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Case Report

Rarity in Rare: Complicated Disseminated Tuberculosis: A Report of Two Cases

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Abstract

Disseminated Tuberculosis (TB) is a severe form of TB that affects multiple organ systems and can lead to complex clinical presentations. Deep Venous Thrombosis (DVT) and Autoimmune Hemolytic Anemia (AIHA) are very rare complications posing diagnostic and therapeutic challenges, requiring a multidisciplinary approach to management. Moreover, In-hospital mortality is higher in patients with such complications compared to those with TB alone. Early recognition and prompt initiation of appropriate therapy are crucial in improving patient outcomes. We report two cases of complicated disseminated TB posing diagnostic and therapeutic challenges. The first case involves a 76-year-old male with a history of chronic smoking, who presented with bilateral leg swelling, fatigue and tooth ache. Diagnostic workup revealed disseminated TB with DVT and AIHA. Despite initial steroid therapy, Blood Transfusion (BT) and Anti-Tuberculosis Treatment (ATT), the patient's hemoglobin levels continued to fall, necessitating Intravenous Immunoglobulin (IVIG) therapy. The second case involves a 50-year-old female presenting with painful swelling of the left lower limb with past history of significant weight loss and cough. Comprehensive imaging and microbiological studies suggested disseminated TB and DVT. Both patients were managed with ATT and anticoagulation. These cases highlight the complex interplay between TB, DVT and AIHA. Management of such patients requires a multidisciplinary approach, careful balance between ATT, choice of anticoagulation and immunosuppressive treatment.

Keywords: DVT; AIHA; ATT; Anti-TB Therapy; Rifampicin; Anticoagulation; IVIG

Introduction

Tuberculosis (TB) continues to be the second most common cause of mortality worldwide caused by a single infectious agent, following COVID-19, with around 10.6 million new cases and 1.3 million deaths globally in 2022. India is a high TB burden country accounting for 27% of the world's TB cases, despite advances in diagnostic and therapeutic interventions [1]. Less than 2% of all TB cases are classified as disseminated TB, a severe form of the disease characterized by widespread dissemination of *Mycobacterium tuberculosis* to multiple organs. This condition often presents with non-specific symptoms, making diagnosis and treatment challenging [2]. Though rare, the association between TB and thromboembolic events, including DVT, is well-documented, significantly increasing morbidity and mortality compared to TB alone [3,4]. TB induced AIHA is a rare entity, characterized by the immune system's destruction of own red blood cells. AIHA exacerbates the clinical presentation and heightens the likelihood of adverse outcomes [5].

Here, we report two patients with disseminated tuberculosis complicated by DVT, with one additionally complicated by AIHA, posing diagnostic and therapeutic challenges, highlighting the necessity for clinical awareness and a comprehensive management strategy.

Case Reports

Case 1

A 76-year-old male, chronic smoker, presented with generalized fatigue, bilateral leg swelling, tooth ache and a burning sensation in the mouth for the past 15 days. He had episodes of cough with whitish mucoid expectoration 15 day prior to admission but without fever.

He appeared cachectic with noticeable pallor and bilateral pitting pedal edema. Multiple firm, non-tender Lymph Nodes (LN) were palpable in the cervical, axillary and inguinal regions. Oral examination revealed crustations in upper labial mucosa, a de-papillated tongue, erythematous lesions on both buccal mucosae. Systemic examination showed mild splenomegaly. Deranged Hemolytic markers (Table 1) and immunohematological workup was suggestive of mixed AIHA.

Diagnostic Workup

Serological tests (Table 2) pertaining to causes of mixed AIHA were evaluated and found to be negative. A left cervical lymph node Fine Needle Aspiration Cytology (FNAC) revealed granulomatous lymphadenitis suggesting either lymphoma or a tubercular pathology. Bone Marrow Examination (BME) did not suggest any infiltration by lymphomatous cells. High-Resolution Computed Tomography (HRCT) of the thorax (Fig. 1), showed a calcified granuloma in the right apical lobe and multiple enlarged lymph nodes in the mediastinal, axillary and cervical regions suggestive of tuberculosis pathology or lymphoma. Contrast-Enhanced Computed Tomography (CECT) of the abdomen (Fig. 2) revealed mild hepatosplenomegaly and multiple lymphadenopathies suggestive of tuberculosis or lymphoma. The Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) of LN aspirate was positive for rifampicin-sensitive TB. A Tuberculin Skin Test (TST) showed an 18 mm induration, indicating TB infection. Doppler Ultrasound (DUS) confirmed DVT in both lower limbs.

Management

As routine management of AIHA, 5 units of group specific PRBC was crossmatched along with auto control to compare and transfuse the least incompatible unit. Despite pulse steroid therapy with IV Methylprednisolone (1 mg/kg daily) for AIHA, hemolysis and low Hb persisted along with high output cardiac failure requiring IVIG therapy and multiple Blood Transfusions (BTs).

The patient was started on the HRZE regimen of Anti-Tuberculosis Treatment (ATT) as per the (national tuberculosis elimination programme) NTEP guidelines of the ministry of health and family welfare, government of India [6]. Anticoagulation therapy with enoxaparin was initiated to manage DVT. Despite all supportive measures the patient developed multi-organ failure, septic shock and succumbed on the 18th day of admission.

Case 2

Clinical Examination and Initial Findings

A 50-year-old female presented with a sudden onset of painful swelling of the left lower limb for two days. She had a history of easy fatigability, significant weight loss and cough with occasional expectoration for two months. On physical examination, the patient exhibited pallor and edema of the left leg with tenderness over the calf. There was no redness or increased temperature over the affected limb.

Initial investigations showed a normocytic anemia with low hemoglobin levels. The serum albumin (1.8 g/dL) was markedly decreased. A Doppler Ultrasound (DUS) of the affected limb showed DVT of the great saphenous, common iliac, common femoral and popliteal veins. The patient was further assessed for other potential underlying factors (Table 3) contributing to DVT of the left leg.

Diagnostic Workup

A chest X-Ray revealed patchy opacities in the bilateral upper zones. HRCT of the thorax (Fig. 3) was suggestive of pulmonary TB. CECT of the abdomen (Fig. 4,5) indicated disseminated TB with DVT. Sputum Acid-Fast Bacilli (AFB) testing was positive (1+).

Management

The patient was started on HRZE regimen for TB and apixaban, a Novel Oral Anticoagulant (NOAC) for DVT management. After improvement in symptoms, the patient was discharged on therapy and follow-up instructions.

Test	Result	Reference Range
Hemoglobin level	5.2 g/dL	13.8-17.2 g/dL
Reticulocyte Count	4.2%	0.5-2.5%
TLC Count	15,200/mm^3	4,500-11,000/mm^3
Platelet Count	170,000/mm^3	150,000-450,000/mm^3
Total Bilirubin	1.91 mg/dL	0.3-1.2 mg/dL
Direct Bilirubin	0.6 mg/dL	0-0.3 mg/dL
Indirect Bilirubin	1.31 mg/dL	0.2-0.8 mg/dL
LDH	432 U/L	140-280 U/L
DAT	Positive	Negative
Anti-IgG	Positive	Negative
Anti-C3d	Positive	Negative
Thermal Specificity of the autoantibody	Positive at 4,22 and 37 degrees Celsius	
Comment peripheral smear	Hemolytic anaemia	
g: gram, mg: milligram, dl: deciliter mm, mm: millimeter, TLC: Total Leukocyte Count LDH: Lactate dehydrogenase, DAT: Direct Antiglobulin Test, IgG: Immunoglobulin G, C3d: Compliment component C3d		

Table 1: Laboratory results of case 1 at the time of admission.

Test	Result
ANA	Negative
HIV	Negative
HBV	Negative
HCV	Negative
Mycoplasma pneumoniae	Negative
EBV	Negative
CMV	Negative

Filarial antigen testing	Negative
AIHA: Auto-immune hemolytic anaemia, ANA: Antinuclear Antibody test, HIV: Human Immunodeficiency Virus, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, EBV: Epstein-Barr virus, CMV: Cytomegalovirus	

Table 2: Serological tests performed in case no 1 and its results.

Test	Result
Beta 2 glycoprotein IgG	11.57 U/mL
Beta 2 glycoprotein IgM	2.58 U/mL
Lupus Anticoagulant Ratio	1.14
Cardiolipin IgG	4.14 U/mL
Cardiolipin IgM	6.8 U/mL
ANA	Negative
U/ml: Unit/milliliter, IgG: Immunoglobulin G, IgM: Immunoglobulin M, ANA: Antinuclear Antibody.	

Table 3: Tests performed in case 2 in view of hypercoagulable state and its results.

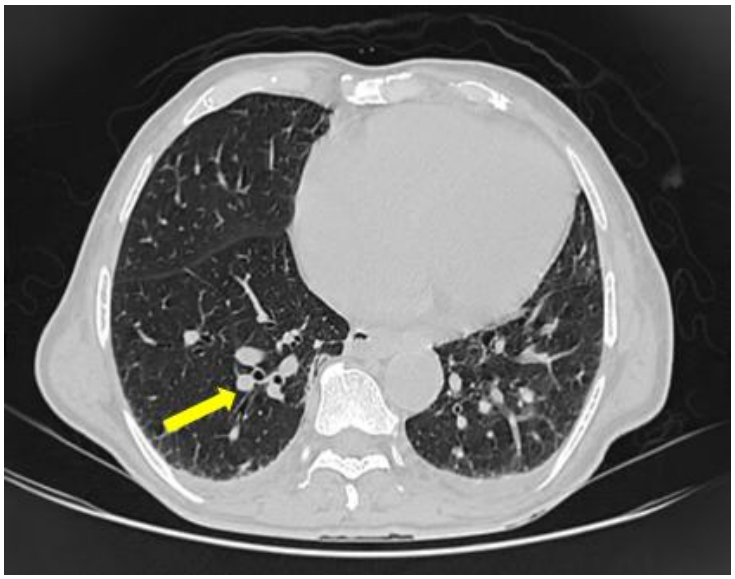

Figure 1: HRCT thorax of Case 1 showing multiple enlarged lymph nodes in the mediastinal, axillary and cervical regions, with a yellow arrow indicating the mediastinal lymph nodes.

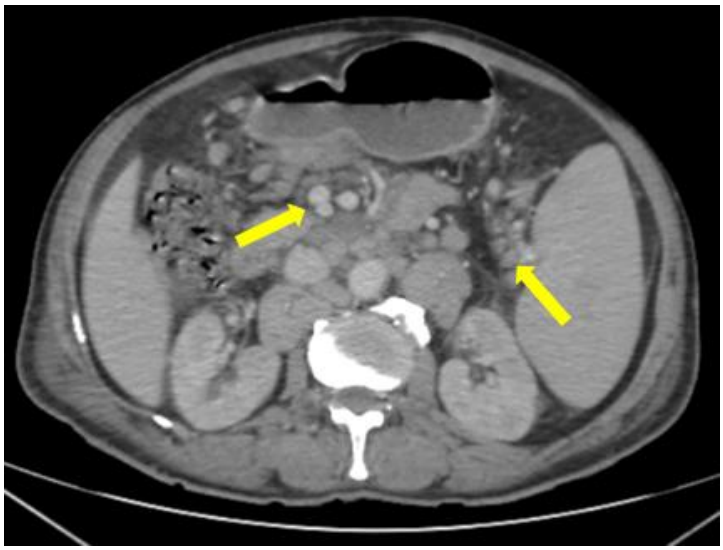

Figure 2: CECT abdomen of Case 1 illustrating multiple lymphadenopathies, with multiple yellow arrows indicating enlarged abdominal lymph nodes.

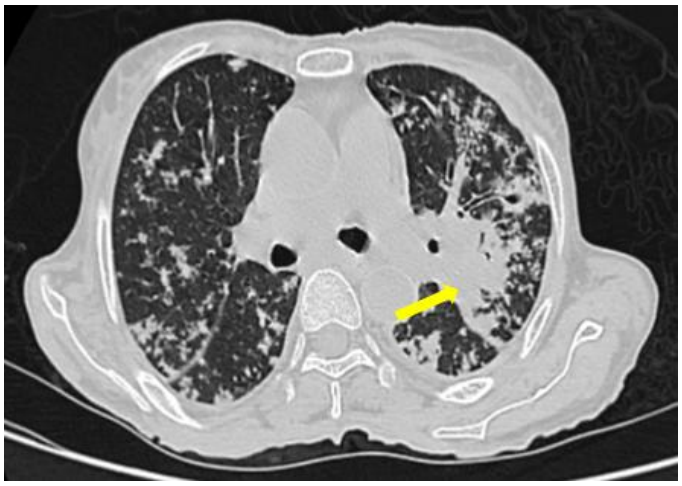

Figure 3: CT thorax of Case 2 showing diffuse consolidation in both upper lobes, cavitation in the basal region of the right lower lobe and a tree-in-bud pattern in the bilateral lung parenchyma. A yellow arrow indicates consolidation in the left lung.

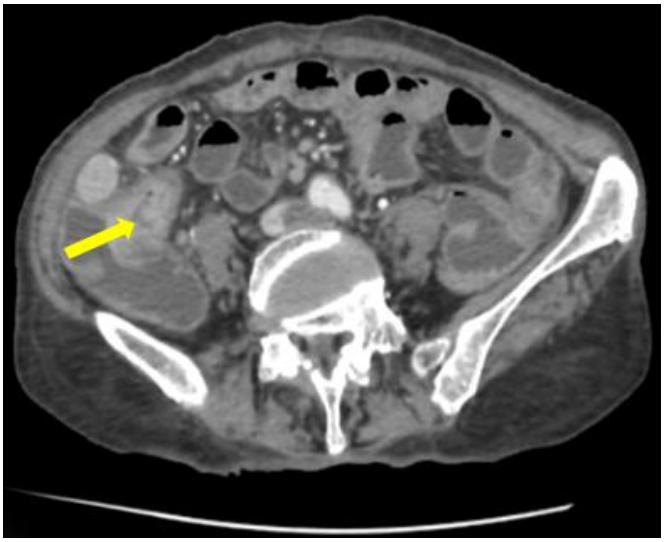

Figure 4: CECT abdomen of Case 2 showing thickening of the terminal ileum and ileocecal junction, indicated by a yellow arrow.

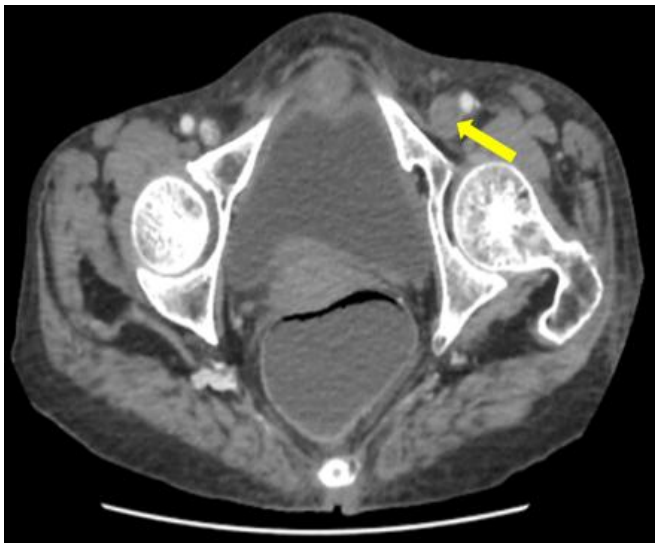

Figure 5: CECT abdomen of Case 2 showing left-sided DVT. A yellow arrow points to a non-enhancing thrombus in the left iliac and femoral veins, causing complete luminal occlusion.

Discussion

The characteristics of lymphadenopathy in lymphoma and TB are similar, leading to misdiagnosis. Both can coexist together, confounding each other, adding to the complexities [7]. Presence of splenomegaly on abdominal examination, an inconclusive HRCT of the thorax and CECT abdomen indicating lymphoma or TB in case 1, added to the diagnostic dilemma. Moreover, coexistence of AIHA and DVT added to the challenges. A battery of assays to delineate cause of AIHA, negative BME, positive CBNAAT, TST, presence of oral buccal mucosa ulceration [9] and matted lymph nodes in case 1 supported the diagnosis of TB, emphasizing the need of for thorough clinical and diagnostic evaluation in suspected disseminated TB cases [9].

The pathophysiological mechanisms linking TB and thromboembolic events are multifactorial, involving chronic inflammation, endothelial dysfunction, and a hypercoagulable state induced by the infection. Studies have reported TB associated anaemia, reactive thrombocytosis, increased in fibrin degradation products, and decreased antithrombin III may favour occurrence of DVT in TB [4]. Here, both patients had anaemia and elevated D-dimer levels and presented with significant venous thrombosis, diagnosed through DUS. Furthermore, the choice of anticoagulants for DVT management in TB is challenging. Studies have also linked DVT to rifampicin use, with a relative risk of 4.74. Rifampicin induces cytochrome P-450 isoenzymes CYP2C9, CYP3A4 and P-glycoprotein which may reduce the efficacy of anticoagulation therapy like warfarin analogues and NOACs. But, NOACs are preferred because of their comparable efficacy to warfarin and their association with a lower risk of ischemic stroke [3]. Here, coexistence of DVT and AIHA as in case 1 required cautious anticoagulation and bleeding risk management and was managed with LMWH and 2nd case with NOACs.

Altered immune response may account for TB induced AIHA, which is mostly warm type (48%) followed by cold type (40%) and mixed type (12%). Disseminated TB induced AIHA predominantly requires steroid support as compared to other type of TBs for control of haemolytic anaemia [5]. Providing steroid support in such cases is challenging as it has to be initiated taking into account the risk of therapy induced worsening of TB. The initiation of steroid therapy to manage AIHA in case 1 might have worsened the situation predisposing to of infectious complications. Moreover, the prevalence of both atypical and opportunistic infections in AIHA is substantial, serving as a risk factor for morbidity and mortality [10]. Here we encountered mixed type (both IgG and IgM mediated antibodies) in disseminated TB unresponsive to steroid therapy, requiring IVIG therapy and died of infectious complications.

These cases illustrate the need for comprehensive diagnostic evaluations and a multidisciplinary approach to management. Further research is warranted to better understand the pathophysiological mechanisms underlying these complications and to optimize treatment strategies for these complex presentations.

Conflict of Interest

The authors have declared no conflict of interest.

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