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Case Report

DEEP VEIN THROMBOSIS-AN ATYPICAL PRESENTATION OF PULMONARY TUBERCULOSIS-A CASE REPORT

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ABSTRACT

Tuberculosis is remarkably the most preventable yet harrowing disorder known to mankind. It remains a worldwide public health problem although the causative organism was discovered more than 100 years ago and highly effective drugs and vaccines are available making Tuberculosis both preventable and curable. The association of an inordinate amount of complications have been proven with Tuberculosis but not much has been confirmed regarding its thrombogenic potential. Even though some recent studies demonstrate prothrombotic activation of pulmonary arterial endothelial cells in TB patients which may further account for thromboembolic events such as deep vein thrombosis but such an occurrence is both rare and undocumented. This report is about a case of a 34-year-old male with, a known case of Pulmonary Tuberculosis(for 3 weeks)currently on 1st-line ATT(for the past 1 week) along with raised blood sugar and BUN levels with Moderate Anemia (Hb-9.2). The patient presented to the Medicine OPD with swelling and tenderness in his right foot and was diagnosed with DVT of the Right superficial femoral vein and popliteal vein upon investigation. Antithrombotics Tab Warfarin and Inj Enoxaparin have been added to his current treatment plan and kept under investigation.

***KEYWORDS*:** Tuberculosis, Deep Vein Thrombosis

INTRODUCTION:

The WHO TB statistics (India) for the year 2021 gave an estimated incidence figure of 2,590,000 million cases which is a rate of 188 per 100,000 population. It is estimated that 40% of the Indian population is infected with Mycobacterium, out of which, the vast majority of whom have latent TB rather than active TB disease [1]. In addition to its obvious medical repercussions, TB also causes an enormous socio-economic burden In India. Deep vein thrombosis (DVT) is a preventable and curable cause of death worldwide. "This is predominantly a disease of the elderly with an incidence that rises markedly with age. There are other several factors that are associated with increased risk of DVT such as major surgeries, prolonged bed rest, oral contraceptive pills, smoking, malignancy, presence of central venous lines, and inherited hypercoagulable states." Studies have shown a probable association between rifampicin and DVT, However, does not contraindicate the use of this drug, but measures to prevent DVT should be taken in inpatients receiving rifampicin[2] Deep venous thrombosis has been associated with 1.5%–3.4% cases of TB[3]. However, is imperative to identify and categorise TB patients who are at high risk of developing venous thromboembolism. Various concepts have been theorised to explain the aetiology of DVT in a TB patient (on ATT). Deep vein thrombosis can occur due to venous flow obstruction caused by retroperitoneal lymphomas and malignant masses[4]. Tubercular lymph node enlargement occurs frequently in the superior mediastinum and

retroperitoneal regions but has not been reported as causing vena cava obstruction leading to deep vein thrombosis. Recent studies demonstrate prothrombotic activation of pulmonary arterial endothelial cells in TB patients which may further account for thromboembolic events and deep vein thrombosis[5] Studies have described the presence of both type 1 plasminogen activator inhibitor and tissue factor antigen associated with pulmonary arterial endothelial cells of patients exhibiting a mycobacterial infection. Our case presented with a myriad of conditions but none of them except Tuberculosis had an apparent correlation with DVT[6] Similar cases have been reported in the past and certain associations have been hypothesised, However, there is no confirmed documentation of a proven aetiology regarding the same[7]

CASE REPORT:

A 34-year-old non-smoker, an alcoholic male labourer was admitted to the Medicine department on July 17, 2022, with the chief complaint of swelling, pitting type(Grade IV)and tenderness in his right lower limb for 6 days. The patient was a known case of Pulmonary Tuberculosis and was under ATT for the past 15 days. The diagnosis was confirmed via AFB staining and HRCT Thorax and Chest X-Ray. The sputum was smear positive for AFB staining(Grade 3+) and CXR findings were as follows Homogenous opacities with fee fibrocystic changes were seen in Right Hemithorax and Left lower zones. Left-Sided Pleural Effusion Similar radiographic density observed in the rest of the lung with normal B/L cardiophrenic and costophrenic angles along with normal bronchovascular markings

Figure 1:Chest X Ray.

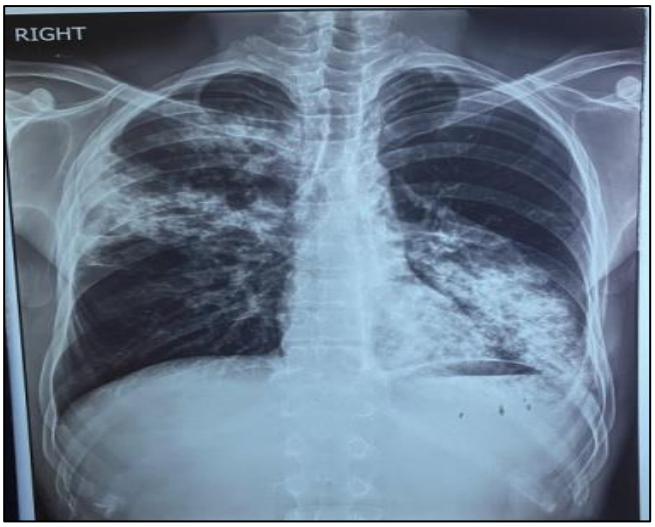
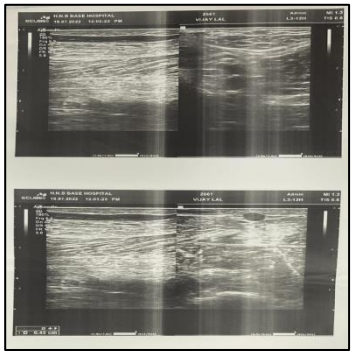
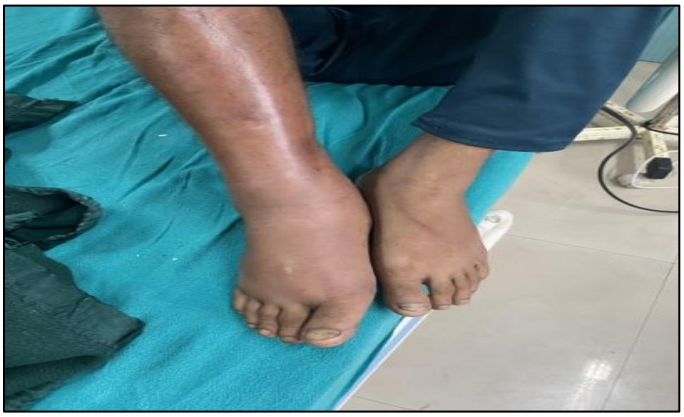


Figure 2:USG Doppler



There was no significant history of diabetes, stroke, cancer or any other genetic disorder in the family. On physical examination, he had tachypnea and tachycardia with mild pallor. He had diffuse rhonchi and coarse crepitations in his chest and used his accessory muscles for respiration and was in a state of respiratory distress. An inspiratory wheeze was audible. Other Cardiovascular, and abdominal examinations were within normal limits. There was no prior history of surgery,trauma,malignancy,prolonged bed rest, chronic smoke exposure,valvular heart disease or stroke. Homan sign (calf pain with flexion of the knee and dorsiflexion of the ankle) and Moses sign or Bancroft's sign (pain with calf compression against the tibia)were elicited in the patient[8].However,it is imprecise for making a diagnosis solely based upon them.Along with other investigations,they were indicative of Deep Vein Thrombosis. USG Venous Doppler study of his right lower limb revealed dilatation of the right superficial vein, Anterior and posterior tibial vein,popliteal vein and femoral vein which was filled with echogenic substances indicative of a thrombotic event[9]Great and short saphenous vein also showed echogenic contents in their lumen suggestive of deep vein thrombosis[10].

Figure 3:Deep Vein Thrombosis of right lower limb(at presentation



The patient was febrile(101 F)and showed elevated TLC and eosinophilia. Provisional diagnosis of DVT was kept and further routine investigations were sent whose results were as follows-

INVESTIGATION	VALUES ON ADMISSION
Hb	9.2 g/dL
WBC	23.28 *10^3/uL
HCT	27.5%
MCV	79.9 fL
MCH	26.8 pg
MCHC	33.5 g/dL
BUN	42 mg/dL
S.Creatinine	0.7 mg/dL
S.Bilirubin(T)	0.5 mg/dL
S.Bilirubin(D)	0.1 mg/dL
SGOT	27 u/L
SGPT	23 u/L
Alkaline Phosphatase	147 u/L
S.Protein(Total)	5.7 mg/dL
S.Albumin	2.4 g/dL
S.Sodium(Ionized)	133 mMol/L
S.Potassium(Ionized)	4.7 mMol/L
S.Calcium	1.07 mMol/L
S.Albumin	2.4 g/dL
AEC	824/cu mm
Malaria Antigen	Negative
Typhidot	Negative
Dengue(Card Test)	Negative
Scrub Typhus	Negative

TREATMENT COURSE

Based on the overall clinical picture and radiological findings, the case was suggestive of pulmonary tuberculosis. Chest XRay showed Homogenous opacities with few fibrocystic changes seen in Right Hemithorax and Left lower zones and Left-Sided Pleural Effusion.

He was registered under DOTS through a healthcare worker as a "newly diagnosed sputum positive

pulmonary tuberculosis" patient and started on standard ATT[four drug anti-tubercular treatment {rifampicin (600mg/d), isoniazid (300mg/d), pyrazinamide (1000mg/d)]
ethambutol (800mg/d)}.
He was also treated with low- molecular-weight heparin [11](injection enoxaparin 40 mg bid subcutaneous) for 3 days and was started on Tab. warfarin 5mg once a day with a target International Normalized Ratio (INR) of 1.5-2.5 [12]He was initially maintained on a nasal prong with oxygen and was slowly weaned off the same. There was significant resolution of oedema of the limb upon treatment. The patient reported relief from painful swelling and was advised to continue with ATT upon discharge.

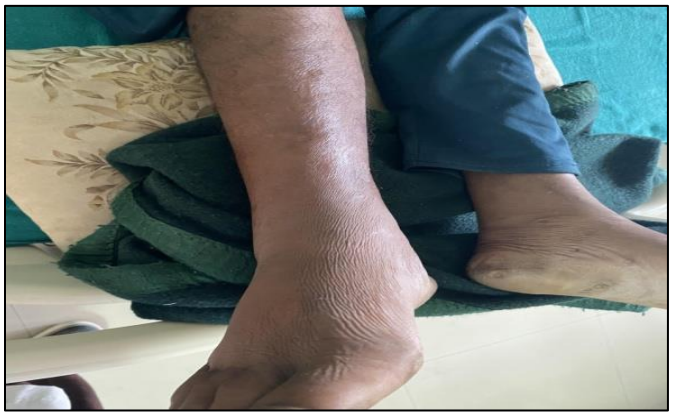


Figure4:Improvement of DVT upon Treatment

DISCUSSION

M.tuberculosis is an acid-fast, Niacin positive and Nitrate reductase positive bacilli responsible for causing tuberculosis[13] It remains a worldwide public health problem although the causative organism was discovered more than 100 years ago and highly effective drugs and vaccines are available making Tuberculosis both preventable and curable. There is higher mortality in late-diagnosed cases due to a subsequent increase in the incidence of complications and advanced stage of the disease. An inordinate number of complications[14], both local (bronchiectasis, pleural effusion, constrictive pericarditis) and systemic (Miliary tuberculosis resulting in Addisonian crisis, disseminated intravascular coagulation) is rampant which makes the control of this disease a monstrous challenge in the face of modern medicine.
In addition to its systemic involvement, haematological complications[15] of tuberculosis, are known but rarely seen. These include bronchial arteritis, Rasmussen aneurysm, thromboembolic events such as deep vein thrombosis etc. There have been reports of protein S deficiency along with concurrent antiphospholipid antibody syndrome in patients of tuberculosis which thereafter can be complicated by a venous thromboembolic episode. Deep venous thrombosis has been associated with 1.5%–3.4% cases of TB, the incidence of which is higher than that in the general population of approximately 0.1%. Deep Vein thrombosis is caused by a disturbance in endothelial function, venous stasis or a hypercoagulable state seen commonly in post-surgical cases on prolonged bed rest[16]. Medical conditions such as thrombophilias, activated protein C resistance, factor V Leiden mutation and prothrombin gene mutations have been commonly implicated in deep vein thrombosis. Our case did not report any recurrent venous thromboembolic event, no history of valvular heart disease or trauma involvement, surgical procedure or prolonged bed rest. There was no significant history of any such bleeding disorder in his family. Unprovoked thrombosis in this particular case, even in absence of hereditary factors, demonstrates that severe pulmonary tuberculosis may be complicated by venous thromboembolism. This event can occur at the time of presentation or later in the course of the disease whilst on ATT. The provisional hypothesis for this occurrence can be-
1-) Direct endothelial injury caused by Koch's bacillus and Induction of an acute phase response brought about by the activation of mononuclear cells, the interaction of which can activate a vascular response releasing pro-inflammatory cytokines and interleukins, rendering the blood hypercoagulable and endothelial surface thrombogenic(They will also lead to a stimulation of hepatic synthesis of coagulation proteins)[17].
2-)Tuberculosis causes anaemia[19] (Our patient had a Hb count of 9.2 g/dL-Moderate Anemia)reactive thrombocytosis(23.38*10^3 u/L)increase in plasma fibrinogen and factor VIII and decrease levels of antithrombin III, and protein C levels, which further increases the incidence of occurrence of a thromboembolic event.[19]
3-)IVC thrombosis may be caused by tubercular lymph nodes. It can be either by a large collective matted mass or due to minor obstruction in the presence of an underlying predisposed hereditary thrombophilic state. Similar description has been given in Cockett's

syndrome [20](left iliac vein thrombosis due to compression by a right common iliac artery), pregnancy, malignant disease, or pelvic surgery.

4-)Rifampicin(ATT drug)acts as a non-specific inducer (hepatic cytochrome P450) thereby affecting the metabolism of multiple drugs.[21] The metabolism of warfarin increases in the presence of rifampicin, and the dose of warfarin sometimes has to be adjusted for a better response. Caution is also needed when using NOAC agents in patients receiving anti-tuberculosis medication, because rifampicin is a CYP3A4 and P-glycoprotein/ ABCB1 inducer[22], and could lead to the decreased s. concentration of anticoagulants such as dabigatran, apixaban and rivaroxaban. Predominantly, thrombosis of lower limbs is more common in patients with pulmonary TB. However, other unusual sites have been reported in the literature in patients with pulmonary TB, namely cerebral venous sinuses or hepatic veins. In this case, the diagnosis of pulmonary tuberculosis was considered because of fever, worsening general status, excessive weight loss(28 kg in 2 months)cough with expectoration sputum positivity for AFB(Grade 3+) and HRCT thorax suggestive of PTB. Anticoagulation and antitubercular therapy were started as soon as possible upon confirmation of the diagnosis to improve the outcome of the lung as well as vascular pathology

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A possibility of DVT is , hence, anticipated in all PTB cases presenting with limb swelling and pain. Peripheral limb oedema may be falsely attributed to hypoproteinemia in patients with TB. However, other signs such as pain and increased temperature(Homan and Moses sign positive) [23]of the affected limb help in the diagnosis of DVT. The emphasis should be laid on a high index of suspicion, early diagnosis, and management of DVT in such patients. In conclusion, DVT may be one of the (atypical)presentations of pulmonary tuberculosis.

CONCLUSION-

This clinical case report emphasizes that patients with severe pulmonary tuberculosis are at risk of developing thromboembolic events, predominantly deep vein thrombosis as one of its many atypical manifestations.

Hence, Anticoagulation prophylaxis must be considered in such cases.[24] Thrombotic event is diagnosed systematically in the TB patients because of the risk of occurrence of this complication, particularly in its extensive and severe forms.

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