists and clinicians should remain vigilant for such rare yet reversible complications in TB-endemic settings.

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Introduction

Cystic lung disease is characterized by air-filled spaces within the lung parenchyma and is typically associated with congenital disorders, infections, neoplasms, or interstitial diseases. Pulmonary tuberculosis (TB), a common infectious disease in endemic regions, rarely presents with cystic changes. Such presentations are uncommon and often misdiagnosed as other cystic lung diseases such as Langerhans cell histiocytosis, lymphangioleiomyomatosis, or *Pneumocystis jirovecii* pneumonia.[1,2]

Pulmonary cysts are a highly uncommon complication of TB and represent one of the rarest manifestations of this globally prevalent disease. These cystic changes may arise at different stages of the illness, varying in severity and clinical outcome. Notably, they can persist even after successful completion of antitubercular therapy (ATT). In this report, we present the case of a young patient with pulmonary TB who developed lung cysts, highlighting a rare and atypical presentation of the disease.

Case Description

Patient Information

A 25-year-old female presented to the emergency department with a 1-week history of shortness of breath and right-sided pleuritic chest pain. Over the past 24 hours, both symptoms had progressively worsened. She also reported a 1-month history of low-grade fever, night sweats, productive cough with yellowish sputum, and generalized fatigue. Notably, 2 months prior, she had been hospitalized with similar symptoms and was recently diagnosed with pulmonary TB (miliary pattern of disease).

The patient had initiated ATT just 1 month ago, after which she began experiencing a worsening of her symptoms.

There was no history of smoking, exposure to biomass fuel, or prior chronic illness such as diabetes or hypertension. The patient is immunocompetent, with no evidence of underlying immunosuppression.

Clinical Examination

On presentation, the patient had an oxygen saturation of 76% on room air, which improved to 98% with intranasal oxygen delivered at 5 L/min. Her vital signs included a blood pressure of 130/70 mm Hg, a pulse rate of 108 beats/min, and a respiratory rate of 26 breaths/min.

Laboratory parameters, including total leukocyte count, were within normal limits. No signs of ATT-induced hepatitis were clinically apparent.

Imaging Findings

Initial chest X-ray (Fig. 1) and high-resolution CT (HRCT) of the chest (Fig. 2) demonstrated a classical miliary pattern, with diffusely distributed 1–3 mm nodules uniform in size and distribution across both lungs, without any evidence of cystic lesions. These findings were consistent with miliary TB. However, there were no cystic lesions observed at that time, indicating a dynamic progression in the radiological findings.

Approximately 1 month after initiation of ATT, a contrast-enhanced CT (CECT) and high-resolution CT (HRCT) scan of the chest was performed using a 64-slice multidetector CT scanner (Ingenuity CT, Philips). Follow-up CT imaging revealed the development of multiple thin-walled cystic lesions predominantly involving the bilateral upper lobes. These cysts were accompanied by areas of consolidation, ground-glass opacities, interlobular septal thickening, and a tree-in-bud pattern suggestive of

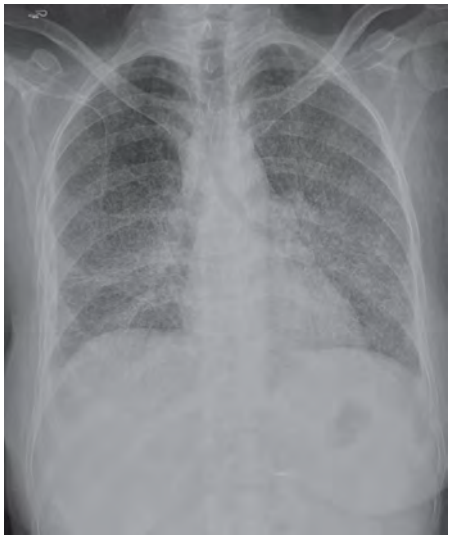

Fig. 1: Frontal chest radiograph showing diffusely distributed fine nodular opacities throughout both lung fields, consistent with a miliary pattern of tuberculosis. No cystic changes are seen at this stage

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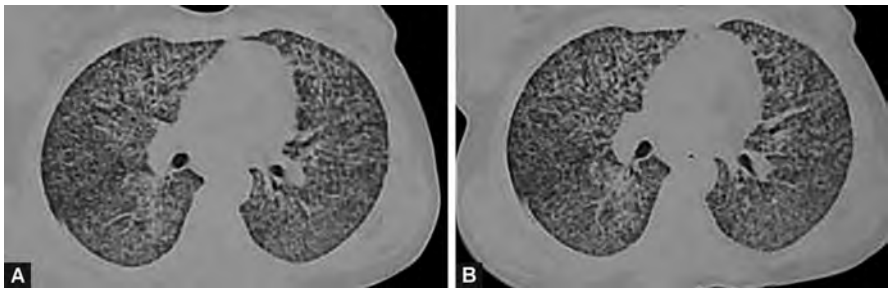
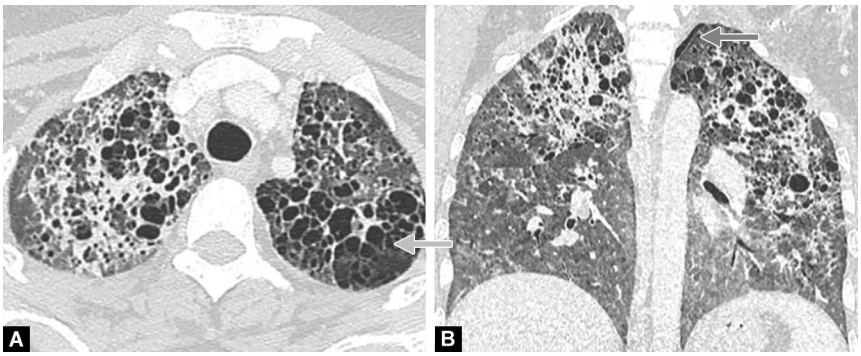
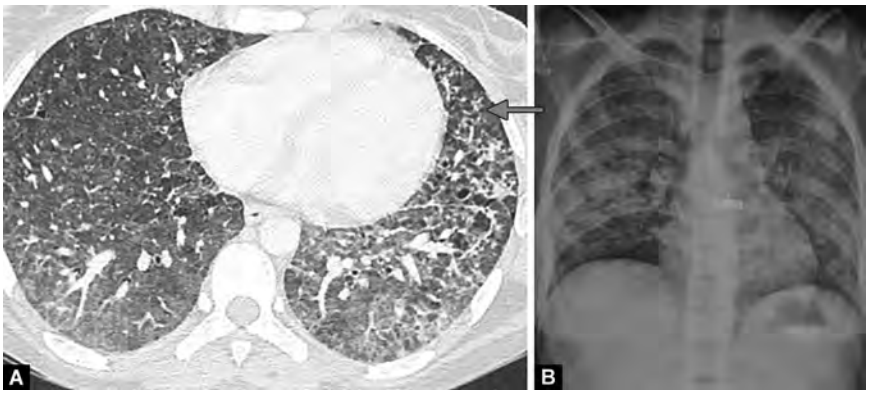


Figs 2A and B: Initial high-resolution CT scan of the chest reveals numerous, uniformly distributed 1–3 mm nodules across both lungs, characteristic of miliary tuberculosis. No evidence of cystic transformation is observed



Figs 3A and B: Follow-up high-resolution axial (A) and coronal (B) CT imaging (1 month post-ATT initiation) shows interval development of multiple thin-walled variably sized cystic lesions (light gray arrow) with surrounding interspersed areas of consolidation in bilateral lungs, predominantly in the bilateral upper lobes. Additional findings include patchy ground-glass opacities, interlobular septal thickening, and a small pneumothorax (dark gray arrow). These findings suggest active endobronchial spread and cystic transformation during treatment



Figs 4A and B: (A) Follow-up high-resolution axial CT imaging (1 month post-ATT initiation) showing multiple soft tissue density centrilobular nodules (gray arrow) are seen scattered in bilateral lungs, giving a tree-in-bud appearance; (B) Patient's frontal chest X-ray (1 month post-ATT initiation) showing diffuse miliary nodules and scattered cystic changes nodules

active endobronchial spread. Additionally, a small right-sided pneumothorax (~5 mm separation) was noted, along with mediastinal lymphadenopathy (Figs 3 to 5).

Interestingly, a subsequent follow-up chest X-ray performed 1 month after the CT scan (i.e., 2 months into ATT) showed interval development of a few cystic changes, correlating with the earlier CT findings and supporting a progressive cystic transformation occurring during the treatment course (Fig. 6).

Follow-up imaging has not been performed yet, as the patient is currently undergoing ATT. Imaging will be considered upon completion or significant progress of treatment.

Discussion

A lung cyst is defined as a well-demarcated, air-filled cavity located within the lung parenchyma, typically measuring more than 1 cm in diameter. It is surrounded by a distinct epithelial or fibrous wall, usually less than 1 mm thick, though it can be up to 2–3 mm in some cases.[3]

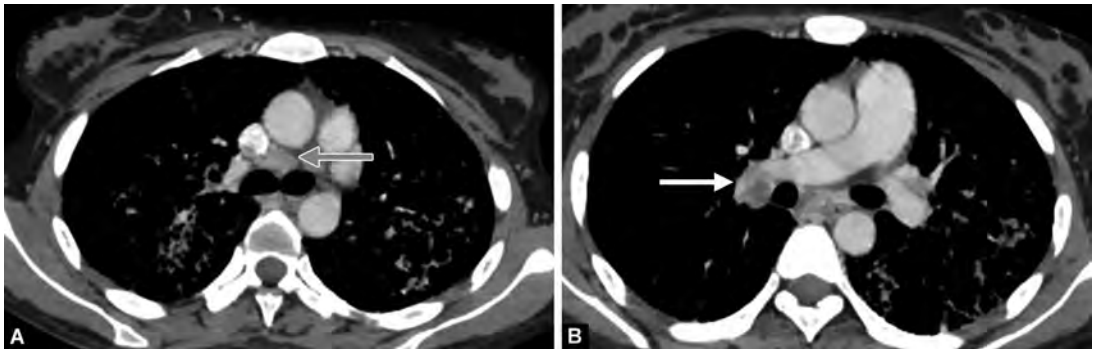
Cystic and bullous transformations of the lung parenchyma due to TB represent an exceptionally rare and striking presentation, with only a handful of cases reported to date. This atypical form of TB is marked by the rapid emergence of numerous cyst-like lesions, primarily affecting the upper lobes of both lungs. Clinically, it is often accompanied by profound respiratory distress and recurrent episodes of pneumothorax, frequently culminating in a life-threatening or even fatal outcome.

Cystic pulmonary TB remains a diagnostic challenge due to its rarity and nonspecific radiological features. The mechanisms implicated in cyst formation include:

- A check-valve mechanism from granulomatous inflammation leading to air trapping.[4,5]
- Caseating necrosis of airway walls progressing to cystic bronchiectasis.[1,2]
- Secondary infection or scarring of larger airways leading to distal dilatation.[5]

Our case aligns with these proposed mechanisms, particularly considering the radiological progression observed. Initial imaging demonstrated no evidence of cystic changes; however, follow-up imaging after 1 month of ATT revealed the development of multiple cystic lesions. This evolution suggests a dynamic interplay between the host's immune response, the effects of ATT, and the underlying pathophysiology of the disease. It raises the possibility that cyst formation may not be a primary manifestation, but rather a secondary consequence of treatment-induced necrosis, bronchial obstruction, or remodeling of the lung parenchyma during the healing process. Similar cases have reported rapid cyst development during or after treatment initiation, with variable outcomes, some resolving, others persisting or resulting in complications such as pneumothorax.[4,5]

On high-resolution CT (HRCT), the cystic lesions are predominantly distributed in the upper and middle lung zones, exhibiting a predilection for subpleural and peribronchovascular regions. These cysts appear as thin-walled, air-filled structures with irregular margins, often associated with centrilobular nodules and a tree-in-bud pattern indicative of endobronchial spread of infection. The surrounding lung parenchyma frequently shows areas of ground-glass opacity and interlobular septal thickening, reflecting active inflammation and interstitial involvement.



Figs 5A and B: Follow-up contrast-enhanced axial CT imaging (1 month post-ATT initiation) showing multiple variably sized heterogeneously enhancing enlarged mediastinal (gray arrow) and hilar (white arrow) lymph-nodes

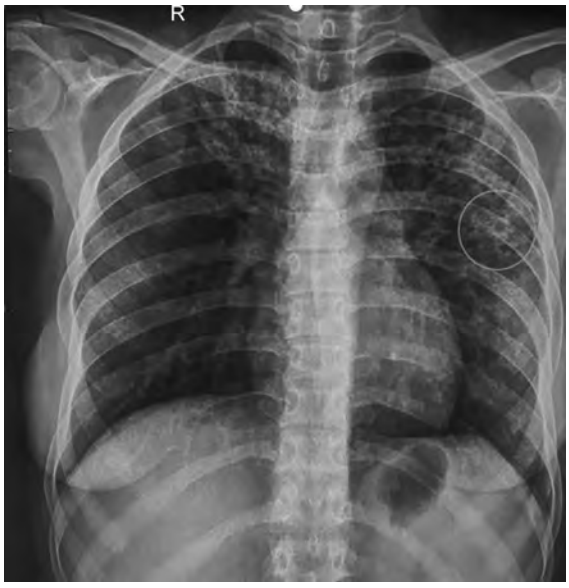


Fig. 6: Follow-up frontal chest radiograph (2 months into ATT) demonstrates interval appearance of a few thin-walled cystic lucencies (shown in circle), correlating with prior CT findings and confirming progressive cystic changes over the treatment course

As the disease progresses, the cystic lesions demonstrate interval enlargement, architectural distortion, and a tendency to coalesce, resulting in multiloculated air spaces. The upper lobe dominance may be explained by the higher ventilation-perfusion ratio and elevated oxygen tension in these zones, conditions that favor the growth and persistence of *Mycobacterium tuberculosis*. This radiologic evolution highlights the dynamic nature of tuberculous lung involvement and underscores the importance of serial imaging in patients with atypical presentations.[6]

Differential diagnoses of diffuse cystic lung disease include lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis, lymphocytic interstitial pneumonia, and *Pneumocystis jirovecii* pneumonia. However, the absence of extrapulmonary findings, a supportive clinical context, and response to anti-TB therapy in this case supported the diagnosis of cystic pulmonary TB.

This case also parallels the findings of Ray et al., who reported cystic transformation during pulmonary TB in a young female, with partial regression of cysts following ATT.[1] The case reinforces the significance of integrating imaging with clinical judgment for diagnosis.

In settings where TB is endemic, such as in our case, it is imperative to consider TB-related complications, such as diffuse cystic lung disease, as a plausible cause of recurrent pneumothorax before exploring rarer entities such as lymphangioleiomyomatosis. Overlooking this connection may delay life-saving treatment. The timely recognition of this atypical but increasingly acknowledged sequela of pulmonary TB is crucial, as appropriate initiation of ATT not only targets the underlying mycobacterial infection but also mitigates the risk of severe, potentially fatal complications such as spontaneous pneumothorax. In high-burden regions, early suspicion and treatment can mean the difference between recovery and rapid clinical deterioration.

Conclusion

This case highlights the critical role of serial imaging in unraveling atypical trajectories of pulmonary TB. Cystic transformation, though rare, can emerge during treatment and masquerade as other diffuse cystic lung disorders, complicating diagnosis. Timely recognition of these evolving patterns enables early therapeutic intervention, potentially reversing cystic changes and averting serious complications. In this context, radiological surveillance is not just supportive; it is central to navigating the dynamic landscape of TB and ensuring precise, life-saving care.

Consent for Publication

All authors give consent for the publication of the manuscript in your esteemed journal.

Authors' Contributions

All authors have contributed to the conceptualization, design, acquisition of data, drafting, and review of this article and approved the version to be published.

Availability of Data and Materials

All data underlying the findings are fully available.

Ethics Approval and Consent to Participate

No ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals.

Informed consent was obtained from the patient included in this study. Consent for publication: The patient gave her written consent to use his personal data for the publication of this case report and any accompanying images.

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CASE REPORT

A Triad of Telltale Clues: Macroglossia Raccoon Eye and Nerve Compression Unveil Amyloid Light Chain Amyloidosis

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Abstract

Systemic amyloid light chain (AL) amyloidosis is a rare but potentially fatal disorder caused by deposition of misfolded immunoglobulin light chains, often presenting with vague, nonspecific symptoms that delay diagnosis. We report a diagnostically striking case of a 65-year-old male presenting with progressive tongue enlargement, periorbital purpura, submandibular swelling, and a prior history of carpal tunnel syndrome—classic yet under-recognized features of AL amyloidosis. Despite negative urine immunofixation and Bence-Jones proteinuria, the markedly elevated free lambda light chains and an abnormal kappa/lambda ratio raised clinical suspicion. Bone marrow biopsy revealed 25% plasma cells with lambda restriction and t(11;14) translocation, confirming AL amyloidosis associated with plasma cell myeloma. Treatment with a daratumumab-, bortezomib-, and dexamethasone-based regimen led to dramatic clinical improvement. This case emphasizes the importance of recognizing subtle external manifestations as early diagnostic clues in AL amyloidosis, especially in the absence of classical laboratory markers. Timely recognition can significantly improve outcomes in a condition where therapeutic delay can be devastating.

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Introduction

Amyloidosis comprises a group of disorders characterized by abnormal folding of specific proteins that aggregate into insoluble fibrils depositing in tissues. These amyloid fibrils share a characteristic beta-pleated sheet structure arranged in an antiparallel configuration, rendering them resistant to degradation. Their accumulation disrupts tissue architecture and function, leading to organ damage.

More than 60 proteins can form amyloid fibrils, but only about half cause human disease. Amyloidosis may be systemic or localized, and inherited or acquired. Clinical presentation varies widely depending on involved organs, commonly affecting heart, kidneys, liver, peripheral nerves, and gastrointestinal tract. Current classification is based on the precursor protein's biochemical nature, with frequent types including AL (immunoglobulin light chain), AA (serum amyloid A), ATTR (transthyretin), and beta-2 microglobulin amyloidosis in dialysis patients.[1,2]

Amyloid light chain amyloidosis, the most common systemic form, results from monoclonal plasma cell disorders producing misfolded light chains that deposit in tissues causing symptoms such as tongue enlargement (macroglossia), periorbital bruising ("raccoon eyes"), submandibular swelling, and entrapment neuropathies such as carpal tunnel syndrome. AL amyloidosis may exist as isolated plasma cell dyscrasia or progress to overt multiple myeloma. In some patients, including ours, the diagnosis revealed plasma cell neoplasia with marrow involvement and cytogenetic abnormalities such as t(11;14), highlighting the need for comprehensive evaluation.[3]

Case Description

A 65-year-old male with ischemic heart disease after percutaneous coronary intervention and obstructive sleep apnea presented with a 1.5-year history of progressive tongue enlargement, increasing neck girth, heaviness, dysphagia, and speech difficulty. He also reported intermittent frothy urine, which was suggestive of proteinuria. Notably, he had undergone carpal tunnel release surgery 1 year prior.

On examination: pulse 82/minute, blood pressure 130/80 mm Hg, respiratory rate 16/minute, oxygen saturation 98% on room air, and temperature 98.6°F. General physical examination, periorbital purpura ("raccoon eyes") (Fig. 1), revealed macroglossia (Fig. 2) and bilateral submandibular swelling (Fig. 3), increased swelling in hands (Fig. 4). No pallor, icterus, cyanosis, lymphadenopathy, or pedal edema was noted. Respiratory system, cardiovascular system, and per abdomen examination revealed no abnormality. Central nervous system examination was within normal limits.

Neck ultrasonography showed diffuse tongue muscle hyperplasia with uniform echotexture. Thyroid imaging indicated early Hashimoto's thyroiditis. Positron emission tomography–computed tomography demonstrated diffuse muscular overactivity, especially in tongue muscles. Stroboscopy revealed generalized laryngeal edema.

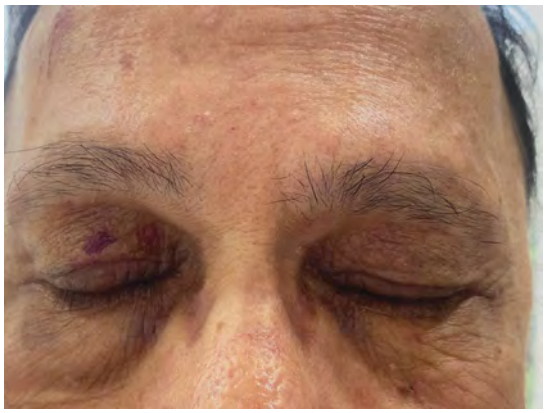

Fig. 1: Periorbital purpura

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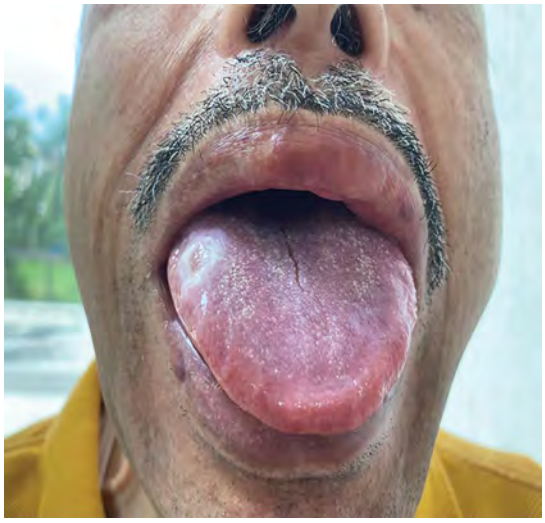

Fig. 2: Macroglossia

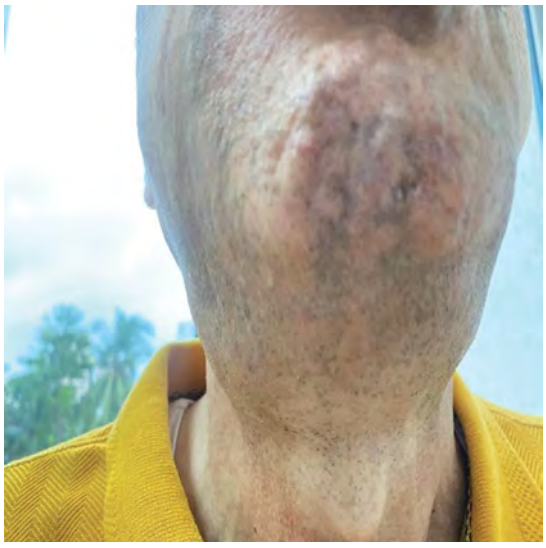

Fig. 3: Submandibular swelling

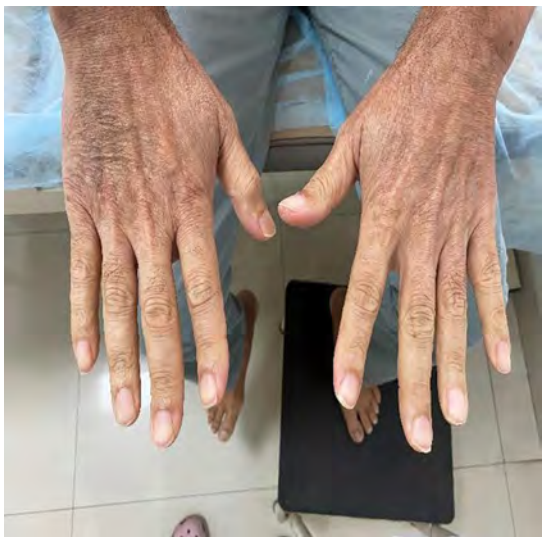

Fig. 4: Increased swelling in hands

Investigations (summarized in one line): Hemoglobin 12.2 gm/dL; total leukocyte count 7,070/µL; platelets 2.79 lakh/µL; erythrocyte sedimentation rate 25 mm/hour; serum creatinine 0.77 mg/dL; aspartate aminotransferase 20.1 U/L; alanine aminotransferase 11.2 U/L; urine protein-to-creatinine ratio 0.24; free lambda light chain 980 mg/L (reference range: 4.23–27.69); free kappa light chain 21.4 mg/L (reference range: 2.37–20.73); kappa/lambda ratio 0.020 (reference range: 0.22–1.74); total protein 6.75 gm/dL; albumin 3.98 gm/dL; albumin/globulin ratio 1.43; serum protein electrophoresis—no M-band; immunoglobulin G/A/M—normal; urinalysis, Bence-Jones protein, and urine immunofixation—negative; 2D echocardiography—ejection fraction 55%, mildly reduced global longitudinal strain (–20.3%).

Abdominal fat pad biopsy was inconclusive with negative Congo red staining. Bone marrow aspiration showed 20% plasma cells with lambda light chain restriction; biopsy confirmed 25% involvement by lambda-restricted plasma cell myeloma. Fluorescence *in situ* hybridization (FISH) detected t(11;14) MYEOV::IgH translocation, confirming AL amyloidosis secondary to plasma cell dyscrasia.

Treatment and Outcome

The patient was treated with daratumumab, bortezomib, and dexamethasone for 14 cycles, with marked reduction in tongue (Fig. 5) and submandibular swelling (Fig. 6) and clinical improvement on follow-up.

Discussion

Systemic AL amyloidosis results from extracellular deposition of misfolded monoclonal immunoglobulin light chains produced by clonal plasma cells. Amyloid fibrils infiltrate multiple organs; combined involvement of tongue, soft tissues, and peripheral nerves strongly suggests systemic amyloidosis.

Macroglossia, although uncommon, is a key clinical clue. Differential diagnoses include neoplasms, vascular malformations, hypothyroidism, and nutritional deficiencies.[4,5] Periorbital purpura ("raccoon eyes") is pathognomonic but under-recognized, due to vascular fragility from amyloid infiltration.[6] Carpal tunnel syndrome may precede amyloidosis diagnosis by months or years, reflecting early soft tissue involvement.[7]

Fluorescence *in situ* hybridization in our patient revealed a MYEOV::IGH fusion, consistent with the classic t(11;14)(q13;q32) translocation, which involves the *CCND1* (cyclin D1) gene on

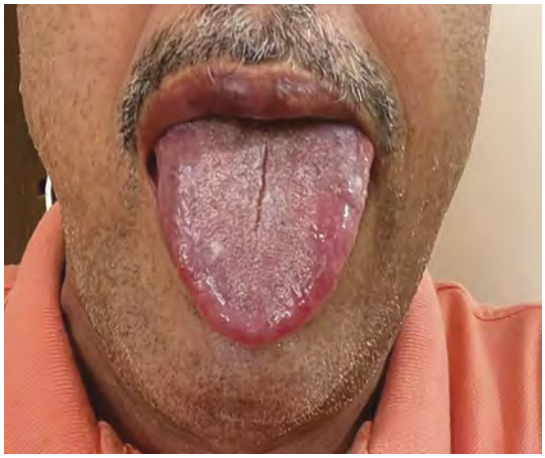

Fig. 5: Reduced tongue size

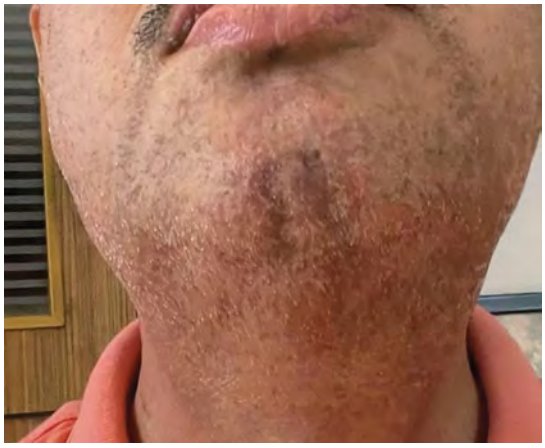

Fig. 6: Reduced submandibular swelling

chromosome 11 and the IgH (immunoglobulin heavy chain) locus on chromosome 14. This translocation results in overexpression of cyclin D1, promoting G1/S cell cycle progression and clonal plasma cell proliferation.

In multiple myeloma, t(11;14) is seen in approximately 15–20% of patients and is considered a standard-risk cytogenetic abnormality. However, in AL amyloidosis, its prevalence is much higher—up to 50%, suggesting a strong biological link between t(11;14) and amyloidogenic plasma cell clones.[3]

The patient's dramatic clinical improvement on daratumumab, bortezomib, and dexamethasone confirms diagnosis and supports this therapeutic approach.

Conclusion

This case of AL amyloidosis vividly illustrates how the body whispers before it screams. Subtle yet classical signs—macroglossia, raccoon eyes, and submandibular swelling—often go unrecognized amidst common differentials, delaying diagnosis in a condition where time is the enemy. What began as vague symptoms evolved into a textbook constellation of systemic amyloidosis, backed by definitive light chain excess, bone marrow involvement, and hallmark t(11;14) cytogenetics. The case reminds clinicians to listen carefully to the "red flag signs" that amyloidosis quietly presents: carpal tunnel, unexplained heart disease, purpura, and tongue changes—signs that should never be dismissed as benign. In an era where diagnostic precision defines patient survival, this case is a call to sharpen our clinical instincts, recognize the zebra in the herd, and act before multiorgan dysfunction sets in. Amyloidosis may be rare—but missing it is deadly.

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CASE REPORT

Erasmus Syndrome: A Case Report and Review of Cases Published from India

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Abstract

Erasmus syndrome is a rare clinical syndrome characterized by the development of systemic sclerosis (SSc) following chronic exposure to silica; however, the presence of silicosis is not a prerequisite for this diagnosis. It is infrequently reported in the literature, and recognizing the association between occupational silica exposure and SSc is crucial for timely diagnosis and management in workplace settings. We report a case of Erasmus syndrome in a stone cutter in his late 30s, who presented with gangrene in both feet, Raynaud's phenomenon, without any evidence of other organ involvement. Anti-Scl-70 antibody was positive on the line immunoassay, supporting the diagnosis. The patient was started on a combination therapy including calcium channel blockers, phosphodiesterase 5 inhibitors, and wound care. At 6-month follow-up, he had no further disease progression with stabilization of gangrene.

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Background

Erasmus syndrome is a rare clinical entity characterized by the development of systemic sclerosis (SSc) after chronic exposure to silica particles; however, silicosis is not a prerequisite for this diagnosis.[1] This term was first introduced in 1957 by a physician who observed multiple cases of SSc among South African gold mine workers.[2] The exact pathophysiological mechanism underlying this syndrome remains poorly understood. One proposed mechanism suggests that prolonged exposure to silica induces chronic inflammation, which in turn activates polyclonal T cells. This activation may result in the survival of apoptosis-resistant, self-reactive T lymphocytes, thereby contributing to autoimmune conditions such as SSc.[3] The first reported case in India was published by Khanna et al. in 1997.[4] The literature includes approximately eight individual case reports from India published in PubMed-indexed journals, along with a case series from Rajasthan documenting five patients.

Recognizing the association between silica exposure, silicosis, and SSc is essential, as it improves diagnostic precision and guides the management of occupationally induced autoimmune disorders in both clinical and occupational health contexts. Early identification of this relationship not only facilitates timely therapeutic intervention but also supports the development of effective occupational health prevention strategies. In this case report, we describe a patient in his late 30s, employed as a stone cutter, who presented with extremity gangrene and was subsequently diagnosed with Erasmus syndrome. This case highlights the need to consider Erasmus syndrome in individuals with chronic silica exposure who present with clinical findings indicative of SSc.

Case Description

A 38-year-old male stone cutter with a known history of silico-tuberculosis presented to the hospital with complaints of gangrene involving multiple toes (Figs 1 and 2) and the right index finger, associated with pain persisting for 2 months. He reported a history suggestive of Raynaud's phenomenon, which had also begun around the same time and was confirmed upon clinical examination. There were no additional clinical features indicative of connective tissue disease or vasculitis.

The patient had a 12-year history of tobacco chewing, which he had ceased a decade prior. His occupational history revealed significant silica exposure, having worked as a stone cutter for 15 years. Notably, he had been diagnosed with pulmonary tuberculosis 2 years earlier, which was appropriately treated.

On physical examination, pitting scars and areas of digital gangrene were noted on both feet and the right index finger. Peripheral pulses were intact and symmetrical, with no evidence of murmurs or bruits. The ankle-brachial index was within normal limits, and there was no inter-limb blood pressure discrepancy. The patient was normotensive, and the fundoscopic examination was unremarkable. The remainder of the systemic examination revealed no abnormalities.

High-resolution computed tomography (HRCT) of the thorax was performed to assess the lung parenchyma in light of the patient's past and present pulmonary history. The imaging demonstrated bilateral ground-glass opacities predominantly in the upper lobes (Fig. 3). Several of these opacities exhibited calcification and coalescence, forming multifocal ground-glass regions and ill-defined conglomerated consolidations, primarily localized in the perihilar areas. These changes were accompanied by emphysematous alterations and marked fibrosis, resulting in significant architectural distortion of the bilateral lung parenchyma. Furthermore, multiple reticulonodular opacities and a characteristic "tree-in-bud" appearance were noted in the upper, lower, and right middle lobes (Fig. 4), findings consistent with silico-tuberculosis. Despite these radiological features, microbiological examination of sputum samples was negative for acid-fast bacilli, thereby ruling out active tuberculosis. Additionally, computed tomography angiography of the lower limbs revealed no intraluminal filling defects, stenosis, or beading in the bilateral common, external, and internal iliac arteries, as well as in the superficial femoral, deep femoral, popliteal, peroneal, anterior tibial, and posterior tibial arteries.

Routine laboratory investigations revealed elevated inflammatory markers, with an erythrocyte sedimentation rate (ESR) of 57 mm/hour and a C-reactive protein (CRP) level exceeding 9 mg/L. Immunological screening demonstrated a positive antinuclear antibody (ANA) by immunofluorescence at a titer of 1:80 with a homogeneous pattern, along with the presence of anti-Scl-70 antibodies detected *via* line immunoassay.

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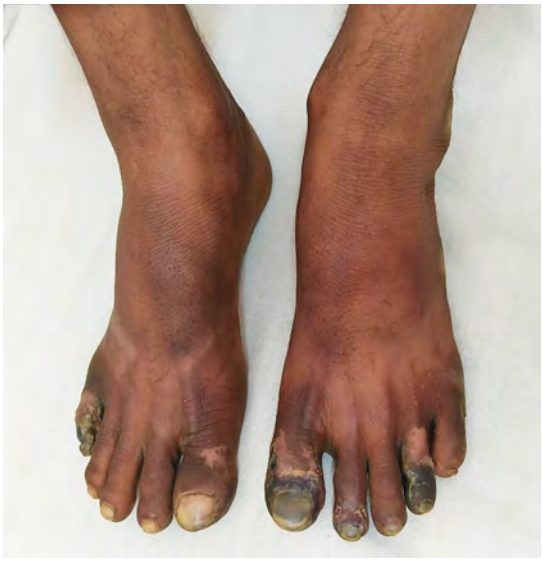

Fig. 1: Dorsal view of bilateral feet depicting gangrene affecting the right foot's big toe, index toe, and little toe, as well as all toes on the left foot

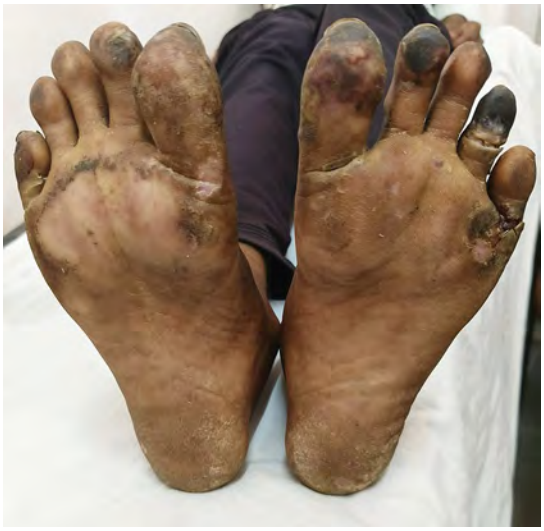

Fig. 2: Palmar view of bilateral feet depicting gangrene affecting the right foot's big toe, index toe, and little toe, as well as all toes on the left foot

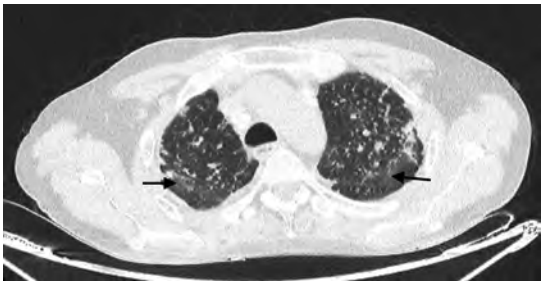

Fig. 3: High-resolution computed tomography (HRCT) of the thorax revealed bilateral ground-glass opacities predominantly in the upper lobes of the lungs

The patient was initiated on a therapeutic regimen comprising a calcium channel blocker (amlodipine), a phosphodiesterase-5 inhibitor (sildenafil), aspirin for symptomatic relief, and appropriate wound care.

At a 6-month follow-up, the patient reported a significant reduction in pain, rating it as 3/10, down from 8/10 at the initial presentation. Additionally, there was no progression of the gangrenous areas, and no functional loss of the toes was observed.

Discussion

Erasmus syndrome refers to a rare disorder in which SSc arises in individuals with a history of silica exposure, regardless of whether silicosis is present. Upon inhalation, silica particles are phagocytosed by alveolar macrophages, leading to the release of pro-inflammatory cytokines such as interleukins (IL-1, IL-2) and tumor necrosis factor-alpha (TNF-α). These cytokines activate T helper cells, causing the incorporation of additional macrophages, leading to an inflammatory surge. To repair the tissue damage caused by this inflammatory cascade, fibroblasts proliferate, producing excess collagen, which in the long run leads to pulmonary fibrosis.[5]

The ongoing immune-mediated tissue injury associated with silica exposure is linked to an elevated risk of many conditions, comprising autoimmune diseases like SSc, systemic lupus erythematosus, and rheumatoid arthritis, as well as interstitial lung disease, pulmonary tuberculosis, and lung cancer.[6] Exploring the potential interrelationships among these conditions may provide valuable insights into their shared pathophysiological mechanisms and their broader implications for patient health.

Systemic sclerosis is a long-term autoimmune disease that affects multiple organ systems, characterized by gradual fibrosis and extensive abnormalities in vascular function. Key clinical manifestations include Raynaud's phenomenon, telangiectasia, subcutaneous calcifications, cutaneous fibrosis, salt and pepper dermopathy, arthralgia, esophageal dysmotility, pulmonary hypertension, and interstitial lung disease.[7] The diagnosis in our patient was made based on established classification criteria for SSc, and considering his prolonged silica exposure history, this case satisfies the criteria for Erasmus syndrome.[8]

As far as we are aware, there are only a few documented cases of Erasmus syndrome from India. Therefore, as part of this case report, we conducted a focused literature review of PubMed-indexed journals and compiled previously reported Indian cases and case series from 2010–2025, aiming to contribute to the existing understanding of this rare but clinically significant occupational autoimmune overlap syndrome (Table 1).[9–17]

Our case adds to the growing body of Indian literature on Erasmus syndrome, with several distinguishing features. Our patient showed positive ANA (1:80) and anti-Scl-70 antibodies, aligning with the autoimmune profile seen in prior cases reported from

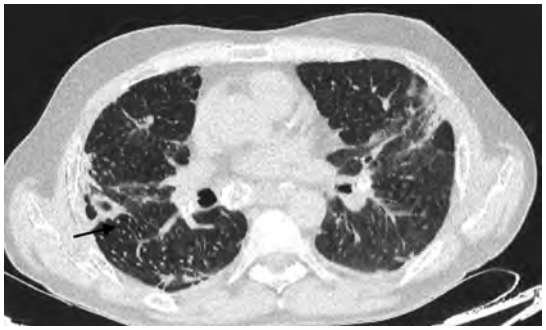

Fig. 4: High-resolution computed tomography (HRCT) of the thorax demonstrated a "tree-in-bud" appearance in the right middle lobe

regions such as Jharkhand, Tamil Nadu, and Himachal Pradesh, where Scl-70 positivity was consistently reported.

Unlike the cases reported from West Bengal (2015) or Sikkim (2013), which highlighted severe pulmonary arterial hypertension or widespread skin fibrosis, our patient had no clinical evidence of pulmonary hypertension or extensive skin involvement, and instead showed a predominant vascular and digital ischemic phenotype.

Therapeutically, our approach of aspirin, vasodilators (sildenafil, amlodipine),

Table 1: Summary of case reports and case series on Erasmus syndrome documented in PubMed-indexed journals (2010–2025)

Reference no.	*State (year)*	*Title*	*Age (in years) and sex (M/F)*	*Organ involvement*	*Antibodies*	*History of TB or coexisting (yes/no)*	*Treatment*
9	Jharkhand (2025)	Erasmus syndrome: diffuse SSc with silicosis	30/M	Mild pulmonary hypertension, Raynaud's phenomenon, salt-and-pepper dermopathy	ANA nucleolar pattern (2+ with a 1:80 end titer), anti-Scl-70 antibodies (3+)	Yes	Mycophenolate mofetil 2 gm/daily, nifedipine, bosentan (for pulmonary hypertension)
10	Tamil Nadu (2022)	Salt-and-pepper dyspigmentation with groove sign in erasmus syndrome: a double jeopardy	55/M	Raynaud's phenomenon, salt-and-pepper dermopathy	Anti-Scl-70 titer was 114.58 units	No	Calcium channel blockers, endothelin receptor blockers, PDE-5 inhibitors, and immunosuppressives
11	Rajasthan (2022)	Erasmus syndrome: a case series of rare co-occurrence of silicosis and SSc	5 patients Mean age = 36 (all male)	Varied	Anti-Scl-70 was positive in all patients	Varied	Included corticosteroids, immunosuppressive agents, antifibrotic therapy, vascular therapy (calcium channel blockers, phosphodiesterase 5 inhibitors, endothelin 1 receptor antagonist)
12	Himachal Pradesh (2020)	Pulmonary tuberculosis in association with Erasmus syndrome	46/M	Raynaud's phenomenon, salt-and-pepper dermopathy	ANA 1: 320 speckled pattern, anti-Scl-70 was also positive	Yes	Antitubercular therapy, calcium channel blocker, and cyclophosphamide
13	Himachal Pradesh (2018)	Erasmus syndrome: association of silicosis and SSc	52/M	Raynaud's phenomenon	ANA 1:64 speckled pattern; Scl-70 was also positive	No	Calcium channel blockers and immunosuppressive treatment
14	Rajasthan (2017)	Erasmus syndrome: silicosis and SSc	42/M	Raynaud's phenomenon, salt-and-pepper dermopathy	ANA was found to be positive. Scl-70 antibody titer 123.03 units	No	Not described
15	West Bengal (2015)	Erasmus syndrome in a 42-year-old male: a rare case report	42/M	Arthralgia, Raynaud's phenomenon, skin tightening over the face and extremities, salt-and-pepper dermopathy, significant pulmonary arterial hypertension	ANA 1:640 nuclear speckled pattern; anti-Scl-70 antibody was also strongly positive	No	Prednisone, cyclophosphamide, nifedipine
16	Sikkim (2013)	Erasmus syndrome: a case report of silicosis-induced scleroderma in a 26-year-old male	26/M	Arthralgia, Raynaud's phenomenon, skin tightening over the face and extremities	Anti-Scl-70 antibody was strongly positive; ANA was also positive	No	Not described
17	Chandigarh (2013)	Erasmus syndrome with pulmonary tuberculosis	60/M	Raynaud's phenomenon, salt-and-pepper dermopathy	ANA titers were elevated	Yes	Not described

ANA, antinuclear antibodies; Anti-Scl-70 antibodies, antibody against a 70-kDa protein, which is a fragment of the larger topoisomerase I protein

telmisartan, and gabapentin contrasts with the immunosuppressive strategies (e.g., mycophenolate, cyclophosphamide) described in several other reports. Remarkably, at 6-month follow-up, our patient demonstrated pain reduction from 8/10 to 3/10 and preservation of digital function, suggesting the effectiveness of supportive vasodilator-based management in cases with predominant vascular manifestations.

Conclusion

This case underscores the relevance of Erasmus syndrome as an uncommon yet noteworthy occupational autoimmune condition, especially in areas with substantial silica exposure. The presentation of digital gangrene and Raynaud's phenomenon in our patient, along with seropositivity for anti-Scl-70 and ANA, aligns with the immunological patterns observed in previously reported Indian cases. However, the absence of pulmonary hypertension or diffuse cutaneous involvement, along with a predominant vascular phenotype, distinguishes this case from many others documented in the Indian context. Moreover, symptom relief and stabilization of gangrene were achieved using vasodilator-based supportive therapy alone, without immunosuppression, highlighting the importance of individualized treatment strategies. In light of limited national data, this report contributes meaningfully to the evolving clinical understanding of Erasmus syndrome, highlighting the importance of early recognition, tailored therapy, and occupational health vigilance in at-risk populations.

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CASE REPORT

ANCA-negative Pauci-immune Vasculitis, an Often-missed Clinical Entity: A Case Report

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Abstract

The kidneys are frequently affected by antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which comprises renal-restricted vasculitis, eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), and granulomatosis with polyangiitis (GPA). The most prevalent kidney disease is glomerulonephritis. On direct immunofluorescence (DIF), they show an absence of any immune complex deposition and hence are regarded as "pauci-immune glomerulonephritis" (PIGN). Around 10–40% of AAV are ANCA negative (seronegative PIGN). They tend to show a more limited disease, fewer extra-renal manifestations, and a lower overall Birmingham Vasculitis Activity Score (BVAS). In the absence of ANCA positivity in blood, a consistent clinical picture supported by tissue diagnosis is the only tool to diagnose such cases.

Here we present a case of a 58-year-old male who presented with a history of prolonged fever, hematuria, and generalized palpable purpura all over the body. His blood for ANCA was negative. After a kidney biopsy, he was finally diagnosed with ANCA-negative pauci-immune vasculitis and was treated with rituximab.

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Introduction

The kidneys are frequently affected by antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which comprises renal-restricted vasculitis, eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), and granulomatosis with polyangiitis (GPA). The most prevalent kidney disease is glomerulonephritis. It is one of the causes of rapidly progressive necrotizing glomerulonephritis. On direct immunofluorescence (DIF), they show the absence of any immune complex deposition and hence are regarded as "pauci-immune glomerulonephritis" (PIGN).

According to Berden's 2010 histological categorization, PIGN can be divided into four classes: sclerotic, mixed, focal, and crescentic.

Despite the development of sophisticated testing techniques, such as antigen-specific immunoassays, some patients do not have detectable levels of circulating ANCA. There is a wide variation in the reported incidence of these seronegative PIGN patients. The incidence ranges from 2 to 6% according to certain research, although greater occurrence rates of up to 33–49.5% have been reported by others, especially those from Asia.[1] One such case is highlighted here.

Case Description

A 58-year-old hypertensive male from Kolkata, West Bengal, India, on tablet telmisartan 40 mg once daily, presented to us with complaints of high-grade fever, hematuria, and purpura in all four limbs for 45 days. His fever started on December 15, 2023 with chills, rigor, and dysuria, when he was diagnosed to have *Klebsiella pneumoniae* infection in urine by culture (>10^6 CFU/mL) and was given tablet cefuroxime 500 twice daily as per culture sensitivity for 10 days from a local practitioner. His fever subsided but recurred 2 days after the 10 days, when he was given tablet nitrofurantoin 100 twice daily for the next 10 days without any relief. Subsequently, he developed gross hematuria and progressively rising urea and creatinine. He was admitted outside and received two units of packed red blood cells for anemia. During the last 10 days of his course of illness, he developed reduced urine output and was referred under our care. On admission to our facility, he had pallor and bilateral pedal pitting edema. There was palpable, nonblanchable purpura over all four limbs. His BP was 100/60 mm Hg, urine output was 600 mL/day, and there was gross hematuria. Blood reports showed progressively rising creatinine reaching up to 8.3 mg/dL from 6.3 mg/dL within 3 days. Baseline hemoglobin was 6.0 gm/dL. Urinalysis showed 2^+ protein, 3^+ blood, and 24-hour urine protein was 1736 mg. Ultrasonography showed right kidney size of 14.10 cm, left kidney size of 12.53 cm, with bilateral mild raised cortical enhancement. Anti-GBM antibody, ANA, anti-PR3, and anti-MPO (by ELISA) were all negative. C3 and C4 levels were normal. Computed tomography (CT) scan of the thorax showed two pulmonary nodules at the lingula and the right lower lobe (Fig. 1). Renal biopsy was suggestive of focal necrotizing glomerulonephritis, fibrocellular crescents without any immune deposits, severe acute tubular injury, and focal chronic interstitial inflammation (Figs 2 and 3). He was given two sessions of hemodialysis in view of oliguric renal failure. We gave an injection of methylprednisolone (MP) 1 gm intravenous (IV) once daily for 3 days for worsening renal function and active urinary sediments.

His hematuria and purpura started resolving following IV MP therapy, and renal function began to normalize. Nephrology opinion was sought, and induction therapy with IV rituximab 375 mg/m^2 weekly for 4 weeks was started. He was discharged on oral prednisolone 1 mg/kg daily. His hemogram, renal function tests, 24-hour urine protein, and inflammatory markers normalized in follow-up visits without any recurrence of symptoms. Complete hemogram, 24-hour urine protein, and renal function tests were monitored.

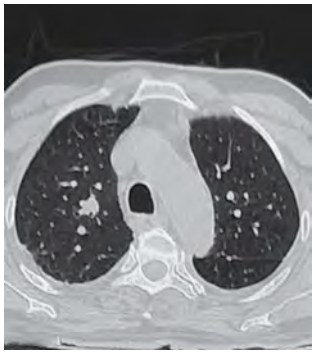

Fig. 1: High-resolution CT of the thorax showing a pulmonary nodule in the right lobe

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Prednisolone was tapered over the next 6 months to below 10 mg daily.

Discussion

Antineutrophil cytoplasmic antibody positivity is noted in almost 90% of cases of GPA and MPA and 60% in cases of EGPA. However, studies on PIGN have revealed that between 10 and 40% of patients have an ANCA-negative result. Among them, significant differences are observed in terms of age, sex, and place distribution of the cases. Sharma et al. conducted a single-center study on 84 patients in India,[2] and the results showed that 46% of the patients were female and the mean age was 35. Comparing them to their ANCA-positive peers, many studies conducted worldwide revealed a more circumscribed disease, a lower prevalence of extrarenal symptoms, and worse renal outcomes.[3]

Proinflammatory cytokines or products of the alternative complement pathway cause "neutrophil priming," which is the immune response triggered by the vascular inflammation in AAV that is partially directed against neutrophilic cytoplasmic antigens. Antibodies formed against the cytoplasmic proteins of these "primed neutrophils" are called antineutrophil cytoplasmic antibodies. Reactive oxygen species and lytic enzymes are released when these antibodies bind to these neutrophilic antigens, causing them to degranulate and create neutrophil extracellular traps, which in turn cause vascular injury and vasculitis. However, the exact pathophysiology behind renal injury caused by ANCA-negative vasculitis is still debatable. A distinct inflammatory mechanism, including additional autoantibodies that are not identified in standard clinical practice, may exist. Human lysosome-associated membrane protein-2 (hLAMP-2), plasminogen, and moesin, with other autoantigens expressed on the glomerular endothelium, have been identified in animal studies.[4] In ANCA assays, antibody reactivity to an alternative epitope could also be the cause of negative ANCA results. Immunoglobulin subclasses other than immunoglobulin G (IgG), which are not picked up by standard immunoassays, could potentially activate neutrophils. When antibodies bind to these antigens, renal vasculitis, apoptosis, and neutrophil activation result.

Histologically, renal involvement in ANCA-negative PIGN is often indistinguishable from their ANCA-positive counterparts. However, predominant meta-analyses have shown the crescentic class to be more common among other Berden classes. Seronegative PIGN has a greater degree of interstitial fibrosis and tubular atrophy (IFTA). This may indicate a delay in diagnosis owing to seronegativity of ANCA in blood.

With regard to treatment outcomes, studies show conflicting results. Antecedent infection often triggers an immune-mediated process by causing immune perturbation in the body. Isolation of *K. pneumoniae* in urine acted as a red herring and initially made us think of infection-related glomerulonephritis (IRGN). Though secondary causes of seronegative PIGN

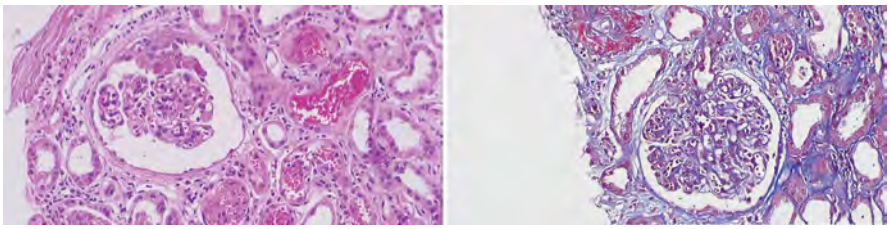


Fig. 2: Fibrocellular crescent in hematoxylin and eosin (H&E) stain, below in periodic acid-Schiff (PAS) stain, showing inflammation and vasculitis

Arteries show medial thickening and fibrointimal sclerosis while arterioles reveal variably thickened walls with hyalinosis lesions and prominent vacuolization in smooth muscle cells of media. Focal necrotizing arterial lesion is also seen.

DIF : Tissue for DIF shows renal medulla and small cortical area including up to 8 glomeruli. Following immunostaining pattern is observed:

Parameter	Result
IgA	Negative
IgG	Negative
IgM	Negative
C3	Negative
C1q	Negative
Kappa light chains	Negative
Lambda light chains	Negative

Impression : Kidney, needle biopsy:

Features are of:

Focal necrotizing glomerulonephritis* featuring fibrinoid tuft necrosis in 2/24 (8.3%) glomeruli and fibrocellular crescents over 3/24 (12.5%) of sampled glomeruli.

DIF studies do not show significant glomerular immune deposits.

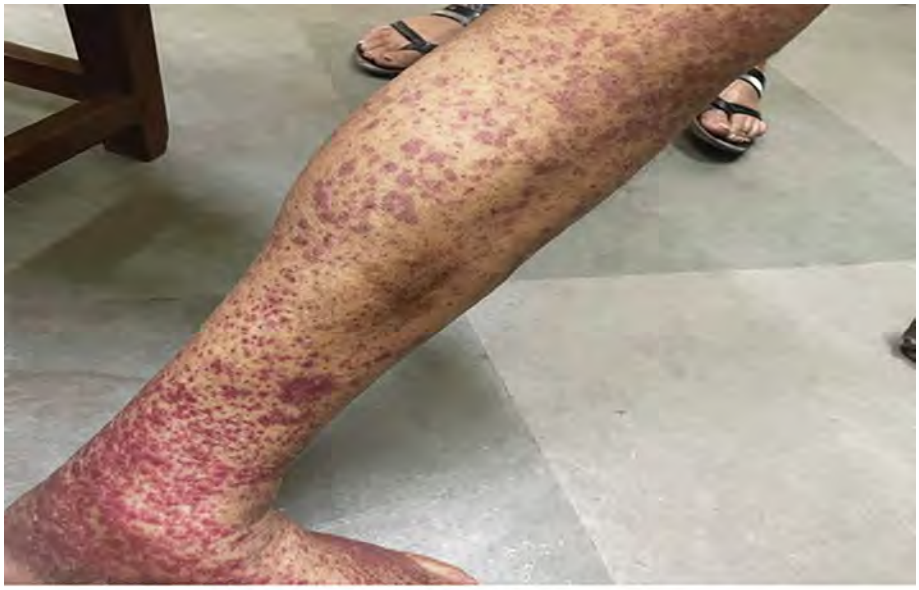
Severe acute tubular injury, focal chronic interstitial inflammation and mild increase in tubulointerstitial chronicity are noted.

Focal arterial necrotizing lesion is noted.

**Please see comments below*

Comments : Present biopsy shows a focal necrotizing glomerulonephritis with crescent

Fig. 3: DIF assay showing no immune deposits



HISTOPATHOLOGY

HP-Skin biopsy
HP- Skin biopsy, tissue/paraffin block
specimen
Skin biopsy.

Gross
Received in formalin single skin covered, soft tissue bit measuring 0.3 x 0.2 x 0.2 cm.
(Entire tissue processed in 1 Paraffin block).

(2HX-4284)

Microscopic examination
The upper dermis has prominent solar elastosis and numerous extravasated erythrocytes.
There is a moderately dense perivascular lymphocytic infiltrate.
No neutrophils or leukocytoclasia seen.

Interpretation
Diagnosis
Purpura without vasculitis.
Possible actinic purpura.

Comments
Please correlate clinically.

Fig. 4: Above, photograph showing purpura in lower limbs on admission, Below, Skin biopsy showing no vasculitis

linked to infection, malignancies, and drug use have been reported, IRGN is a transient phenomenon and follows a self-limiting course. Moreover, the vast majority of IRGN shows immune complex-mediated glomerulonephritis on renal biopsy. Hence, a detailed history, thorough clinical evaluation, and tissue biopsy are the only keys to pick up these cases (Fig. 4). In our scenario, a history of protracted illness with evidence of multisystem involvement (kidneys, lungs, and skin), absence of immune complex deposits in the glomeruli on DIF, and presence of fibrocellular crescents led to a diagnosis of ANCA-negative pauci-immune vasculitis.[5]

Conclusion

The main learning point we offer here is that the occurrence of ANCA-negative PIGN must be acknowledged in case of serological ANCA negativity. This entity exhibits more chronic alterations in the kidney biopsy but less extrarenal involvement. The majority of patients receive treatment with conventional immunosuppressive drugs such as rituximab, cyclophosphamides, or corticosteroids. Compared to ANCA-positive PIGN, seronegative PIGN has inferior kidney outcomes. Therefore, a meticulous clinical review supported by early tissue diagnosis is essential so that appropriate therapy can be instituted to prevent irreversible organ damage.

It is still unknown if ANCA-negative PIGN is a unique illness or a component of the AAV spectrum. The etiology, organ-based outcome markers, and long-term prognosis in these patient subgroups are therefore the subject of more research.

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CASE REPORT

Improvement in Severe Mitral Regurgitation and Left Ventricular Dysfunction with Intravenous Iron in Severe Anemia: A Case Report

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Abstract

Background: Anemia and iron deficiency are frequently observed in patients with heart failure (HF) and are independently linked to adverse outcomes. Although intravenous (IV) iron supplementation is well studied in HF with reduced ejection fraction, its impact on coexisting significant valvular disease remains poorly understood.

Case description: A 67-year-old female with a known history of coronary artery disease, diabetes, hypertension, hypothyroidism, and chronic kidney disease presented with exertional breathlessness and fatigue. Workup revealed severe anemia (hemoglobin 6.1 gm/dL), reduced left ventricular ejection fraction (LVEF 45%), severe mitral regurgitation (MR), and mild tricuspid regurgitation (TR). She was managed conservatively with IV iron and two units of leukocyte-depleted packed red blood cells (LD PRBCs). Over the next few days, the patient experienced marked clinical improvement. Repeat echocardiography demonstrated normalization of LVEF, downgrading of MR severity from severe to mild, regression of TR, and complete resolution of pericardial effusion. Her hemoglobin improved to 8.0 gm/dL.

Discussion: This case underscores the role of severe anemia as a modifiable factor contributing to cardiac dysfunction, including reversible valvular insufficiency and reduced systolic performance. Restoration of hemoglobin levels led to significant clinical and echocardiographic recovery, pointing to anemia as a potential therapeutic target in such cases. The use of IV iron proved beneficial in facilitating this improvement.

Conclusion: In older patients with multiple comorbidities and new or worsening cardiac dysfunction, severe anemia should be considered a treatable cause. Early diagnosis and targeted therapy using IV iron and transfusion can result in substantial clinical gains and may help avoid unnecessary invasive procedures.

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Introduction

Iron deficiency is frequently observed in patients with heart failure (HF), with nearly half of this population affected, and is recognized as an independent predictor of poor outcomes, regardless of the presence of anemia.[1] It contributes to impaired oxygen transport, diminished energy production, and mitochondrial dysfunction, all of which can negatively impact both cardiac and skeletal muscle performance.[2]

The use of intravenous (IV) iron therapy has become a validated strategy to manage iron deficiency in HF. Evidence from clinical studies has shown that IV iron not only replenishes iron stores but also improves exercise tolerance, symptom burden, and overall quality of life in these patients.[3] Trials such as FAIR-HF and CONFIRM-HF demonstrated that treatment with ferric carboxymaltose improved New York Heart Association (NYHA) classification, extended 6-minute walk distances, and led to better patient-reported outcomes.[3,4]

Despite strong evidence supporting IV iron use in HF with reduced ejection fraction, its role in patients with concurrent valvular heart disease, particularly severe mitral regurgitation (MR) and tricuspid regurgitation (TR), remains insufficiently studied. The interaction between iron deficiency, significant valvular lesions, and left ventricular (LV) dysfunction in the setting of severe anemia has not been extensively examined, representing a gap in current cardiology literature.

This case report is motivated by the need to explore the possible hemodynamic and symptomatic benefits of IV iron in complex cases presenting with severe MR, TR, LV systolic dysfunction, and profound anemia. By presenting improvement in these parameters following IV iron administration, this report aims to stimulate further investigation into the broader cardiovascular effects of iron repletion therapy in such multifactorial cases.

Case Description

A 67-year-old woman presented to the emergency department at Max Super Speciality Hospital, Patparganj, with complaints of shortness of breath on exertion and generalized fatigue persisting for the past month. She denied experiencing chest pain, orthopnea, gastrointestinal bleeding, or syncope. Her medical history included diabetes mellitus, hypertension, hypothyroidism, and coronary artery disease, for which she had undergone percutaneous transluminal coronary angioplasty (PTCA) in March, 2024, with a recorded left ventricular ejection fraction (LVEF) of 60%. She was also a known case of chronic kidney disease.

On clinical examination, she was alert and oriented. Pallor was noted, and her blood pressure was 160/60 mm Hg. Given the clinical picture and suspected anemia-induced decompensation, a comprehensive diagnostic evaluation was initiated. Laboratory findings revealed a hemoglobin level of 6.1 gm/dL, serum iron of 139.64 µg/dL, and transferrin saturation of 35.69%, confirming the diagnosis of severe anemia. Her electrocardiography (ECG) showed no acute ischemic changes.

Transthoracic echocardiography demonstrated a reduced LVEF of 45% and significant mitral valve abnormality. The anterior mitral leaflet (AML) appeared thickened and calcified, along with evidence of severe MR. Additionally, mild TR was noted, with an estimated right ventricular systolic pressure (RVSP) of 36 mm Hg. A small pericardial effusion was also present. These echocardiographic findings raised the possibility that anemia was contributing to hemodynamic compromise and worsening of mitral valve function.

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The patient received conservative management with IV iron therapy and transfusion of two units of leukocyte-depleted packed red blood cells (LD PRBCs) administered over 2 days. She showed significant clinical improvement, with better exertional capacity and resolution of fatigue. Follow-up echocardiography revealed notable recovery of cardiac function and valvular parameters, with LVEF improving to baseline levels and MR decreasing from severe to mild. TR also regressed, and the pericardial effusion resolved. Post-treatment hemoglobin rose to 8.0 gm/dL.

This clinical scenario suggests that the initially severe MR was likely functionally aggravated by profound anemia, and correction of the anemia resulted in hemodynamic improvement and partial reversal of valvular dysfunction.

Discussion

This case illustrates a clinically significant and potentially underrecognized relationship between severe anemia and reversible cardiac dysfunction, particularly functional MR and reduced LVEF. The observed improvement in valvular and myocardial parameters following correction of anemia highlights a pathophysiological connection that may have important implications for clinical decision-making in similar settings.

In patients with chronic comorbidities such as diabetes mellitus, hypertension, coronary artery disease, and chronic kidney disease, as seen in this case, cardiac compensatory mechanisms may already be compromised. Superimposed anemia imposes additional hemodynamic stress by reducing oxygen-carrying capacity and promoting high-output circulatory states, which can exacerbate existing structural or functional cardiac abnormalities.[5] This may explain the unexpected decline in LVEF and emergence of severe MR in a patient previously documented to have preserved systolic function.

Functional MR is frequently dynamic and volume-dependent. In the presence of severe anemia, increased preload and reduced afterload can lead to ventricular dilatation and altered mitral valve coaptation, thereby worsening regurgitation. Correction of anemia can reverse these changes, leading to improved leaflet approximation and regression of MR severity.[6] This mechanism is supported by the rapid echocardiographic improvement observed in this patient after hemoglobin restoration.

Moreover, the normalization of LVEF post-treatment suggests that the LV dysfunction was likely secondary to impaired myocardial oxygen delivery, a condition that mimics myocardial stunning. Although not ischemic in nature, such myocardial suppression may occur in severe anemia and is known to be reversible once oxygen delivery is optimized.[7]

While the management of MR traditionally focuses on anatomical causes and surgical or interventional options, this case underscores the importance of identifying and correcting systemic contributors such as anemia, particularly in elderly or multimorbid patients. Additionally, the role of IV iron therapy, apart from blood transfusion, should not be understated, especially in patients with chronic kidney disease or those at risk of transfusion-related complications. IV iron not only replenishes iron stores efficiently but may also facilitate faster hematological and functional recovery.[8]

Furthermore, this case raises a pertinent clinical consideration that functional valvular regurgitation and reduced ejection fraction may sometimes represent transient, correctable manifestations of systemic disturbances rather than irreversible cardiac pathology. Recognizing this possibility could help avoid unnecessary or premature interventions and instead support a strategy of targeted medical optimization.

Conclusion

This case highlights the reversible nature of functional mitral and TR, as well as LV dysfunction, in the setting of severe anemia. Correction of the underlying hematological deficit led to significant clinical and echocardiographic improvement, suggesting that anemia may play a causative role in transient cardiac decompensation. Timely recognition and targeted treatment of anemia, particularly with IV iron and transfusion support, may prevent unnecessary interventions and improve cardiac outcomes in similar patient populations.

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CASE REPORT

Severe Hypertriglyceridemia Leading to Acute Pancreatitis in a Case of Diabetic Ketoacidosis: A Report of Type IV Familial Hyperlipidemia

Kashish Siwach[1*], Tushar Singh[2], Ashok Kumar[3], Debapriya Sarkar[4], Neha Gupta[5]

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Abstract

We describe an uncommon instance of a female patient, age 35, with type 1 diabetes mellitus who developed DKA (diabetic ketoacidosis) that was exacerbated by acute pancreatitis and severe hypertriglyceridemia. The patient had abdominal pain, vomiting, and biochemical evidence of DKA upon admission. Physical examination was notable for xanthomas, and laboratory tests showed extremely high triglyceride levels and milky plasma. Clinical improvement resulted from the patient receiving IV insulin treatment and lipid-lowering medications. This example emphasizes the significance of early diagnosis and treatment when hypertriglyceridemia-induced pancreatitis complicates DKA.

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Introduction

Diabetic ketoacidosis (DKA) is a serious complication mainly linked with type 1 diabetes mellitus due to absolute deficiency of insulin.[1] The failure to take insulin, infection, trauma, and severe pancreatitis are the risk factors.[2,3] A lack of insulin leads to raised levels of amino acids and free fatty acids from muscle and adipose tissue. Higher levels of fat absorbed by the liver result in higher levels of very low-density lipoprotein (VLDL), which raises the risk of hypertriglyceridemia.[2,3] Acute pancreatitis is seldom caused by hypertriglyceridemia, which accounts for 1–4% of cases. In some situations, extremely high levels of triglycerides above 1,000 mg/dL can be seen, which are dangerous in terms of causing acute pancreatitis and other complications.[2,3]

Triglyceride elevations are frequently observed in insulin-deficient conditions, such as DKA. The activity of lipoprotein lipase (LPL), which hydrolyzes and breaks down triglycerides transported by chylomicrons and VLDLs, depends on insulin. Severe hypertriglyceridemia with "milky" plasma is uncommon; however, mild hypertriglyceridemia is frequently observed in DKA and poorly managed diabetes.[4]

Case Report

The patient was a 35-year-old woman from Mussoorie, Uttarakhand, who had been experiencing vomiting episodes and steadily worsening stomach pain for 4 days. She said she had not been taking her insulin as prescribed and has a history of type 1 diabetes mellitus. Her family history included notable elements such as hyperlipidemia and type 2 diabetes mellitus in first-degree relatives.

On clinical examination, she appeared conscious, oriented, and moderately nourished. Vitals showed that the patient was afebrile, with blood pressure of 130/76 mm Hg, a heart rate of 106 bpm, and respiratory rate of 24/minute. Dermatological examination showed xanthomas near the nasal bridge (Fig. 1) and on the extensor tendons of the hands. Abdominal examination revealed hepatosplenomegaly without signs of peritonitis. The initial laboratory evaluation revealed metabolic acidosis on arterial blood gas analysis, positive urine ketones, and hyperglycemia with random blood sugar values of 482 mg/dL. Complete blood counts showed mild anemia and thrombocytopenia. Serum biochemistry revealed normal renal and hepatic parameters. Notably, the serum appeared lactescent (Figs 2 and 3), and lipid profile analysis confirmed severe hypertriglyceridemia with triglyceride levels reaching 2895 mg/dL. Raised serum amylase and lipase levels were noted. Abdominal ultrasonography indicated features suggestive of pancreatitis. After being admitted to the intensive care unit, the patient was treated with fenofibrate, insulin infusion, and intravenous fluids. Glycemic control improved progressively, and triglyceride levels decreased significantly by the time of discharge. Dermatological consultation suggested a diagnosis of rosacea with xanthogranulomatous diabetic dermopathy. Autoimmune screening was negative. She was discharged in stable condition after five days of hospitalisation.

Discussion

Insulin deficiency in DKA increases lipolysis, with resultant hypersecretion of free fatty acids and hepatic production of VLDLs, contributing to hypertriglyceridemia.[5] At the same time, dysregulation of LPL further reduces triglyceride clearance.[6] Although mild triglyceride elevation is frequent, extreme hypertriglyceridemia is uncommon and requires immediate detection because of its relationship with acute pancreatitis and other complications.

Familial lipid disorders, such as type IV hyperlipidemia, can exacerbate the triglyceride burden during DKA episodes.[7] Acute pancreatitis resulting from hypertriglyceridemia is believed to occur through hydrolysis of triglyceride-rich chylomicrons within pancreatic capillaries, generating free fatty acids that induce local tissue injury and inflammation.[8,9] Amylase levels may be falsely low in hyperlipidemic pancreatitis due to analytical interference; thus, clinicians should rely on a combination of clinical presentation, imaging, and triglyceride levels for diagnosis.[10] In our patient, initial amylase levels were only

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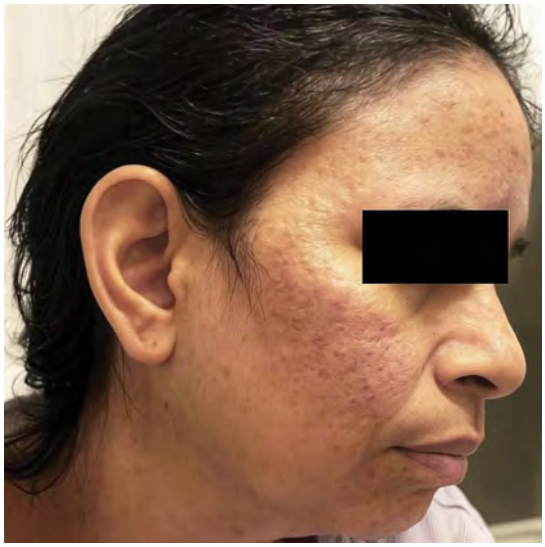

Fig. 1: Presence of xanthomas

Fig. 2: Lactescent serum

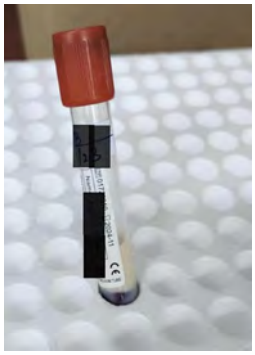

Fig. 3: Lactescent serum

mildly elevated, despite evidence of pancreatitis on imaging.Treatment includes aggressive fluid resuscitation, insulin infusion to decrease triglyceride levels by increasing LPL activity, and lipid-lowering drugs such as fibrates.[11,12] Plasmapheresis can be used in resistant cases or when triglyceride levels are more than 2,000 mg/dL with systemic involvement.[13]

Conclusion

Severe hypertriglyceridemia should be suspected in DKA patients presenting with milky plasma, xanthomas, or abdominal pain suggestive of pancreatitis. Prompt insulin therapy remains the cornerstone of treatment, with lipid-lowering agents playing an adjunctive role. Early identification and targeted management are critical to improving outcomes in these patients.

Consent for Publication

The patient gave their written, informed consent. The materials and data are available upon request.

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CASE REPORT

An Unusual Case of Refractory Seizures

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Abstract

A 54-year-old female presented with recurrent episodes of altered sensorium. The episodes lasted 4–6 minutes with snoring and unresponsiveness, and confusion during resolution. She was found to have recurrent hyponatremia and hypoglycemia. The hyponatremia was hypo-osmotic with raised urinary sodium excretion managed with hypertonic saline and oral extra salt. Electroencephalogram (EEG) showed epileptiform discharges. The recurrent seizure episodes persisted in spite of antiepileptic drugs. Cerebrospinal fluid (CSF) examination showed: glucose 174.7 mg/dL, protein 60.4 mg/dL, total leukocyte count (TLC) 5. acid-fast bacilli (AFB), Gram stain—no organism, culture sensitivity sterile, Cryptococcus antigen, cobwebbing absent, BioFire CSF meningitis/encephalitis panel was negative. Serum autoimmune encephalitis panel was positive for leucine-rich glioma-inactivated 1 (LGI1) antibody (2+) (titer 1:10). The patient was initially treated with IV immunoglobulin 170 gm over 5 days. The nonconvulsive seizure activity reduced but remained persistent. The patient was further treated for syndrome of inappropriate antidiuretic hormone secretion (SIADH)-induced hyponatremia with fluid restriction and desmopressin. In view of persistent hyponatremia and altered sensorium, and positive autoimmune encephalitis panel, rituximab infusion was given on 2 occasions, 2 weeks apart. The sensorium showed a gradual but significant improvement with cessation of seizure activity and improved activities of daily living.

Our patient presented with nonconvulsive seizure activity and persistent hyponatremia and recurrent hypoglycemia. The anti-leucine-rich glioma inactivated 1 (LGI1 antibody) is a rarely found entity first described in 2010. It is associated with electrolyte abnormalities, namely hyponatremia and hypoglycemia. A PubMed search revealed very few cases reported of LGI1 antibody encephalitis in association with nonconvulsive seizure activity. The electrolyte abnormalities associated with the entity make the management difficult. The recommended immunosuppressive regimen consists of IV pulsed steroids, which was precluded in our patient due to poorly controlled diabetes. Inadequate response seen after IVIg infusion prompted further immunosuppression with rituximab. Satisfactory control of the seizure activity was attained after the second rituximab dose.

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Introduction

A 54-year-old lady presented with recurrent hyponatremia, hypoglycemia, and nonconvulsive seizures. After extensive investigations, her serum autoimmune encephalitis panel was found to be positive for leucine-rich glioma-inactivated 1 (LGI1) autoimmune marker. Immunosuppressants (IVIg and rituximab—2 cycles) were given, and the patient became seizure-free with stable electrolytes on follow-up.

Case Description

A 54-year-old lady presented with complaints of drowsiness, slurred speech, and facial twitching. She was taken to a local hospital where her random blood sugar (RBS) was 50 mg/dL, which was managed with 50% dextrose. Her head computed tomography (CT) revealed mild brain atrophy. On further evaluation, she was hyponatremic with Na 117 mEq/L. Sodium levels were corrected, and she was discharged home with a serum Na of 130 mEq/L.

Postdischarge, the patient remained stable for 2 weeks when she again complained of abnormal facial movements, right-sided upper limb jerks, altered sensorium, and lip smacking. She was admitted to the same local hospital where her Na was 121 mEq/L, K 3.43 mEq/L, and C-reactive protein (CRP) 79.26 mg/L.

A magnetic resonance imaging (MRI) of the brain showed nonspecific ischemic changes in bilateral frontal periventricular regions. Tiny ischemic foci also were noted in the deep white matter of bilateral centrum semiovale. A high-resolution computed tomography (HRCT) of the chest revealed multiple centrilobular nodular ground-glass opacities, minimal bilateral pleural effusion, and marginal cardiomegaly with pericardial effusion.

For the next 10 days of hospitalization, her serum sodium ranged between 121 and 133 mEq/L in spite of aggressive correction with normal saline and later hypertonic saline. Her serum potassium ranged between 3.28 and 3.80 mEq/L. Despite adopting these corrective measures, her serum sodium showed a rapid fall on the tenth day to a lowest of 113 mEq/L, after which she was shifted to Max Super Speciality Hospital, Saket.

On arrival, the patient had waxing and waning of sensorium, with periods of complete obtundation interspersed with periods of lucidity. She had facial twitchings. She was managed in the intensive care unit (ICU). Initial serum sodium 126 mEq/L, K 3.8 mEq/L, thyroid-stimulating hormone (TSH) 2.35 mIU/L, T4 0.75 µg/dL, T3 3.75 ng/dL, serum albumin 2.9 gm/dL. Sodium correction was done with normal saline as the patient was mildly dehydrated. Antibiotic cover was provided with doripenem and clindamycin.

Antiepileptics included levetiracetam and sodium valproate. Electroencephalogram (EEG) showed generalized slowing. Blood culture showed growth of *Klebsiella pneumoniae*. Cerebrospinal fluid (CSF) analysis revealed total leukocyte count (TLC) 5/mm^3, lymphocytes 100%, adenosine deaminase (ADA) 0.9 IU/L, cobweb absent, glucose 174 mg/dL, and protein 60.4 mg/dL. Encephalitis panel was negative. Antinuclear antibody (ANA) vasculitis panel showed SSA/Ro 60 kD 97.00 U. Serum autoimmune encephalitis panel was positive 2(+) for LGI1.

Positron emission tomography–computed tomography (PET CT) showed multiple faintly fluorodeoxyglucose (FDG)-avid and nonavid enlarged necrotic right axillary lymph nodes, largest ~1.8 × 1.4 cm, with no other significant FDG-avid lesion. The lymph node when biopsied revealed lymphoid tissue with infarcted necrosis, negative for tuberculosis and malignancy. The patient was planned for immunosuppression with IVIg, total of 170 gm over 5 days. Hyponatremia was managed with free

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water restriction and extra oral salt, and her sodium level corrected. On completion of intravenous immunoglobulin, the patient was alert, seizure-free, accepting orally, and was discharged.

After 3 days, she again presented with altered sensorium secondary to low sodium along with hyperammonemia. She was readmitted. Rituximab immunosuppression was planned. Inj. rituximab 1 gm was given, and the same dose was repeated after 2 weeks. Recurrent hyponatremia was initially managed with free water restriction and oral supplemental salt, but later desmopressin spray was added. On review at 2 weeks after the last rituximab infusion, the patient was independently mobile with no episodes of altered sensorium.

Discussion

Immune-mediated autoimmune encephalitis is a relatively newly described entity. The clinical presentation is spread over a wide spectrum, varying from mild cognitive impairment with insidious onset to refractory seizures and signs of encephalopathy. Since the presentation is variable, reaching a diagnosis on the basis of clinical features is a challenge. The signs and symptoms may mimic a variety of pathological entities. Diagnosis on the basis of imaging may again be challenging, but characteristic findings described in the limbic structures should prompt an autoimmune workup. Each autoimmune encephalitis subtype has a specific antibody to antigens located in specific areas of the CNS against which the immune-mediated attack occurs. Thus, autoimmune encephalitis is a group of disorders with closely related clinical findings that share similar radiological findings. The resulting inflammation leads to the clinical and radiological findings, which depend on the area of the central nervous system (CNS) involved.[1]

A subset of autoimmune encephalitis, LGI1 is a recently recognized entity. LGI1 antigen in the limbic system is a recently recognized target of autoimmune encephalitis.[2] The clinical manifestations include limbic symptoms characterized by memory lapses, behavioral involvement, and seizures, of which facio-brachial dystonic seizures (FBDS) are very characteristic. The seizures typically involve short episodes of dystonic movements of the face and upper limb. The same were noted in our patient. Lower limb involvement is also seen. The presentation may also include peripheral neuropathy or autonomic dysfunction. Unusual presentations include spells of vertigo, autonomic or sensory seizures, and episodes of piloerection.[3]

There are no definitive guidelines for the management of LGI1 autoimmune encephalitis. The mainstay of treatment revolves around antiepileptics and immunosuppressants. Corticosteroids and IVIg have both been shown to be effective.[4] According to some studies, early immunotherapy has long-term beneficial effects on cognition. Untreated FBDS may lead to cognitive decline in the long run.[5,6] There are no guidelines prescribing appropriate immunotherapy in cases of LGI1 encephalitis, but studies indicate treatment with corticosteroids shows better outcomes in terms of improvement in FBDS, other seizure types, mRS score, and Kokmen STMS scores after acute treatment. However, long-term differences in outcome were not seen vs IVIg.[4]

Initial immunosuppressive therapy applied on an empiric basis is pulsed dose of methylprednisolone at doses of 1 gm per day for 3–7 days. Paraneoplastic etiology shows better response to corticosteroids than other etiologies. Intravenous immunoglobulins (IVIg) given over 2–5 days at doses of 2 gm/kg body weight are an alternative immunosuppressive option. They are especially useful when steroids are contraindicated. Plasma exchange (PLEX) can also be used in cases where steroids are contraindicated. Five to ten sessions are typically needed. The above first-line therapies may be used in combination, either together or in sequence, if the initial immunosuppressive regimen shows suboptimal response.

Second-line agents used as immunosuppressants are rituximab and cyclophosphamide. Rituximab has a more favorable toxicity profile as compared to cyclophosphamide. Rituximab is used in the dose of 375 mg/m^2 of BSA weekly for 4 weeks or 2 doses of 1000 mg given 2 weeks apart. Cyclophosphamide is given in doses 600–1000 mg/m^2 of BSA. Less commonly studied immunosuppressants are bortezomib, tocilizumab, and low-dose IL-2.[7]

Hyponatremia is commonly associated with LGI1 encephalitis, seen in 60–88% of the patients. It may range from mild-moderate to severe. Our patient had recurrent, severe hyponatremia. It is thought to precede the development of seizures but is usually diagnosed on seizure presentation, at which time it is attributed to be the cause of the seizures. This in turn causes delay in the LGI1 encephalitis diagnosis and subsequent immunotherapy. The mechanism of hyponatremia is not completely delineated but is thought to be a result of syndrome of inappropriate antidiuretic hormone secretion (SIADH).[8]

Our patient showed the classical symptoms of FBDS associated with hyponatremia, which complicated her initial diagnosis. On retrospective history taking, it was determined that the symptoms consistent with FBDS started much before presentation to a medical facility. Attendants reported facial twitching about 8–10 months before the first episode of hyponatremia. They also reported subtle memory failures arising in the same time frame. The etiology of the seizures was initially thought to be due to the hyponatremia, which remained the focus of the management in the first phase of illness. The persistence of the nonconvulsive seizures after the correction of serum sodium levels and the lability of the GRBS prompted further investigation. Another confounding factor in the diagnosis of our patient was the absence of typical radiological signs in the CNS imaging performed. We encountered recurrent hyponatremia later also in the course, after rituximab infusion. Restriction of free water intake and desmopressin ultimately resulted in stabilization of serum sodium levels.

Conclusion

Leucine-rich glioma-inactivated 1 autoimmune encephalopathy is a recently recognized clinical entity. The presence of the LGI1 antigen in the limbic system correlates well with the clinical features seen once the damage subsequent to the autoimmunity takes place. FBDS is a characteristic seizure type associated with LGI1 autoimmune encephalopathy. Correlation of the FBDS with recurrent hyponatremia is required to initiate a search for the antibody. The presence of the antibody on autoimmune encephalitis panels has made the diagnosis simpler. Although guidelines are lacking for the treatment of LGI1 encephalitis, the mainstay of treatment is immunosuppression. Few studies highlight the superiority of glucocorticoids to IVIg in the short term, but long-term superiority has not been proven. It is essential to rule out any occult infections prior to immunosuppression. The associated hyponatremia is thought to be a result of SIADH and shows response to targeted management.

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CASE REPORT

Good's Syndrome—A Rare Cause of Acquired Adult Immunodeficiency: A Case Report

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Abstract

Human immunodeficiency virus (HIV)-negative acquired adult immunodeficiency diseases are rare and relatively difficult to diagnose and treat. Good's syndrome is one such rare immunodeficiency syndrome occurring in middle to late adulthood. It is an association of combined B-cell and T-cell immunodeficiency along with hypogammaglobulinemia with a background of thymoma. Here, we describe a case of a 57-year-old male who presented to us with recurrent streptococcal pneumonia. He had a past history of an operated thymoma, cytomegalovirus retinitis, and pure red cell aplasia (PRCA). Evaluation revealed hypogammaglobulinemia along with CD4+ T-cell and B-cell lymphopenia, thus indicating Good's syndrome. Our case highlights the importance of including Good's syndrome in the differential diagnosis of HIV-negative, acquired, adult immunodeficiency and elucidates the general principles of management of this rare clinical entity.

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Introduction

Good's syndrome is a rare immunodeficiency syndrome with an adult onset, characterized by combined T-cell and B-cell immunodeficiency in association with thymoma. Patients may present with signs and symptoms suggestive of mediastinal mass or may present with recurrent infections. Given the rarity of the condition, no formal diagnostic criteria or standardized guidelines exist, and management is typically individualized.

Case Description

A 57-year-old diabetic male was admitted with a 5-day history of fever and dry cough. His past history was significant for an operated thymoma (WHO type B2) in 2014 and pure red cell aplasia (PRCA) diagnosed a year later, for which he was on cyclosporine and danazol, which were eventually tapered and stopped after 2 years. In 2018, the patient had recurrent periodontitis leading to teeth loss. In addition, the patient had cytomegalovirus (CMV) retinitis in 2020 and was on valganciclovir since then. X-ray, on admission, showed left lower lobe pneumonia. Blood cultures grew *Streptococcus pneumoniae*. The patient was treated with appropriate culture-guided antibiotics (ceftriaxone) and discharged. However, a month later, he was readmitted with a right lower lobe pneumonia with blood cultures again growing *S. pneumoniae*. Recurrent pneumonia led to the suspicion of an immunodeficiency disease. HIV serology was negative. Serum immunoglobulin (Ig) levels were suggestive of hypogammaglobulinemia: IgA—41 mg/dL (normal: 70–400 mg/dL), IgM—25 mg/dL (normal: 40–230 mg/dL), IgG—396 mg/dL (normal: 800–1600 mg/dL). Absolute CD4+ (387/mm^3) and CD8+ (865/mm^3) counts revealed CD4/CD8 ratio reversal (normal CD4+: 500–1600/mm^3; normal CD8+: 150–1000/mm^3). Peripheral blood flow cytometry showed B-cell lymphopenia with a CD20 value of 1.43% (normal: 3–20%). In an attempt to find out the cause of hypogammaglobulinemia and B-cell lymphopenia, whole exome sequencing was done but did not show any pathogenic mutations/loci which would explain the patient's presentation.

To summarize, a middle-aged individual with a history of thymoma and PRCA, recurrent periodontitis, and CMV infection, presenting with recurrent bacterial pulmonary infections, with hypogammaglobulinemia, CD4/CD8 reversal, and B-cell lymphopenia was diagnosed with Good's syndrome.

We started our patient initially on meropenem and teicoplanin, considering the possibility of a hospital-acquired sepsis as a plausible explanation for the patient's second presentation, given the fact that he was admitted just a month ago. However, antibiotics were deescalated 48 hours later to ceftriaxone after the culture reports, which was continued for the next 12 days (thus totaling 14 days of antibiotics). In addition, we also administered a weight-based dose of intravenous IG. With treatment, there was an improvement in the patient's general condition along with a reduction in his oxygen requirements. He made a full recovery and was eventually discharged.

Discussion

Good's syndrome, first described by Robert Good in 1954, is an immunodeficiency syndrome, characterized by the association of combined B and CD4+ T-cell lymphopenia, hypogammaglobulinemia, and thymoma. It is a disease of late adulthood with most of the cases presenting in the fourth or fifth decade.[1] Thymoma, which is benign and localized in 90% cases,[2] may precede or follow the appearance of immunodeficiency. The associated immunodeficiency is not known to reverse post-thymectomy.[3] Patients may present with a mediastinal mass or with recurrent sinopulmonary, urinary, or skin infections, as well as opportunistic infections. Encapsulated bacteria, such as *S. pneumoniae*, are among the most common bacterial pathogens isolated. CMV appears to be the most common viral pathogen involved. Greater than 50% cases are associated with anemia, with PRCA being the most common cause,[4] others being aplastic, pernicious, and hemolytic anemias. Low serum IgG, IgM, and IgA levels are found in roughly 100%, 92%, and 86% of Good's syndrome patients, respectively.[4] Hypogammaglobulinemia, with B-cell and CD4+ T-cell lymphopenia, CD4:CD8 ratio reversal, and impaired T-cell mitogenic responses are the salient immunological features of Good's syndrome (Table 1).

The late age of onset of Good's syndrome suggests a defect at the translational or epigenetic level. Hence, patients should be worked up with whole exome sequencing, comparative genomic hybridization, and protein expression quantification. There is a lack of standard treatment guidelines for Good's syndrome. Thymoma should be resected surgically. Patients should be regularly screened

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Table 1: Good's syndrome's key features compared with idiopathic CD4+ lymphocytopenia and common variable immunodeficiency (CVID)

Characteristics	*Good's syndrome*	*Idiopathic CD4+ lymphocytopenia*	*CVID*
Age-group (years)	40–60	10–70	20–40
Thymoma	+	–	–
Hypogammaglobulinemia	+	–	+
B-cell lymphopenia	+	–	Rare
CD4+ lymphopenia	+	+	–
Red cell disorders (most common)	PRCA	AIHA	AIHA

Data compiled from references 2 and 5; PRCA, pure red cell aplasia; AIHA, autoimmune hemolytic anemia.

for opportunistic infections and treated wherever appropriate. Intravenous IG replacement should be done in patients with immunoglobulin deficiency, in order to maintain adequate trough levels of IgG. Due to lack of any definitive treatment, timely diagnosis of immunodeficiency and prevention of opportunistic infections is the key to management of these patients.

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CASE REPORT

Post-Coronavirus Disease-2019-associated Multisystem Inflammatory Syndrome in Adults: A Case from India

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Abstract

Multisystem inflammatory syndrome in adults (MIS-A) is a postacute hyperinflammatory condition associated with prior SARS-CoV-2 infection. While predominantly reported in children (MIS-C), MIS-A is increasingly recognized in adults and is characterized by multiorgan dysfunction, elevated inflammatory markers, and evidence of recent COVID-19. Timely diagnosis remains challenging due to clinical overlap with other infectious and inflammatory conditions.

We report a case of a 36-year-old previously healthy male from Bihar, India, who presented with severe epigastric pain, progressive dyspnea, and systemic symptoms. Clinical examination revealed tachypnea, hypotension, pedal edema, ascites, and hemorrhagic rashes over the abdomen. Laboratory evaluation showed leukocytosis, thrombocytopenia, acute kidney injury, transaminitis, coagulopathy, markedly elevated inflammatory markers, and cardiac biomarkers. Chest imaging revealed bilateral subpleural opacities and mild pleural effusions, indicating pulmonary involvement. Despite a negative SARS-CoV-2 RT-PCR result, high antibody titers confirmed a recent COVID-19 infection. Imaging of the abdomen confirmed acute interstitial edematous pancreatitis. Extensive evaluation excluded tropical, autoimmune, and other infectious etiologies.

The present case was managed with high-dose corticosteroids, vasopressors, mechanical ventilation, anticoagulation, and supportive therapy. He showed gradual improvement and was discharged after 6 weeks. MIS-A should be considered in patients with recent SARS-CoV-2 exposure presenting with systemic inflammation, including respiratory and extrapulmonary organ dysfunction. Early recognition and immunomodulatory therapy are essential for favorable outcomes.

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Introduction

Multisystem inflammatory syndrome in adults (MIS-A) is an uncommon but serious hyperinflammatory condition that has emerged as a postinfectious complication following SARS-CoV-2 infection. First recognized in children (MIS-C), the adult counterpart was later identified and defined by the Centers for Disease Control and Prevention (CDC) in 2020, characterized by fever, laboratory evidence of inflammation, and multisystem organ involvement without severe respiratory illness.[1] Although rare, MIS-A poses a diagnostic challenge due to its overlapping features with sepsis, tropical infections, and autoimmune disorders, especially in regions like India, where such differentials are prevalent.[2] The underlying cause has been reported to involve dysregulated immune responses and a cytokine storm following SARS-CoV-2 infection,[3] with enlarged clinical symptoms linked to the clinical profile.[4,5]

Reports from India are limited, highlighting the necessity for enhanced awareness and early detection to avert morbidity and mortality. Herein, we present a case of MIS-A in a previously healthy adult male from India, contributing to the expanding clinical spectrum of post-COVID-19 complications.

Case Description

In February 2022, a 36-year-old previously healthy male from Bihar, northern India, with no known comorbidities or history of COVID-19 vaccination, was admitted to the medicine department with complaints of severe epigastric abdominal pain and progressive shortness of breath for 5 days. The abdominal pain was intense, localized to the epigastric region, and relieved on sitting upright. Dyspnea, initially exertional, progressed to occur even at rest. Notably, the patient reported a self-limiting, low-grade fever 2 weeks prior, which lasted 3 days and was responsive to paracetamol.

On clinical examination, the patient was afebrile, tachypneic, and tachycardic, with a SpO_2 of 95% on room air and hypotension (BP 90/68 mm Hg). A general examination revealed bilateral pitting pedal edema, epigastric tenderness, and diminished breath sounds. Abdominal examination revealed ascites with shifting dullness and hemorrhagic rashes distributed over the abdomen. Given the ongoing pandemic and lack of vaccination, SARS-CoV-2 infection was initially suspected. However, nasopharyngeal RT-PCR performed twice was negative. Serological testing revealed markedly elevated anti-SARS-CoV-2 antibody titers (>4,000 IU/mL), suggestive of a recent infection.

Autoimmune workup (ANA, ANCA) and viral markers (hepatitis B, C, HIV) were negative. Tropical febrile illnesses, including dengue, chikungunya, leptospirosis, malaria, and enteric fever, were ruled out. The procalcitonin level was 0.968 ng/mL. Other laboratory investigations revealed leukocytosis (TLC 18,000/µL), neutrophilic predominance (N 89%), thrombocytopenia (platelet count 50,000/µL), elevated liver enzymes (SGOT/SGPT 330/220 IU/L), hyperbilirubinemia (2.3 mg/dL), hypoalbuminemia (1.9 gm/dL), azotemia (urea 120 mg/dL, creatinine 2.5 mg/dL), raised LDH (857 U/L), CRP (45.5 mg/L), ferritin (1,200 ng/mL), D-dimer (2,400 ng/mL), troponin T (327 pg/mL), NT-proBNP (7,300 pg/mL), and creatine kinase (CK) of 45,820 U/L. Coagulation parameters were deranged (INR 2.45, aPTT 43 seconds). Thyroid function was normal. Blood and urine cultures were sterile.

Imaging revealed bilateral ill-defined peripheral opacities on chest X-ray and bilateral subpleural opacities with mild pleural effusion on HRCT thorax. Abdominal ultrasonography showed a bulky pancreas with minimal peripancreatic collection, bilateral pleural effusion, ascites, mild hepatomegaly, and renal parenchymal changes. Ascitic fluid was low-SAAG; pleural fluid was transudative.

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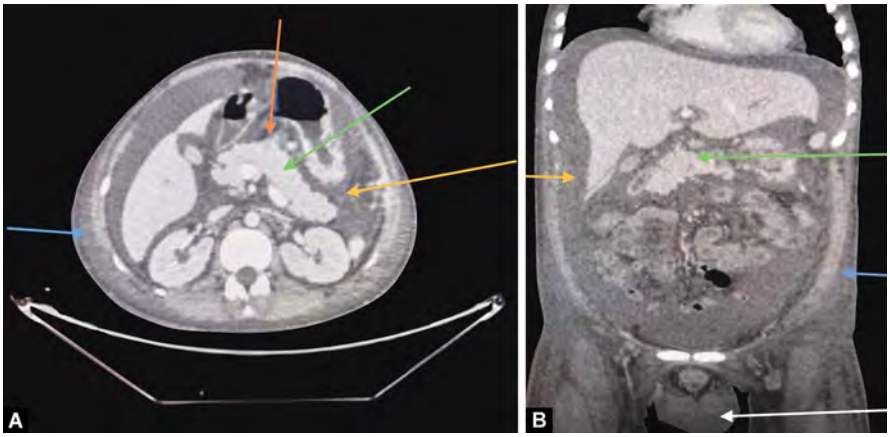

Figs 1A and B: CECT abdomen (A) Axial section showing diffusely enlarged pancreas with loss of feathery margin (green arrow), mild peripancreatic fat stranding around tail of pancreas (yellow arrow), peripancreatic fluid (orange arrow), and subcutaneous edema (blue arrow); (B) Coronal section showing diffusely enlarged pancreas (green yellow), gross ascites (yellow arrow), subcutaneous edema (blue arrow) and bilateral mild hydrocele (gray arrow)

CT abdomen with contrast demonstrated features of acute interstitial edematous pancreatitis (CTSI score 4/10), without necrosis or significant collection (Fig. 1).

Given the multiorgan involvement—pancreatitis, myocarditis (elevated troponin, NT-proBNP), hepatitis, DIC (disseminated intravascular coagulation), and acute kidney injury—alongside positive anti-COVID-19 serology, a diagnosis of post-COVID-19 multisystem inflammatory syndrome in adults (MIS-A) was considered.

Management

The patient required intensive care with mechanical ventilation, vasopressor support, and broad-spectrum antibiotics. Intravenous methylprednisolone was administered at a high dose of 1,000 mg per day for 3 days, followed by a tapering regimen of oral prednisolone (1 mg/kg body weight) over the next 14 days. Prophylactic low-molecular-weight heparin was also given. The patient showed gradual clinical improvement and was discharged after 6 weeks with stable hemodynamic parameters and normalized inflammatory markers.

Discussion

Multisystem inflammatory syndrome in adults (MIS-A) is a rare but serious postinfectious complication associated with SARS-CoV-2. Initially described in children as MIS-C, the adult variant typically presents weeks after the acute phase of COVID-19, often with negative RT-PCR results and positive serologic markers.[1] The pathophysiology of MIS-A is thought to involve a dysregulated immune response characterized by cytokine storm, endothelial injury, and multiorgan inflammation, likely triggered by prior SARS-CoV-2 exposure.[3]

The present case exhibited classic features of MIS-A, including fever history, positive SARS-CoV-2 antibody titers, and involvement of multiple organ systems: gastrointestinal (acute pancreatitis), cardiovascular (myocarditis with elevated troponin T and NT-proBNP), renal (acute kidney injury), hepatic (transaminitis and hyperbilirubinemia), and hematologic (thrombocytopenia and elevated D-dimer). Notably, hemorrhagic abdominal rashes and elevated inflammatory markers such as CRP, ferritin, and LDH further supported a systemic hyperinflammatory state, consistent with prior reports of MIS-A from India and globally.[1,2]

The diagnosis is often challenging due to clinical overlap with tropical febrile illnesses (e.g., dengue, leptospirosis, rickettsial infections), sepsis, and autoimmune disorders. In this patient, extensive negative microbiological and autoimmune workup helped exclude alternative causes. According to CDC criteria, a diagnosis of MIS-A requires hospitalization in individuals aged 21 years or older with positive SARS-CoV-2 serology or recent infection, elevated inflammatory markers, and dysfunction of 2 or more organ systems without severe respiratory symptoms.[6]

Acute pancreatitis is an uncommon but increasingly recognized manifestation of COVID-19 and MIS-A, potentially linked to direct viral cytotoxicity or secondary immune-mediated damage.[5] Furthermore, the exclusion of negative etiologies for pancreatitis strengthens the current diagnosis.[7]

Myocardial involvement, frequently documented in MIS-A, results from diffuse myocardial inflammation and can mimic acute coronary syndromes or viral myocarditis.[8]

Immunomodulation with corticosteroids is the cornerstone of treatment. In this case, high-dose intravenous methylprednisolone followed by oral tapering led to clinical improvement. Anticoagulation with low-molecular-weight heparin was also employed due to the elevated thrombotic risk, as supported by current therapeutic guidelines.[9] Other supportive measures, including organ-specific management and intensive care, remain critical for favorable outcomes.

Conclusion

This case contributes to the scarce yet expanding literature on MIS-A from India, particularly emphasizing uncommon symptoms such as concomitant acute pancreatitis and disseminated intravascular coagulation. It emphasizes the necessity for increased clinical vigilance and prompt immunosuppressive treatment to diminish morbidity and mortality. Increased awareness, especially in post-COVID patients presenting with systemic symptoms and laboratory derangements, is crucial for early diagnosis and intervention.

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CASE REPORT

Intracranial IgG4-related Disease: Insights from Two Cases

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Abstract

Introduction: Immunoglobulin G4-related disease (IgG4-RD) is a rare autoimmune fibroinflammatory condition that can affect multiple organs. Central nervous system (CNS) involvement is seen in only 2–4% of cases. Due to its rarity and heterogeneous presentation, it often mimics malignancies, infections, or other inflammatory conditions, leading to delayed diagnosis. We report two cases illustrating the spectrum of CNS IgG4-RD and highlight diagnostic and therapeutic considerations.

Case 1: A 29-year-old male presented with new-onset generalized tonic-clonic seizures. Brain magnetic resonance imaging (MRI) revealed a left-sided, extra-axial dural-based enhancing lesion with vasogenic edema. Serum IgG4 was elevated (3.25 gm/dL), but whole body positron emission tomography–computed tomography (PET-CT) ruled out systemic involvement. Surgical resection of the lesion was performed. Histopathology revealed a lymphoplasmacytic infiltrate with fibrosis and an IgG4:IgG plasma cell ratio of 20%. The patient was treated with tapering corticosteroids and methotrexate, leading to complete radiological resolution and seizure control.

Case 2: A 44-year-old woman with longstanding hypothyroidism presented with headache, tinnitus, polydipsia, and polyuria. Laboratory investigations revealed panhypopituitarism. Imaging revealed an enlarged pituitary with systemic fluorodeoxyglucose (FDG)-avid lesions on PET-CT. Serum IgG4 was elevated (3.01 gm/L). A diagnosis of probable IgG4-related hypophysitis with multisystem involvement was made. She was managed with pulse methylprednisolone followed by oral steroids, methotrexate, and desmopressin. Follow-up showed clinical and radiological improvement, and serum IgG4 levels normalized.

Discussion: These cases demonstrate the clinical heterogeneity of CNS IgG4-RD, ranging from isolated pachymeningitis mimicking neoplasia to multisystem hypophysitis with systemic uptake. While the 2020 diagnostic criteria emphasize an IgG4:IgG ratio ≥40%, case 1 underscores that lower ratios (e.g., 20%) may still be diagnostically relevant, particularly in meningeal disease. Both patients responded well to corticosteroids and methotrexate, supporting their role as effective first-line treatment. These cases add to the growing evidence base for CNS-specific IgG4-RD and emphasize the need for organ-specific diagnostic flexibility and long-term immunosuppressive strategies.

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a fibroinflammatory autoimmune condition that can affect multiple organ systems. Central nervous system (CNS) involvement in IgG4-RD is rare, with large cohort studies estimating a prevalence of 2–4%.[1] Hypophysitis is the most frequently reported manifestation, followed by hypertrophic cranial pachymeningitis, hypertrophic spinal pachymeningitis, intracranial mass lesions, cavernous sinus involvement, and orbital disease.[2] CNS involvement may present in isolation or as part of a multisystem disease. Its rarity and heterogeneous presentation often lead to misdiagnosis as malignancy, infection, or other inflammatory conditions, underscoring the importance of early recognition to initiate timely treatment and prevent irreversible fibrotic sequelae. We present two cases of intracranial IgG4-RD that highlight its diverse clinical spectrum, diagnostic challenges, and therapeutic responses.

Case 1

A 29-year-old male presented with three episodes of generalized tonic-clonic seizures, without fever, headache, or focal deficits. Brain magnetic resonance imaging (MRI) revealed an extra-axial, dural-based lesion along the left convexity with perilesional vasogenic edema (Figs 1A and B). Laboratory reports were—erythrocyte sedimentation rate (ESR): 2 mm/hour, C-reactive protein (CRP): 17.4 mg/dL (0–5 mg/dL), angiotensin-converting enzyme (ACE): 59.2 U/L (16–85 U/L), antineutrophil cytoplasmic antibody (ANCA): negative, antinuclear antibody (ANA): 1:100 1^+ speckled, and serum IgG4: 3.25 gm/dL (normal <1.35 gm/dL). Whole body positron emission tomography–computed tomography (PET-CT) scan showed a metabolically inactive 3.7 × 0.9 cm lesion along the left parietal calvarium, with no other systemic involvement.

Initial management included antiepileptics and corticosteroids. Once the seizures stabilized, an elective craniotomy and debulking of the dural lesion were done. Histopathological examination (HPE) revealed fibrosis with lymphoplasmacytic infiltrate (Fig. 2B). Immunohistochemistry confirmed IgG4-positive plasma cell infiltration with an IgG4:IgG ratio of 20% (Fig. 2A). Cultures for bacteria, mycobacteria, and fungi were negative. Based on these findings, a final diagnosis of meningeal IgG4-related disease was made.

The patient was treated with a tapering course of prednisolone (40 mg daily) along with methotrexate (15 mg weekly) as a steroid-sparing agent. At the 3-month follow-up, he reported symptomatic improvement, with resolution of seizures and a decline in serum IgG4 and CRP levels. Repeat MRI with contrast demonstrated resolution of the dural mass and associated vasogenic edema (Figs 1C and D). Methotrexate and antiepileptics were continued for long-term disease and seizure control.

Case 2

A 44-year-old woman with a 10-year history of hypothyroidism (controlled on thyroxine 75 µg/day) presented in August 2024 with left-sided frontoparietal headache, left ear blockage, tinnitus, polydipsia, polyuria, nausea, and vomiting. Neurological examination was normal. MRI brain with contrast revealed an enlarged pituitary gland (14 × 14 × 10 mm) and pansinusitis. Relevant laboratory reports were—ESR: 44 mm/hour, CRP: 2.43 mg/L (range), thyroid-stimulating hormone (TSH): 0.04 µIU/mL (0.4–5.5 µIU/mL), serum cortisol: <0.5 µg/dL (5–25 µg/dL), follicle-stimulating hormone (FSH): 3.41 mIU/mL (25.8–134 mIU/mL), luteinizing hormone (LH): 0.3 mIU/mL (14.2–52.3 mIU/mL), and serum IgG4: 3.01 gm/L (normal <1.35 gm/L). ANA, ANCA, ACE, complement level were unremarkable. Water deprivation test confirmed central diabetes insipidus. Whole body PET-CT showed fluorodeoxyglucose (FDG) uptake in the pituitary, cervical lymph nodes, left lung, and pancreatic tail, indicating multisystem IgG4-RD

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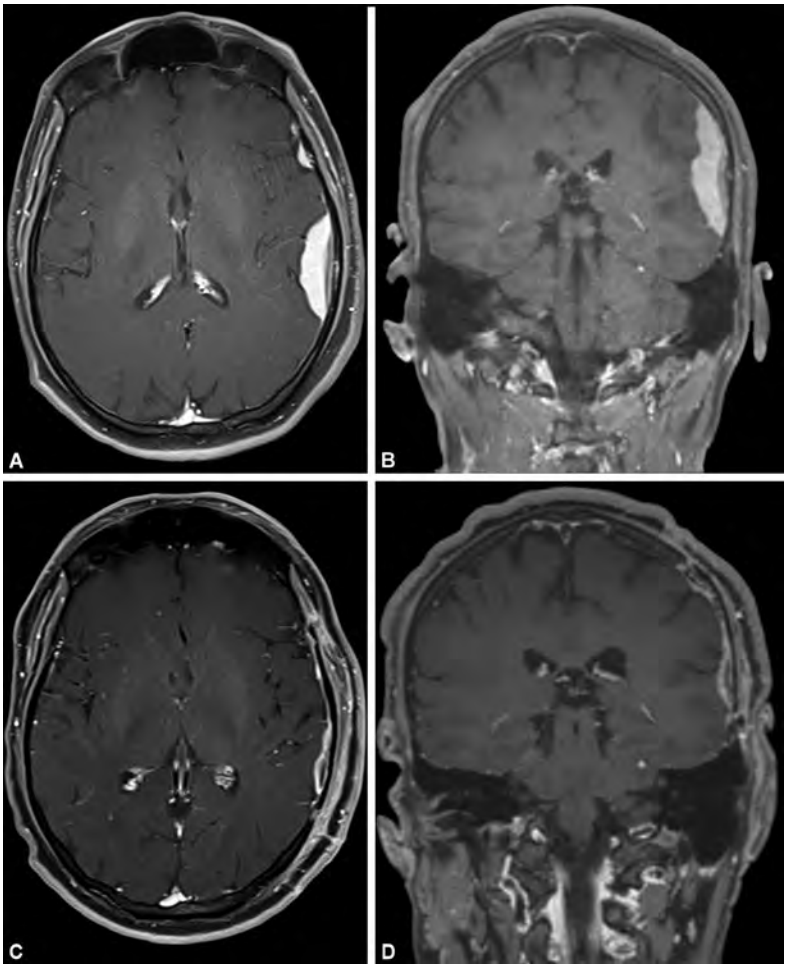
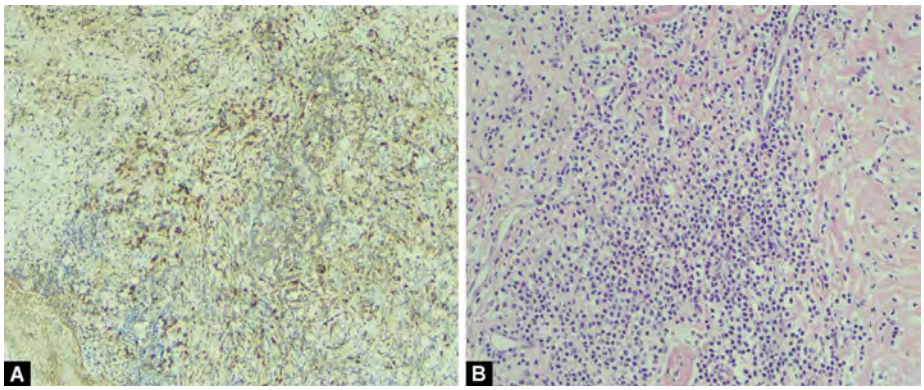


Figs 1A to D: Axial (A and C) and coronal (B and D) contrast-enhanced MRI brain images of case 1: (A and B) Pretreatment images showing a left-sided, extra-axial, dural-based enhancing lesion along the frontotemporoparietal convexity with associated perilesional vasogenic edema, mimicking a meningioma; (C and D) Follow-up MRI performed 3 months posttreatment with corticosteroids and methotrexate, showing complete resolution of the dural lesion and associated edema



Figs 2A and B: Histopathological features of the dural lesion in case 1: (A) Immunohistochemistry showing numerous IgG4-positive plasma cells (brown staining), consistent with IgG4-related disease (×200); and (B) hematoxylin and eosin staining demonstrating dense lymphoplasmacytic infiltrate within fibrotic stroma (×200)

(Figs 3A and B). A probable diagnosis of IgG4-related hypophysitis was established. Biopsy of the lung and pancreatic lesion was offered but the patient declined. Treatment involved pulse intravenous methylprednisolone (1 gm/day for 3 days), followed by oral prednisolone (60 mg/day, tapered), desmopressin, and methotrexate (15 mg/week). By March 2025, clinical improvement was evident, with follow-up imaging showing reduced pituitary size and systemic FDG uptake (Figs 3C and D). Serum IgG4 normalized to 0.94 gm/L. Methotrexate was increased to 20 mg/week, and prednisolone tapered to 5 mg/day. The patient remains stable under close follow-up.

Discussion

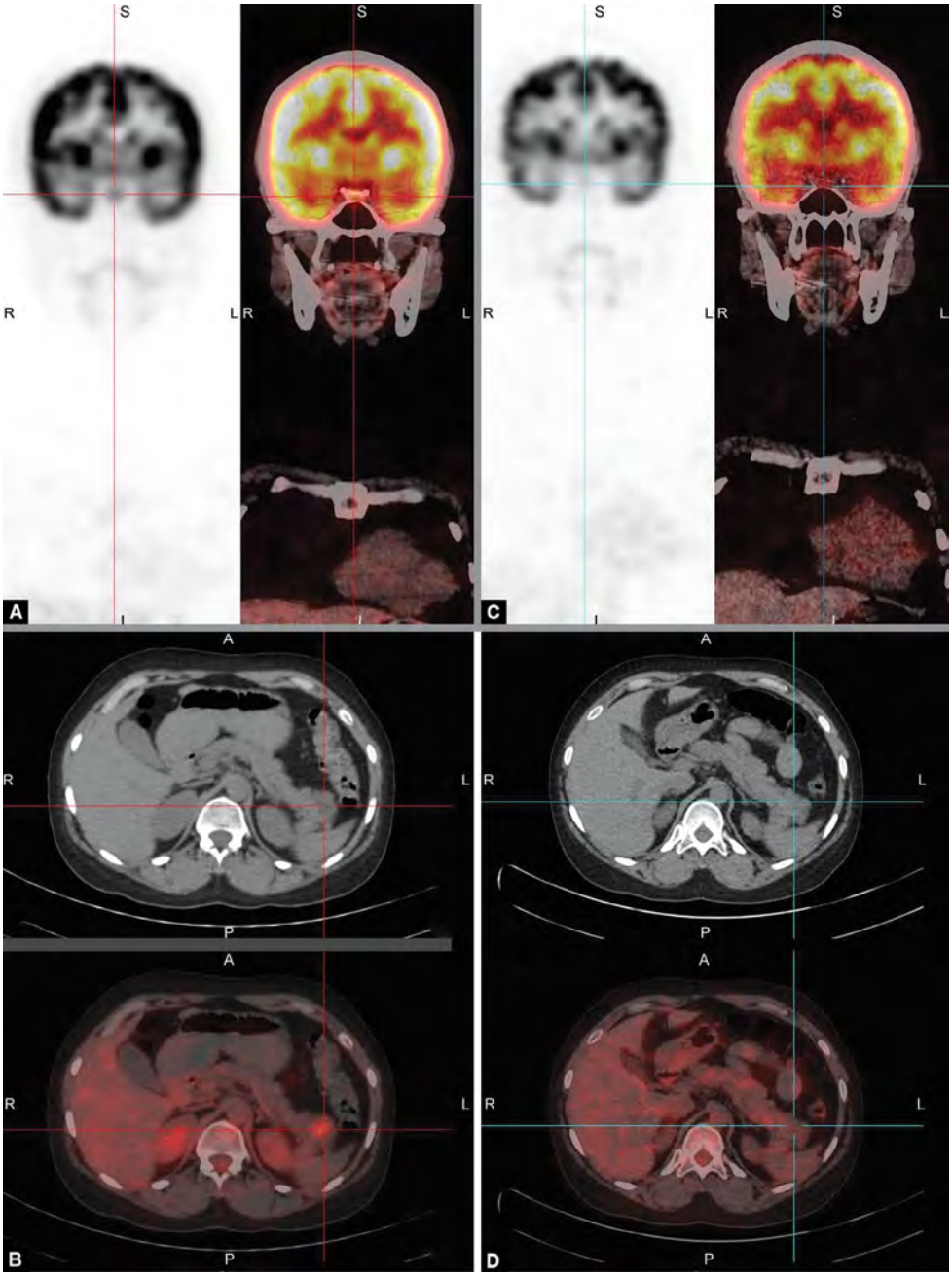
Immunoglobulin G4-related disease was first described in 2001 by Hamano et al.[3] Since then, over the past few decades, the understanding and management of this protean disease is still evolving. CNS IgG4-RD is a rare entity with varied presentation.

Case 1 highlights an isolated presentation of CNS IgG4-related disease without systemic involvement, where the intracranial lesion closely mimicked malignancy and was only diagnosed following surgical resection. Unlike most reported cases, which predominantly occur in older individuals,[2] our patient with IgG4-related hypertrophic pachymeningitis was a young adult. In case 2, although there were CNS symptoms, the PET-CT revealed multisystem involvement, underscoring the need for systemic imaging to detect subclinical disease.

The need for biopsy and the histopathological criteria in IgG4-RD, in different organs, is also an evolving subject. In case 1, the histopathology showed an IgG4:IgG ratio of 20%, well below the 2020 comprehensive diagnostic criteria's ≥40% threshold.[4] However, similar lower ratios in meningeal disease have been well documented, highlighting the diagnostic flexibility needed for HPE criteria for IgG4-RD in different organs.[5] In case 2, although HPE was not possible, the type of organ system involvement on PET-CT and the elevated serum IgG4 level suggested the diagnosis, and the response to therapy was consistent with the diagnosis.

Corticosteroids are still the first-line treatment for IgG4-RD, with steroid-sparing agents often added from the beginning to get better disease control, reduce relapses, and reduce the adverse effects of steroids. Azathioprine, mycophenolate mofetil, methotrexate, 6-mercaptopurine, cyclophosphamide, and tacrolimus have been used[1] as steroid sparers in anecdotal evidence. Rituximab has been a promising agent in glucocorticoid-refractory disease and frequent relapses, but more evidence of its use in pachymeningeal involvement is warranted. Most of the data on B-cell depleting therapy is in multisystemic non-CNS involvement. Newer biologics have also been studied.[6]

In case 1, prednisolone and methotrexate achieved seizure control and lesion resolution within 3 months, supported by MRI and



Figs 3A to D: (A and B) Pretreatment images showing increased FDG uptake in the pituitary gland, left lung, and pancreatic tail, suggestive of multisystem IgG4-related disease; (C and D) Posttreatment images after corticosteroids and methotrexate showing marked reduction in FDG uptake across all previously involved sites, indicating therapeutic response

declining IgG4 levels. In case 2, pulse intravenous methylprednisolone followed by oral prednisolone and methotrexate normalized IgG4 and reduced pituitary and systemic involvement, confirmed by PET-CT.

These cases highlight the heterogeneity of CNS IgG4-RD, from isolated meningeal disease to multiorgan disease presenting as hypophysitis. They reinforce the role of corticosteroids and methotrexate as effective initial treatment options for CNS IgG4-RD. They add to the existing literature of this rare condition.

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CASE REPORT

Atypical Presentation of Myelin Oligodendrocyte Glycoprotein Antibody Disease as Pyrexia of Unknown Origin with Meningitis: A Case Report

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Abstract

Background: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a rare autoimmune neuroinflammatory disorder. While it typically presents as optic neuritis, myelitis, or acute disseminated encephalomyelitis (ADEM), its manifestation as pyrexia of unknown origin (PUO) with subsequent meningitis is extremely rare.

Case description: We report a 17-year-old male who presented with persistent fever and headache, without focal neurological deficits. Extensive infectious workup was inconclusive. Cerebrospinal fluid (CSF) analysis revealed mild pleocytosis, and empirical antibiotics were initiated without clinical improvement. A repeat CSF analysis demonstrated worsening pleocytosis, prompting an expanded autoimmune and neuroinflammatory panel. MOG-IgG antibodies were detected in both serum and CSF, confirming the diagnosis of MOGAD. The patient responded well to high-dose corticosteroids followed by mycophenolate mofetil for maintenance therapy.

Conclusion: This case highlights the importance of considering MOGAD in patients with unexplained fever and headache with inflammatory CSF. Early recognition and prompt immunotherapy initiation are essential for optimal outcomes. A favorable outcome was observed following timely immunotherapy.

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Introduction

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an autoimmune demyelinating disorder characterized by antibodies targeting the myelin oligodendrocyte glycoprotein (MOG). Although it shares overlapping features with multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD), it is clinically and pathologically distinct.[1]

This report aims to describe an atypical presentation of MOGAD as pyrexia of unknown origin (PUO) with inflammatory CSF findings, to raise awareness of this rare diagnostic possibility.

While MOGAD commonly presents with optic neuritis, transverse myelitis, or acute disseminated encephalomyelitis (ADEM), atypical manifestations such as meningitis and PUO are extremely rare.[2–4] This report describes a unique case of MOGAD presenting as PUO with persistent headache, later diagnosed as aseptic meningitis. It underscores the importance of considering neuroinflammatory etiologies in unexplained febrile syndromes associated with headache.

Case Description

A 17-year-old male presented with a one-week history of fever (maximum temperature of 103°F), headache, nausea, and vomiting. Clinical examination revealed no neck stiffness, seizures, focal neurological deficits, or altered sensorium.

The initial suspicion was an infectious etiology. Blood and urine cultures were sent, and empiric intravenous antibiotics (ceftriaxone and azithromycin) were started for suspected enteric fever.[5] Despite treatment, the patient remained febrile, prompting further evaluation.

Initial laboratory investigations, including dengue NS1 antigen, malarial smear, typhoid IgM/IgG, and blood and urine cultures, were negative. Abdominal ultrasound and brain MRI were also unremarkable. As the fever persisted, a neurologist was consulted, and a lumbar puncture was performed.

The first cerebrospinal fluid (CSF) analysis revealed mild pleocytosis (WBC count: 129/µL; protein: 37 mg/dL; glucose: 54 mg/dL) with 61% lymphocytes. CSF was negative for bacterial, viral, and fungal pathogens including HSV PCR, cryptococcal antigen, and *Brucella* IgM.[6] Empiric broad-spectrum antibiotics (meropenem and vancomycin) were initiated, but there was no clinical improvement.

Given the persistent fever and headache, a whole-body PET scan was performed, which did not reveal any malignancy or inflammatory focus. An extended autoimmune and inflammatory panel (ANA, APLA, C3, C4, and IgG4 levels) was unremarkable.

Due to lack of clinical improvement, a second lumbar puncture was performed. This CSF analysis showed worsening pleocytosis (WBC count: 284/µL; protein: 154 mg/dL; glucose: 48 mg/dL) with 92% lymphocytes. This raised the suspicion of an autoimmune or inflammatory etiology. Additional testing for pan-encephalitis markers, MOG-IgG, and NMOSD antibodies was sent.[7]

MOG antibodies were detected in both CSF and serum, confirming a diagnosis of MOGAD-associated meningitis. The patient was started on intravenous methylprednisolone (1 gm/day for 3 days), followed by a tapering course of oral corticosteroids over 3 weeks. After completing the oral steroid course, mycophenolate mofetil (500 mg twice daily) was initiated. The patient showed significant clinical improvement on follow-up, with complete resolution of fever and headache.[8]

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Clinical timeline as below:

Day	*Events*
Day 1	Onset of fever (max 103°F), headache, nausea, vomiting
Day 3	Initial evaluation, started on ceftriaxone + azithromycin for suspected enteric fever
Day 5	No improvement; cultures negative; dengue, malaria, typhoid ruled out
Day 6	Neurology consult; LP performed (mild pleocytosis); CSF negative
Day 8	Started empirical meropenem + vancomycin
Day 10	PET scan—no abnormal focus; autoimmune panel negative
Day 12	Second LP: worsening pleocytosis; autoimmune panel sent
Day 14	MOG-IgG detected in CSF and serum; MOGAD confirmed
Day 15	Started IV methylprednisolone (1 gm/day × 3 days)
Day 18	Started oral steroid taper + mycophenolate mofetil (500 mg BD)
Day 25	Resolution of fever/headache; discharged with follow-up plan

Discussion

MOGAD is a recently recognized autoimmune CNS disorder, with meningitis as an uncommon manifestation. This case is unique due to the following reasons:

- Initial presentation as PUO without neurological deficits delayed suspicion of neuroinflammation.
- The patient remained febrile despite extensive infectious screening and empiric antimicrobials.
- MOGAD was only diagnosed after serial lumbar punctures revealed worsening pleocytosis, emphasizing the value of repeat CSF analysis in unexplained CNS inflammation.

MOGAD is an immune-mediated CNS demyelinating disorder distinct from multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). It presents with a spectrum of symptoms, including optic neuritis, myelitis, and rarely, meningitis. While most MOGAD cases follow a relapsing opticospinal course, this report highlights an atypical initial presentation, emphasizing the importance of broad differential diagnoses in neuroinflammatory syndromes.

Challenges in Diagnosis

Diagnosing MOGAD can be difficult due to overlap with other inflammatory and infectious conditions. In this case, the initial presentation as PUO with persistent headache led to an infectious disease-focused evaluation, delaying neuroimmunological consideration.

Several key points made diagnosis challenging:

- Serial CSF analysis was pivotal: The first lumbar puncture showed only mild pleocytosis, which did not strongly suggest an autoimmune process. The second LP, however, showed significantly worsened pleocytosis, shifting focus toward neuroinflammation.
- Infectious workup remained negative: Extensive testing for bacterial, viral, fungal, and mycobacterial infections was noncontributory. Empiric antibiotics failed to produce a response, further supporting a noninfectious etiology.
- Normal MRI findings do not rule out MOGAD: Early in the disease course, MOGAD can present with normal or nonspecific MRI findings. In this case, a normal initial MRI likely contributed to the delayed suspicion of CNS demyelination. Nonetheless, worsening CSF pleocytosis prompted appropriate antibody testing.

Pathophysiological Insights

MOGAD is characterized by autoantibodies targeting myelin oligodendrocyte glycoprotein (MOG), a surface protein expressed on oligodendrocytes. This autoimmune response leads to demyelination and CNS inflammation. Unlike aquaporin-4 (AQP4)-positive NMOSD, which is primarily an astrocytopathy, MOGAD predominantly involves oligodendrocytes. The pathological process includes complement activation, perivascular lymphocytic infiltration, and disruption of the blood–brain barrier.[9]

Differentiating Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease from Other Central Nervous System Demyelinating Disorders

MOGAD differs from multiple sclerosis (MS) and NMOSD in multiple aspects. Clinically, MS usually demonstrates a progressive accumulation of disability, while MOGAD follows a more relapsing-remitting course. MRI in MS typically shows periventricular white matter plaques, whereas MOGAD tends to involve subcortical white matter, the brainstem, and spinal cord. Unlike AQP4-IgG-positive NMOSD, which has hallmark features such as longitudinally extensive transverse myelitis and area postrema syndrome, MOGAD may present with optic neuritis, seizures, or isolated meningitis—as seen in this case.

Treatment Considerations

Early initiation of high-dose corticosteroids is critical for optimal outcomes in MOGAD. Our patient received intravenous methylprednisolone, followed by an oral taper and maintenance therapy with mycophenolate mofetil. Mycophenolate was selected over rituximab based on cost, tolerability, and the need for long-term immunosuppression.

Key therapeutic principles include:

- Acute phase treatment: Intravenous corticosteroids remain the first-line therapy. For steroid-refractory cases, escalation to intravenous immunoglobulin (IVIG) or plasmapheresis may be warranted.
- Maintenance immunosuppression: Agents such as mycophenolate mofetil, azathioprine, or rituximab are effective in preventing relapses.[10]
- Monitoring: Regular clinical assessment and MRI surveillance are crucial to detect subclinical disease activity and manage relapses effectively.

Study Limitations

This case report is limited by its single-patient nature and the short duration of follow-up. Additionally, advanced diagnostic confirmation, such as tissue biopsy or MOG-specific MRI pattern analysis, was not performed. These limitations may affect the generalizability of our observations. Nevertheless, the case provides valuable insights into a rare and atypical presentation of MOGAD.

Key Takeaways for Clinical Practice

- MOGAD can present atypically as PUO and meningitis, especially in the absence of classic neurological deficits.
- Serial CSF analysis is essential when the initial lumbar puncture is inconclusive.
- Autoimmune testing should be considered early in cases of unexplained CNS inflammation.

- Prompt initiation of immunotherapy can prevent long-term sequelae and improve outcomes.

Conclusion

This case underscores the importance of considering MOGAD in patients with unexplained CNS inflammatory syndromes, even when presenting with PUO and mild meningitis-like symptoms. A high index of suspicion, repeat CSF analysis, and timely autoimmune workup are essential for early diagnosis and effective treatment. Favorable clinical outcomes can be achieved through prompt immunotherapy and maintenance immunosuppression.[11,12]

Patient Consent

Written informed consent was obtained from the patient and/or their guardian for publication of this case report and any accompanying data or images. The identity of the patient has been anonymized to protect privacy.

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CASE REPORT

Pericardial Hydatid Cyst Causing Focal Right Atrial Tamponade: A Case Report

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Abstract

Cystic echinococcosis (CE) caused by *Echinococcus granulosus* presents a significant public health concern globally, with varied clinical presentations ranging from asymptomatic to life-threatening complications. We report a case of a 58-year-old female with extensive hydatid disease involving multiple cysts in the abdominal, pelvic, and pericardial cavities, resulting in substantial morbidity. Despite the complexity of the case and the therapeutic dilemma it posed, a tailored management approach combining medical therapy with either surgical intervention or minimally invasive procedures was employed. This case highlights the challenges in managing advanced CE infections and underscores the importance of individualized treatment strategies guided by a comprehensive understanding of the disease and its potential complications.

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Introduction

Cystic echinococcosis (CE), an infection caused by *Echinococcus granulosus*, occurs when eggs excreted in the feces of infected canines are inadvertently ingested by humans. This leads to the development of hydatid cysts, predominantly found in the liver (70%) and lungs (20%). The remaining 10% of cases may present cysts anywhere in the body, including, but not limited to, the brain, muscles, heart walls, kidneys, orbital cavity, and bone marrow. In contrast, the metacestodes of *Echinococcus multilocularis* manifest as a conglomerate of small, interconnected cysts, primarily in the liver (98–100%), with potential for metastatic spread to other organs in advanced stages of infection.[1]

A previous study conducted over two decades in North India reported a seroprevalence of 15.1% among individuals clinically suspected of having CE.[2]

In this report, we discuss an extensive case of hydatid disease characterized by the widespread distribution of cysts throughout the abdominal, pelvic, and pericardial cavities. This extensive involvement resulted in a significant mass effect, notably including focal collapse of the right atrium. This case underscores the potential severity and widespread impact of CE, highlighting the need for increased awareness and improved diagnostic and therapeutic strategies.

Case Description

This case presents a complex management challenge involving a 58-year-old female patient, primarily engaged in farming, who presented with mild shortness of breath, abdominal pain, low appetite, and intermittent low-grade fever persisting for 4–5 months. The patient has a history of hypertension and chronic kidney disease (CKD) but has been noncompliant with medication. Despite consulting multiple physicians, her condition necessitated referral for advanced management.

Upon evaluation, the patient was found to be conscious, oriented, pale, and underweight with a body mass index (BMI) of 15, exhibiting tachypnea [respiratory rate (RR)—26] and tachycardia [heart rate (HR)—112]. Blood pressure was measured at 114/72 mm Hg in the right arm. Physical examination did not reveal any chest or abdominal asymmetry, but palpation identified multiple hard, nontender swellings in the abdomen and pelvis, with liver tenderness but without organomegaly. A grade III pansystolic murmur was auscultated at the tricuspid region without radiation, and the apex beat was normal.

Laboratory investigations indicated anemia (hemoglobin—9.1 gm/dL), and slightly elevated serum creatinine (1.6 mg/dL) and blood urea (47 mg/dL). Imaging studies, including ultrasound and computed tomography (CT) of the abdomen, revealed multiple cystic lesions in the liver, the largest being approximately 9.5 × 11.5 cm in segment V, and a 12 × 16 cm cyst in the subhepatic region with internal daughter cysts. Cystic lesions were also noted in the peritoneum of the abdomen and pelvis (Fig. 1), along with subcapsular cystic lesions on the spleen and liver (Fig. 2). Echocardiography identified a large pericardial cyst (7 × 6.5 cm) exerting significant mass effect and causing focal tamponade on the right atrium (Fig. 3), with an ejection fraction of 45%, mild mitral regurgitation, and moderate tricuspid regurgitation [mean pulmonary artery pressure (mPAP) ~ 44 mm Hg].

The patient was initiated on albendazole 400 mg twice daily for 3 months to reduce the risk of anaphylaxis during intervention and to attempt parasitic eradication.

The therapeutic dilemma centers on choosing between surgical removal of as many cysts as possible, despite the high risk of anaphylaxis, and performing a PAIR (puncture, aspiration, instillation, and reaspiration) procedure on the largest cysts in the liver and pericardium to mitigate morbidity and improve the patient's quality of life.

Over a 2-month period, the patient was treated with albendazole and subsequently initiated on tablet Praziquantel 800 mg twice daily for 1 month. Following this regimen, there was a notable reduction in the size of the pericardial cyst and significant improvement in the patient's quality of life.

Consequently, a decision was made to pursue conservative management without procedural intervention for the cyst. The patient experienced a marked improvement in appetite and was able to resume daily activities without difficulty.

Consultation with the surgical department recommended continued conservative management due to the presence of multiple cysts involving the liver, intestine, and pelvis, posing challenges for surgical intervention. Given the patient's improving clinical status, surgical intervention was withheld until absolutely necessary.

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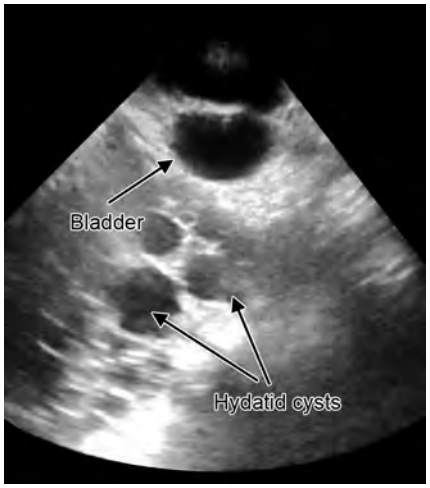

Fig. 1: Multiple hydatid cysts in pelvis

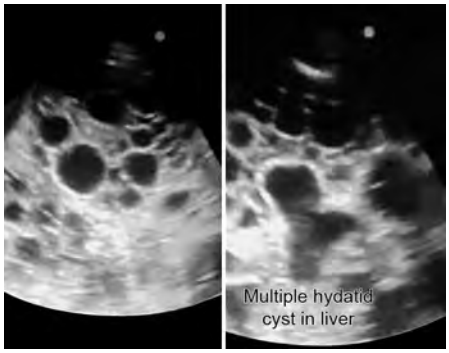

Fig. 2: Multiple hydatid cysts in liver

Discussion

Echinococcus granulosus and *E. multilocularis* are the primary parasitic pathogens affecting the liver, leading to infections that may remain asymptomatic for years before clinical manifestation. Due to the lack of universally accepted treatment guidelines for these parasites, management strategies can vary. Dogs and other canids serve as definitive hosts for these parasites, whereas intermediate hosts include livestock such as sheep, goats, and pigs. Humans are accidental hosts, typically acquiring infection through the unintentional consumption of parasitic eggs.

The treatment regimen for these infections involves the administration of Albendazole at a dosage of 10–15 mg/kg for a duration of 3–6 months. Alternatively, Mebendazole

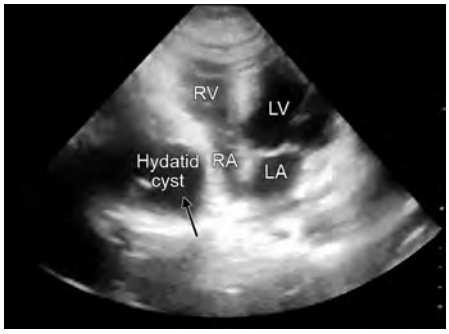

Fig. 3: Hydatid cyst causing focal collapse of right atrial free wall

may be prescribed, with doses starting at 40–50 mg/kg.[3] It is recommended that cysts larger than 5 cm undergo percutaneous drainage, while surgical intervention is advised for managing multiple cysts.

Percutaneous drainage, particularly for hepatic cysts, has been shown to be as effective as surgical intervention in the treatment of uncomplicated hydatid cysts. This approach is associated with reduced complication rates and shorter durations of hospital stay. Furthermore, long-term follow-up of a substantial patient cohort with hepatic hydatid cysts has demonstrated excellent outcomes, with no evidence of local, peritoneal, or systemic spread.[4] While major complications are rare, instances of hemobilia, cyst infections, anaphylaxis, and pneumonia have been reported.[5]

Surgical treatment becomes the preferred option in cases of relapse or when hepatic cysts communicate with the biliary tree. Surgery is also recommended for multiple cysts that do not respond adequately to pharmacological treatment.[6]

Conclusion

In the case presented, the patient exhibits multiple cysts due to *E. granulosus* infection, complicating the treatment strategy. Although surgical removal is generally preferred for managing multiple cysts, the extensive involvement of both the pelvic and abdominal cavities presents significant surgical challenges. Accessing and effectively removing all cysts during surgery could be exceedingly difficult due to their widespread distribution.

Alternatively, the PAIR technique, particularly targeting the large hepatic and pericardial cysts, emerges as a viable option. This minimally invasive approach could potentially enhance the patient's quality of life by alleviating the mass effect and associated symptoms without the major risks linked to extensive surgical procedures.

This case underscores the therapeutic conundrum faced by healthcare providers in selecting the optimal intervention strategy. The decision between pursuing comprehensive surgical cyst removal and opting for the more conservative PAIR technique for specific cysts reflects the complexity of managing advanced *E. granulosus* infections. Through reporting this case, we aim to illuminate the intricacies of clinical decision-making in such scenarios, emphasizing the need for a tailored approach that considers both the potential benefits and the risks of intervention.

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CASE REPORT

Exploring Etiologies of Hypokalemic Paralysis: A Case Series

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Abstract

Background: Hypokalemic paralysis is a rare but potentially life-threatening neuromuscular emergency characterized by the sudden onset of flaccid weakness due to reduced serum potassium. While inherited channelopathies represent primary causes, secondary etiologies—particularly endocrine, renal, and metabolic disorders—are more frequently encountered and require timely recognition to avoid complications.

Case summary: We report four patients presenting with acute flaccid paralysis associated with documented hypokalemia (serum potassium <3.5 mmol/L). The first case involved a pregnant woman with primary hyperaldosteronism due to an adrenal adenoma, managed initially with spironolactone and subsequently cured by adrenalectomy. The second case was a normotensive female diagnosed with distal renal tubular acidosis (dRTA) in the setting of Sjögren's syndrome, treated with potassium citrate and sodium bicarbonate. The third case was a young male with thyrotoxic periodic paralysis (TPP) secondary to Graves' disease, who improved with antithyroid drugs and beta-blockers. The fourth case described a young male with primary hypokalemic periodic paralysis (HPP), presenting with exertion-induced weakness, successfully treated with intravenous potassium supplementation.

Conclusion: This case series underscores the diverse etiologies of hypokalemic paralysis, spanning endocrine, renal, autoimmune, and genetic causes. A systematic diagnostic approach, guided by clinical and biochemical evaluation, is essential for timely treatment. Identifying the underlying cause not only ensures effective acute management but also prevents recurrence and reduces the risk of serious complications, including cardiac arrhythmias.

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Introduction

Hypokalemia can be described by low serum potassium levels, usually <3.5 mEq/L. When potassium levels drop below 2.5 mEq/L, severe as well as fatal hypokalemia develops. Up to 20% of hospitalized patients exhibit hypokalemia, although it is clinically significant in only 4–5% of cases. Severe hypokalemia is relatively rare. Serum potassium levels must drop below 3.0 mEq/L for hypokalemia symptoms to appear. Symptoms might vary from nonexistent to fatal cardiac arrhythmias, depending on the severity of hypokalemia. When hypokalemia is corrected, symptoms normally go away.[1] Hypokalemia symptoms can be grouped based on systems that are impacted: metabolic acidosis and rhabdomyolysis in the renal system; weakness, paresis, leg cramps, as well as ascending paralysis in the neuromuscular system; constipation as well as intestinal paralysis in the gastrointestinal system; respiratory failure in the respiratory system; and variations in electrocardiogram (ECG) such as T wave flattening, ST-segment changes, as well as U waves, cardiac arrhythmias (sometimes lethal), or heart failure in the cardiovascular system. These symptoms reflect the broad and potentially severe impact of hypokalemia on various body systems, highlighting the importance of timely diagnosis and treatment.[2,3] Numerous factors can contribute to hypokalemia, which occasionally calls for immediate medical intervention to avoid potentially fatal consequences like cardiac arrhythmias and respiratory failure.[4] We report four patients with various causes of hypokalemic paralysis who had been admitted to a tertiary care center in Northern India. Each patient had acute onset of flaccid weakness along with a serum potassium level of <3.5 mEq/L.

Case 1

A 29-year-old multigravida woman who has had hypertension for 4 years, well controlled on antihypertensives, presented to the emergency department at 3 months of gestation. She complained of gradual onset of weakness in all four limbs over a period of 6 days and an inability to hold her neck up for a period of 5 days. She had been hospitalized at a nearby hospital 2 years ago after experiencing a similar incident, although no documentation was available.

There was no history of intense exercise or heavy carbohydrate meals within the previous 24 hours, and no history of vomiting, dry mouth, bone pain, diarrhea, dry eyes, fractures, kidney stones, or thyroid disorders. There was no family history of similar episodes. Medications other than antihypertensives were ruled out, including diuretics, β_2-agonists, insulin, laxatives, and antipsychotics. On admission, her blood pressure (BP) was 110/70 mm Hg. Neurological tests showed that all four limbs had muscle power of 2/5, reduced muscle tone, as well as deep tendon reflexes. No evidence of sensory or autonomic deficits was noted. Other systemic examinations were unremarkable.

Initial investigations indicated severe hypokalemia (serum potassium 1.2 mmol/L). Blood gas analysis confirmed hypokalemia with mixed alkalosis. Serum magnesium was within normal limits. ECG showed hypokalemic changes, including T-wave inversions and U waves. Quadriparesis improved with intravenous potassium supplementation through a central line, with potassium chloride administered initially at 10 mmol/hour in regular saline under continuous cardiac monitoring, followed by gradual tapering.

Further workup for hypokalemia included calculating the urine potassium-to-creatinine ratio, which was 112 mmol/gm (a ratio >15 mmol/gm suggests renal potassium loss). The following formula was utilized to calculate transtubular potassium gradient (TTKG):

$$TTKG = (K^+_{urine})\ Osm_{serum} / (Osm_{urine})\ K^+_{serum}$$

Yielding a value of 59, indicating distal potassium loss (TTKG >4). Elevated plasma aldosterone levels of 476 pg/mL or 1747 pmol/L (normal levels, 3–28 pg/mL or <450 pmol/L) with low renin activity, 0.33 ng/mL/hour (normal levels between 0.7 and 3.3 ng/mL/hour), as well as a higher ratio of aldosterone-to-renin of 5293 (normal levels <70), suggested primary hyperaldosteronism. A saline suppression test showed nonsuppression of plasma aldosterone (756 pmol/L or 206 pg/mL) (postsaline

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suppression, normal plasma aldosterone value is expected to be <140 pmol/L or <38 pg/mL), further confirming primary hyperaldosteronism (Table 1). Abdominal magnetic resonance imaging (MRI) showed a left adrenal adenoma (Fig. 1).

The patient had been initiated on spironolactone 50 mg twice daily, with serial electrolyte monitoring. A surgical endocrine consultation recommended laparoscopic unilateral adrenalectomy, which was planned for postpregnancy. Unfortunately, the patient experienced a spontaneous abortion at 5 months' gestation. Following this, laparoscopic unilateral adrenalectomy was successfully performed. During subsequent follow-up visits, she remained normokalemic.

Case 2

A 41-year-old woman who has had Sjögren's/overlap syndrome for 2 years, receiving treatment for the same from the Department of Rheumatology, arrived in the emergency department with chief concerns regarding gradually progressive weakness over a period of 3 days. There was no prior record of intense exercise, heavy carbohydrate meals within the previous 24 hours, diarrhea, vomiting, bone pain, fractures, hypertension, or thyroid disorders. There was no family history of similar episodes. Medication use, including antipsychotics, diuretics, laxatives, insulin, and β_2-agonists, had been ruled out. On admission, her BP was 96/60 mm Hg. Neurological testing showed that the left upper and lower limbs had 3/5 muscle power, while the right upper and lower limbs had 1/5. Additionally, all four limbs had reduced muscle tone with diminished tendon reflexes. There was no evidence of sensory or autonomic deficits. Other systemic examinations were unremarkable.

Initial investigations indicated severe hypokalemia (1.6 mmol/L serum potassium). Blood gas analysis confirmed hypokalemia with normal anion gap metabolic acidosis. Serum magnesium was within normal limits. Quadriparesis improved with intravenous potassium supplementation *via* a central line under continuous cardiac monitoring, and acidosis responded to sodium bicarbonate infusion.

Further workup for hypokalemia included calculating the urine potassium-to-creatinine ratio, which was 119 mmol/gm (a ratio >15 mmol/gm suggests renal potassium loss). TTKG was determined, yielding a value of 26, indicating distal potassium loss. Given her normal BP along with normal anion gap metabolic acidosis, a diagnosis of renal tubular acidosis (RTA) had been considered. With preexisting Sjögren's/overlap syndrome and further investigations showing a urine pH of 7 [pH >5.5 suggests distal renal tubular acidosis (dRTA)] and low 24-hour urinary citrate, a dRTA (type I) diagnosis was confirmed (Table 2).

The patient was sent home taking potassium citrate orally along with sodium bicarbonate supplements for dRTA, along with tablet hydroxychloroquine 300 mg OD and tablet pilocarpine 5 mg BD for Sjögren/overlap syndrome. She was monitored with serial electrolyte reports and remained normokalemic during subsequent visits.

Table 1: Values suggestive of primary hyperaldosteronism

	Values suggestive of primary hyperaldosteronism	*Patient*
Urine potassium-to-creatinine ratio (mmol/gm)	>15	112
TTKG	>4	59
Plasma aldosterone level (pmol/L)	>450	1,747
Aldosterone-to-renin ratio (pmol/L:ng/mL/hour)	>750	5,293
Postsaline suppression test (pmol/L)	>140	756

Case 3

One of our patients, 35-year-old male, arrived with acute paralysis in both his upper and lower limbs, leaving him unable to stand or walk unassisted for a day. He had no history of other medical conditions. History of any precipitating factors, including medication history, was ruled out.

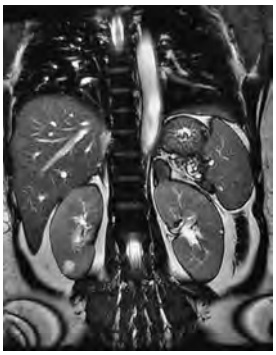

Fig. 1: Relatively well-defined T1/T2 isointense lesion in left suprarenal region s/o left adrenal adenoma (white arrow)

On admission, his BP was 112/60 mm Hg. On inspection, he exhibited exophthalmos. Neurological evaluation revealed weakness with 1/5 power in his lower limbs and 2/5 power in his upper limbs. Additionally, he had absent tendon reflexes and no sensory or autonomic deficits.

Results of laboratory testing revealed hypokalemia at 2.2 mmol/L (normal range: 3.5–5.3 mmol/L), although liver function, kidney, and blood count tests were all within normal ranges. Serum magnesium was found to be low, and intravenous magnesium correction was given.

He was administered intravenous fluids and potassium replacement therapy, alongside oral potassium supplements. His weakness resolved with intravenous potassium supplementation *via* central line. A thyroid function test revealed thyrotoxicosis, with a serum thyroid-stimulating hormone (TSH) level <0.01 uIU/mL and elevated free thyroxine (FT4) (3.34 ng/dL) levels. Additionally, tests for TSH receptor antibodies (TRAb) (30.73 IU/mL), antithyroid peroxidase (anti-TPO) (479 IU/mL), and anti-thyroglobulin antibodies (5.8 IU/mL) were positive. A technetium-99m thyroid uptake scan was done, indicating findings that confirmed Graves' disease (Fig. 2).

Treatment was started with tablet carbimazole 10 mg TDS and tablet propranolol 40 mg BID. Follow-up appointments were scheduled for outpatient visits to monitor serum electrolytes and thyroid function. The patient was euthyroid on subsequent follow-up with no similar complaints.

Case 4

A 20-year-old male farmer was brought to our facility with sudden onset of generalized weakness affecting his upper as well as lower limbs, leaving him unable to stand or walk unassisted for the past 24 hours. He reported engaging in strenuous physical activity before the onset of weakness. Notably, the patient had experienced two similar episodes in the past, both of which were also preceded by physical exertion. He denied any history of

Table 2: Values suggestive of dRTA

	Values suggestive of dRTA	*Patient*
Urine potassium-to-creatinine ratio (mmol/gm)	>15	119
TTKG	>4	26
Blood pH	<7.35	7.3
Urine pH	>5.5	7

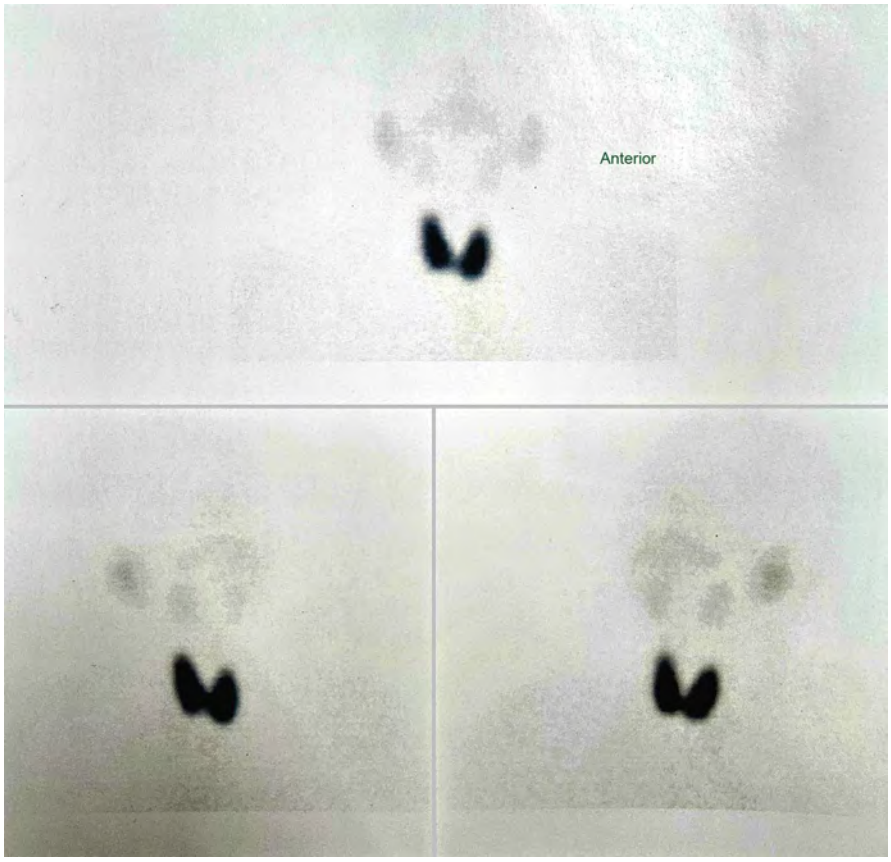

Fig. 2: Technetium-99m thyroid uptake scan showing both thyroid lobes appearing enlarged in size and homogeneously increased radiotracer uptake. The salivary glands are faintly visualized. No retrosternal extension of the thyroid gland was noticed

chronic medical conditions, medication use, or substance abuse.

When the patient was admitted, their BP was 112/60 mm Hg. Neurological examination revealed significant motor weakness with muscle power 2/5 in all limbs. Tendon reflexes were absent, though sensory as well as autonomic functions remained intact.

Initial laboratory investigations revealed hypokalemia, with a serum potassium level of 2.3 mmol/L. Blood pH was 7.372. Other laboratory values, including liver enzymes, serum magnesium levels, complete blood count, and renal function, were within normal limits. Tests for thyroid function were likewise normal. The urine potassium-to-creatinine ratio (5.89 mmol/gm) was found to be normal, ruling out renal potassium wasting. There was no history of gastrointestinal losses (e.g., diarrhea or vomiting) to suggest potassium loss *via* that route. Given the history of repeated episodes of weakness following physical exertion, hypokalemic periodic paralysis (HPP) was diagnosed.

In addition to oral potassium supplements, the patient received treatment with intravenous fluids as well as potassium replacement. His muscle strength significantly improved following potassium supplementation. Although genetic testing to confirm the diagnosis was not performed due to financial constraints, clinical presentation and laboratory findings were strongly suggestive of HPP.

Discussion

One of the primary triggers of acute flaccid muscle paralysis observed in emergency rooms is hypokalemic paralysis, which shows response to potassium correction.[5] Patients are classified into primary HPP or secondary hypokalemic paralysis. Primary HPP stems from channelopathies affecting calcium channels (type I) or sodium channels (type II).[6] Potassium depletion brought on by conditions including RTA or diuretics usually results in secondary hypokalemic paralysis. Regardless of subtype, patients usually arrive with abrupt muscle weakness without any bowel or bladder issues or sensory abnormalities, perhaps involving the respiratory system.[7] The two categories vary, nonetheless, in terms of length, causes, intensity of weakness, biochemical markers, arterial blood gas analysis, as well as long-term care. The cause of hypokalemia can usually be determined from the patient's history, focusing on gastrointestinal losses (vomiting, diarrhea), underlying cardiac conditions, and a detailed review of medications such as insulin, beta-agonists, or diuretics.[8] Our discussion in this article is limited to secondary hypokalemic paralysis.

The presented case series highlights the diverse etiologies of hypokalemic paralysis, underscoring the significance of precise diagnosis as well as tailored therapy. Each case demonstrates unique mechanisms leading to hypokalemia and subsequent paralysis, emphasizing the necessity of thorough clinical evaluation and targeted therapy.

Case 1: Conn's Syndrome (Primary Hyperaldosteronism)

Primary hyperaldosteronism, characterized by excessive aldosterone production, is a rare but significant cause of hypokalemic paralysis. The adrenal cortex produces too much aldosterone on its own, which results in arterial hypertension, hypernatremia, and, as in our case, potentially dangerous hypokalemia.[9]

This instance emphasizes how crucial it is to take endocrine etiologies into account when treating patients who have hypertension as well as hypokalemia that cannot be explained. The patient's hypokalemia was severe, necessitating urgent correction to prevent cardiac and neuromuscular complications. Diagnostic confirmation through hormonal assays and imaging enabled definitive treatment with adrenalectomy, resulting in sustained normokalemia and symptom resolution. This case highlights the need for high clinical suspicion and comprehensive hormonal evaluation in similar presentations.

Case 2: Distal Renal Tubular Acidosis

This patient had dRTA, a medical condition linked to Sjögren's disease, which resulted in hypokalemic paralysis. The patient's presentation with normotensive hypokalemia and normal anion gap metabolic acidosis directed diagnostic focus toward renal causes. Urine pH and low urinary citrate levels were pivotal in diagnosing dRTA. In dRTA, new bicarbonate as well as hydrogen ions cannot be produced if the distal tubule's alpha-intercalated cells are damaged. This results in an increased urine pH because the kidneys cannot excrete acid or produce acidic urine, even during metabolic acidosis. Additionally, this condition is linked to hypokalemia because of H/K ATPase malfunction.[10] Effective management with potassium and bicarbonate supplementation in our case resulted in symptomatic improvement and maintained electrolyte balance. This case emphasizes the critical role of acid-base

assessment and targeted treatment in patients with autoimmune disorders presenting with hypokalemic paralysis.

Case 3: Hyperthyroidism (Graves' Disease)

Thyrotoxic periodic paralysis (TPP), although uncommon, is an important differential in patients presenting with acute flaccid paralysis and hypokalemia. An increased potassium inflow into skeletal muscle cells causes TPP, which leads to severe hypokalemia as well as paralysis. Epinephrine as well as insulin also stimulate Na–K-ATPase pumps, which, when hyperthyroid, are overexpressed, contributing to this condition.[11] The patient's diagnosis of Graves' disease, confirmed through thyroid function tests and antibody assays, guided initiation of antithyroid medications and beta-blockers, resulting in symptom resolution. This case underscores the importance of thyroid evaluation in hypokalemic paralysis, particularly in the presence of clinical signs such as exophthalmos. Prompt recognition and treatment of the underlying hyperthyroidism are crucial for preventing recurrent episodes.

These cases collectively illustrate that hypokalemic paralysis can result from a variety of underlying pathologies, including endocrine disorders, renal dysfunction, and metabolic imbalances. A systematic approach to diagnosis, incorporating detailed patient history, clinical examination, and targeted laboratory tests, is essential for identifying the etiology and directing appropriate treatment.

Case 4: Hypokalemic Periodic Paralysis (Primary Hypokalemic Paralysis)

Hypokalemic periodic paralysis is a rare, although significant, differential diagnosis in young individuals exhibiting acute flaccid paralysis and hypokalemia, especially when gastrointestinal or renal potassium losses are absent. HPP is a genetic disorder classified under the primary causes of hypokalemic paralysis, commonly resulting from mutations in calcium (type I) or sodium (type II) ion channels.[12] In this case, the patient presented with recurrent episodes of muscle weakness triggered by strenuous physical activity, a hallmark of HPP. The patient's biochemical profile showed isolated hypokalemia without metabolic acidosis or any evidence of renal or gastrointestinal potassium loss, confirming the diagnosis of HPP.

Despite the unavailability of genetic testing, the diagnosis was supported by clinical history and laboratory findings. Treatment involved potassium supplementation, leading to muscle strength recovery. The case underscores the necessity for early recognition of primary HPP, particularly in patients with a history of recurrent, exertion-induced weakness, and highlights the critical role of potassium replacement in managing this condition.

The case study underscores the necessity of evaluating hereditary channelopathies in the differential diagnosis of hypokalemic paralysis and demonstrates the remarkable efficacy of potassium replacement therapy in HPP patients.

The following flow diagram depicts the diagnostic approach to a case of hypokalemia (Fig. 3).

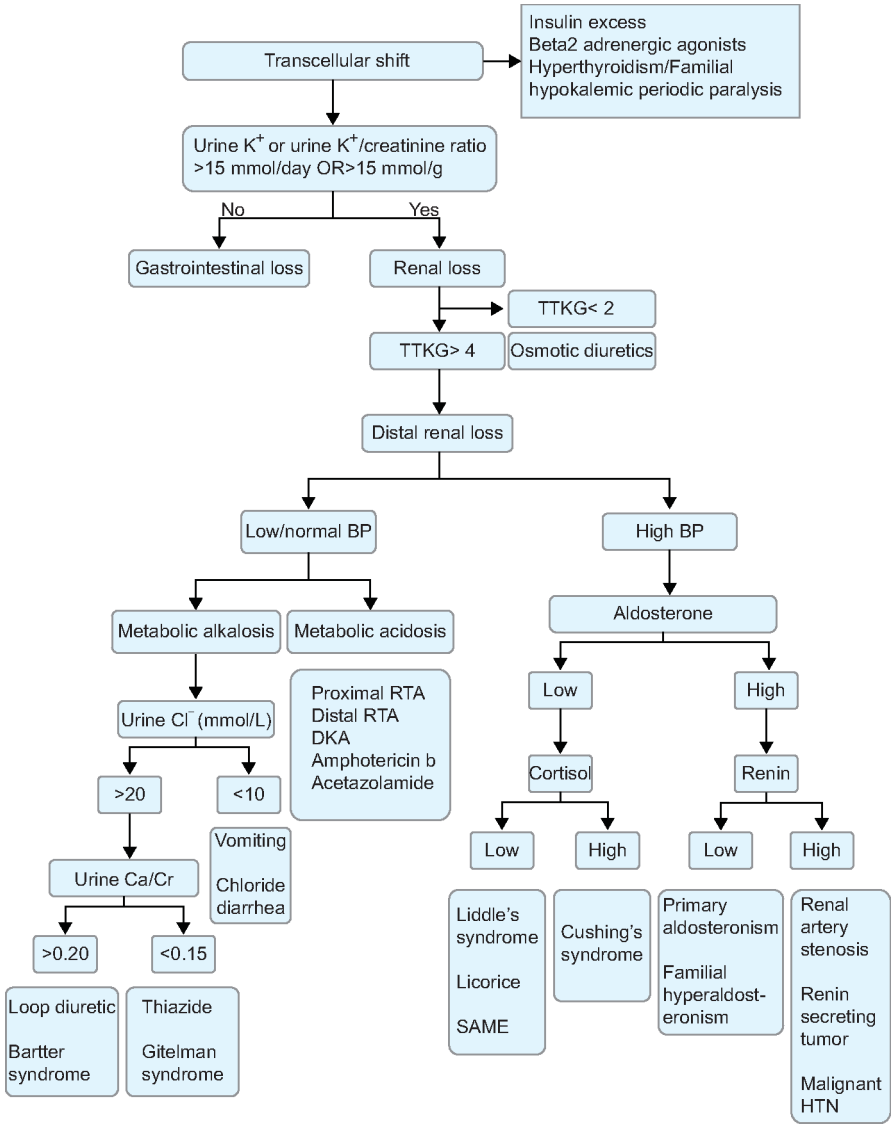

Fig. 3: Flowchart depicting approach to a case of hypokalemia

Conclusion

This case series highlights the multifaceted nature of hypokalemic paralysis, with each case having unique diagnostic challenges and management strategies. Clinicians must maintain a high index of suspicion as well as employ comprehensive diagnostic methods to identify the exact fundamental etiology of hypokalemia. Timely and appropriate action can significantly improve patient outcomes and prevent recurrent episodes of paralysis.

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