Case Report

Pulmonary tuberculosis - An emerging risk factor for venous thromboembolism: A case series and review of literature

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ABSTRACT

One-third of patients with symptomatic venous thromboembolism (VTE) manifest pulmonary embolism, whereas two-thirds manifest deep vein thrombosis (DVT). Overall, 25%–50% of patients with first-time VTE have an idiopathic condition, without a readily identifiable risk factor, and its association with tuberculosis (TB) is a rare occurrence. Deep venous thrombosis has been associated with 1.5%–3.4% cases of TB. Early initiation of anti-TB treatment along with anticoagulant therapy decreases the overall morbidity and mortality associated with the disease. We report three cases of DVT associated with pulmonary TB who were diagnosed due to high index of suspicion as the risk factors for the development of DVT were present in these cases.

KEY WORDS: Antitubercular therapy, tuberculosis, venous thrombosis

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INTRODUCTION

India is the second most populated country in the world and it contributes to 23% of the incident cases of tuberculosis (TB) annually out of total 9.6 million incident cases of TB worldwide.[1] Being a chronic disease, TB has a long-lasting effect on the human body with complications which are less common and may be life-threatening.

Although a rare event, deep vein thrombosis (DVT) has been associated with TB in 1.5%–3.4% of cases.[2] It is pivotal to identify TB patients who are at high risk of developing venous thromboembolism (VTE).

CASE REPORTS

We report three cases of pulmonary TB associated with DVT.

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Case 1

A 25-year-old male was admitted with a painful swelling of the left lower limb for 15 days duration. He also complained of fever and productive cough for the past 2 months. Previously, he had received antitubercular therapy (ATT) 3 years back and responded. General physical examination revealed a poorly built, malnourished man with poor general condition. His left leg was swollen and tender to touch. Cardiovascular and abdominal examination was normal.

Chest X-ray demonstrated bilateral infiltrations and multiple cavitary lesions in both lungs [Figure 1]. Sputum examination showed acid-fast *bacilli*-positive smear. In view of swelling and tenderness in calf, possibility of DVT was considered. Ultrasound (USG) Doppler of the

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left lower limb revealed deep venous thrombosis in the left saphenofemoral vein [Figure 2].

Standard ATT with retreatment regimen as per the national guidelines was initiated. The patient was treated with enoxaparin subcutaneously and warfarin. On treatment, his general state improved and he responded well to anticoagulation therapy. Swelling in the limb subsided with decrease in tenderness. No adverse effects were seen. He was discharged 14 days after admission to continue follow-up. Follow-up Doppler at 3 months showed resolution of the thrombus with only minimal sluggish flow.

Case 2

A 16-year-old female diagnosed a case of sputum-positive multidrug-resistant pulmonary TB presented to our hospital with complaints of swelling of the right leg for 1 month. The swelling had been initially progressive and associated with calf pain. The patient was not ambulatory due to severe dyspnea and weakness. Examination of the abdomen and cardiovascular system was unremarkable.

The local examination of the right limb showed a swollen and tender calf. The movements in the affected limb induced calf pain. Chest X-ray showed bilateral disease with fibrosis of the left lower zone [Figure 3].

USG Doppler of the peripheral veins of lower limbs revealed thrombosis of popliteal vein of the right lower limb [Figure 4]. USG of the abdomen was unremarkable. She was already on the second-line antitubercular drugs for the past 1 month. She was put on enoxaparin subcutaneously and warfarin. Since therapeutic international normalized ratio (INR) level was difficult to maintain with high doses (15 mg) of warfarin, acenocoumarol was initiated to maintain INR of 2.5 after stopping warfarin. The swelling in the limb subsided and patient was pain-free by the 10th day of admission. Subsequently, she was discharged after 30 days of hospital stay. Follow-up Doppler after 3 months showed partial resolution of the thrombus.

Case 3

An 80-year-old male, nonsmoker, was admitted as a diagnosed case of sputum-positive pulmonary TB already on ATT for a week. Examination of the chest and abdomen was unremarkable. Peripheral edema of the right lower limb was found. The patient was confined to bed for most of his days at home and hospital in the last few months.

Chest X-ray demonstrated consolidation with associated collapse on the right upper lobe [Figure 5].

USG Doppler of the lower limb revealed sluggish flow with rouleaux formation with echogenic material, suggestive of thrombus in right popliteal vein with thickening of venous valves in both lower limbs [Figure 6].

ATT was continued and he was started on low-molecular-weight heparin (LMWH). He was not shifted to oral anticoagulants because of their poor safety profile as the patient was old and had unpredictable liver functions due to concurrent ATT. Patient responded to treatment and peripheral edema disappeared in 2 weeks'

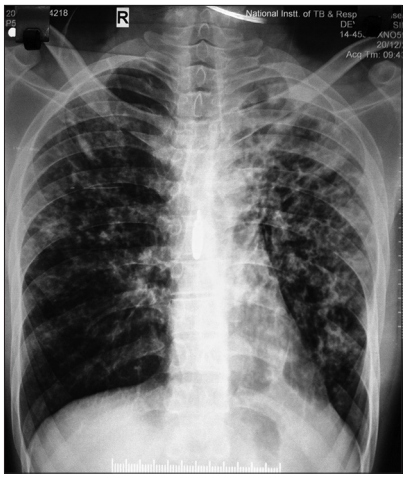

Figure 1: (Case 1) Chest X-ray on admission

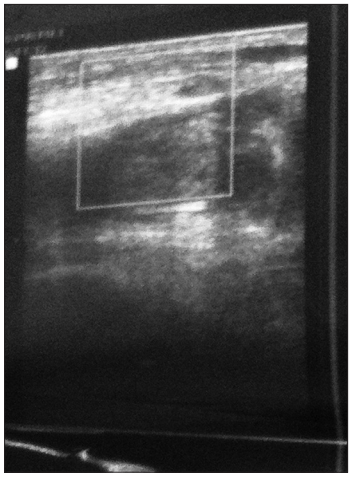

Figure 2: (Case 1) Leg ultrasound showing thrombus in Left saphenofemoral vein

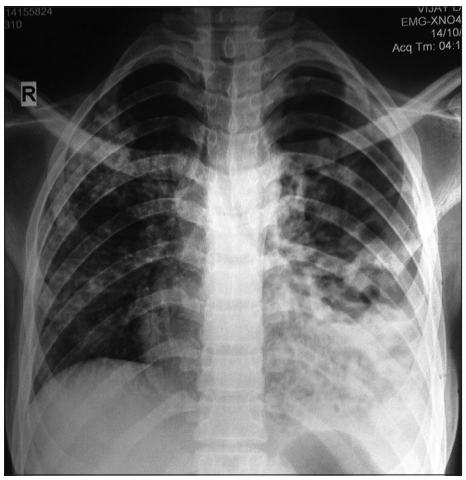

Figure 3: (Case 2) Chest X-ray on admission

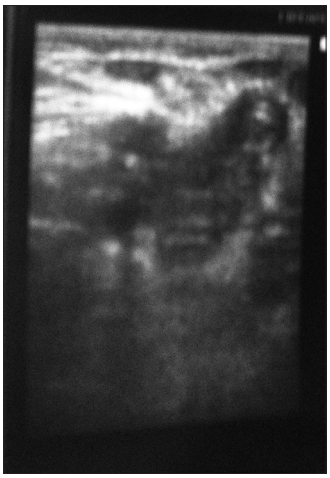

Figure 4: (Case 2) USG Doppler showing thrombus in Rt. Popliteal vein

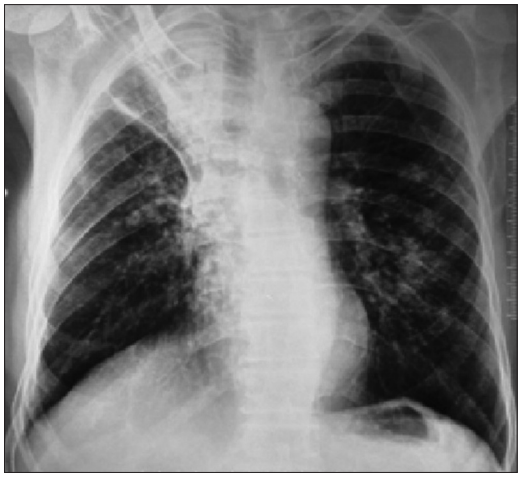

Figure 5: (Case 3) Chest X-ray on admission

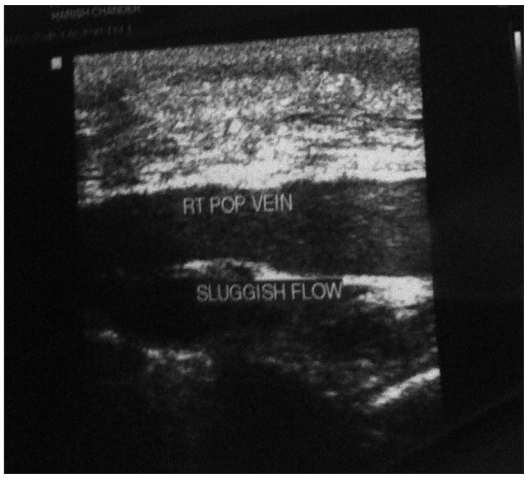

Figure 6: (Case 3) Ultrasound right lower limb showing thrombus with sluggish flow

time. USG Doppler was repeated at 3rd week which demonstrated complete resolution of echogenic material.

DISCUSSION

Approximately one-third of patients with symptomatic VTE manifest pulmonary embolism (PE), whereas two-thirds manifest DVT alone. VTE recurs frequently in the first few months after the initial event, with a recurrence rate of 7% at 6 months. Overall, 25%–50% of patient with first-time VTE have an idiopathic condition, without a readily identifiable risk factor. Death occurs in 6% of DVT cases and 12% of PE cases within 1 month of diagnosis.[3,4] DVT is commonly seen in postoperative patients and in patients who are admitted to the intensive care unit for a prolonged period. Its association with TB is a rare occurrence, and very few cases have been reported in literature.[5] However, increased awareness along with availability of noninvasive tests such as Doppler USGs, the number of cases of TB with associated DVT are on rise.

Our cases showed that VTE may complicate severe pulmonary TB and such events can occur anytime during the disease. A possibility of DVT was kept in all three cases as they were nonambulatory and presented with limb swelling and pain. All of them responded well to the treatment with antitubercular drugs and anticoagulants. Peripheral limb edema may be falsely attributed to hypoproteinemia in patients of TB. However, other signs such as pain and increased temperature of the affected limb are important signs that help in diagnosis of DVT. The emphasis should be laid on high index of suspicion, early diagnosis, and management of DVT in such patients.

Review of case series and case reports of coexistence of TB and DVT are shown in Table 1.

Most of the studies done in the past are retrospective in nature and have not mentioned about the treatment given and duration of treatment. In one study conducted by Kouismi *et al.*,[11] treatment with LMWH and warfarin was given for 3 months in 25 cases, and in three cases, treatment was extended further for 3 months. In nine patients, only enoxaparin was given due to difficulty in attaining target prothrombin time. In our case one and two, we have used enoxaparin followed by warfarin or acenocoumarol, and in case three, we have only used enoxaparin due to difficulty in attaining target INR.

A study done by Bikdeli[8] in 2010 and Marjani *et al.*[10] in 2012 mentioned the use of color Doppler, D-dimer, and computed tomography as the diagnostic modality for diagnosis of VTE. We have used USG Doppler for the diagnosis of DVT in our cases as other means were not available. One retrospective study was done to clarify the association between TB and VTE in a multiethnic population, with a generally good level of public sanitation and low incidence of TB, using data from the United States. The study found that the prevalence

of VTE among patients with active TB was 2.07%. In a multivariate analysis model, adults with active TB had a greater risk of VTE than those without ($P < 0.001$), close to the previously reported risk associated with neoplasia. No particular link was found between pulmonary TB and PE or between extrapulmonary TB and DVT. This may suggest the preponderant role of a systemic hypercoagulable state over an intrathoracic venous compression mechanism.

In-hospital mortality of patients with both active TB and VTE was higher than mortality of patients with only active TB ($P < 0.001$). The conclusion of the study was that TB must be considered as a pertinent risk factor for VTE and should be included in thromboembolism risk evaluation similar to any acute and severe infection.[22]

The mechanism responsible for development of DVT in TB is unclear. All the three parts of Virchow's triad, i.e., hypercoagulability, venous stasis, and endothelial dysfunction, may play a role in pathogenesis of the disease. Increase in plasma fibrinogen and factor VIII and reactive thrombocytosis might be reasons of hypercoagulability in TB patients. Hypoprothrombinemia is seen in DVT and one-third of cases of TB have prothrombin deficiency.[7,23,24] Pro-inflammatory cytokines due to the disease process also make the vascular endothelium more thrombogenic which in turn also increase the synthesis of coagulation proteins by liver.[5,24]

One study has shown that patients with active PTB have anemia, reactive thrombocytosis, elevations in plasma fibrinogen degradation products, tissue plasminogen activator, and inhibitors with depressed antithrombin III levels which may favor the development of DVT in disseminated TB.[25]

Turken *et al*.[26] also made similar observations regarding these hemostatic disturbances in 45 patients of active TB. High frequency of antiphospholipid antibodies detected in patients with TB is also mentioned in the literature. These hematological parameters worsen during the first 2 weeks of therapy in many cases, but they normalize after a month of ATT. The return of these hematological parameters to a normal level is a good indicator of disease control.[23]

Thrombosis can also result from venous compression by lymph nodes, for example, retroperitoneal adenopathies may cause inferior vena cava thrombosis.[27]

Patients of pulmonary TB having extensive disease are not ambulatory for a long duration, which is one of the risk factors of developing VTE. Studies have shown that the risk of developing deep venous thrombosis is proportional to the severity of tubercular disease as there is a close correlation between the hematological abnormalities and the severity of clinical findings of pulmonary TB. The studies have revealed that hematological abnormalities are relatively more common in severe pulmonary TB.[23,28]

Studies also demonstrated a possible association between DVT and the use of rifampicin with a relative risk of 4.74 in patients treated with rifampicin-containing regimens.[2]

Table 1: Review of case series and case reports of deep vein thrombosis associated with tuberculosis over the past few years

Author	Type of study	Year of publication	Cases of DVT	Modality used for diagnosis of DVT	Interval between start of ATT and diagnosis of DVT	Treatment used
White[2]	Case series	1989	46	Not mentioned	Not mentioned	Not mentioned
Ambrosetti *et al*.[6]	Case series	2006	5	Not mentioned	Not mentioned	Not mentioned
El Fekih *et al*.[7]	Case series	2009	14	Not mentioned	Not mentioned	Not mentioned
Bikdeli[8]	Case series	2010	46	Color Doppler and CT pulmonary angiography	Not mentioned	Not mentioned
Shitrit *et al*.[9]	Case series	2012	5	Not mentioned	1 month	Not mentioned
Marjani *et al*.[10]	Case series	2012	23	Leg ultrasonography and CT of chest	14 days	Not mentioned
Kouismi *et al*.[11]	Case series	2013	30	Venous Doppler and D-dimer	17 days	Enoxaparin
Sharma *et al*.[12]	Case report	2007	1	Venous Doppler USG	5 days	Unfractionated heparin + warfarin
Goncalves *et al*.[13]	Case report	2009	2	Venous Doppler and CT angiography	0 day and 13 days	Enoxaparin + warfarin
Kumar *et al*.[14]	Case report	2011	1	Venous Doppler	4 days	Unfractionated heparin + warfarin
Shah *et al*.[15]	Case report	2011	1	Venous Doppler	2 months	Enoxaparin + warfarin
Sarkar *et al*.[16]	Case report	2012	2	Venous Doppler and CT angiography	18 days and 14 days	Enoxaparin + warfarin
Rammurthy *et al*.[17]	Case report	2014	1	Venous Doppler	0 day	Unfractionated heparin + acenocoumarol
Muley *et al*.[18]	Case report	2014	2	Venous Doppler USG	0 day and 2 days	Unfractionated Heparin + warfarin
Kumarihamy *et al*.[19]	Case report	2015	1	Venous Doppler USG	0 day	Enoxaparin + warfarin
Sangani *et al*.[20]	Case report	2015	1	Venous Doppler USG	0 day	Enoxaparin + warfarin
Koç *et al*.[21]	Case report	2015	1	CT angiography	0 day	Not mentioned

CT: Computed tomography, DVT: Deep vein thrombosis, ATT: Antitubercular therapy, USG: Ultrasound

ATT should be immediately started supplemented with anticoagulant therapy as hemostatic changes improve during the 1st month of treatment.[26] The use of anticoagulant therapy in these patients is also of concern due to the interaction of ATT, particularly rifampicin with warfarin analogs, whose efficiency may be reduced due to enzyme induction. The newer Xa inhibitors offer several advantages over traditional therapy with parenteral anticoagulant such as faster onset of action, the lack of need for a heparin lead-in phase, and lesser bleeding events compared with standard therapy. Concomitant use with rifampicin leads to decrease in the plasma concentration of these drugs by 50%–54%.[29]

CONCLUSION

Our cases highlight the importance of a high index of suspicion of DVT in patients of pulmonary TB. Early initiation of ATT along with anticoagulant therapy can prevent the potentially fatal complication of the disease. LMWHs are safer and require minimal monitoring. The overall morbidity and mortality is also decreased. Thus, patients of PTB having predisposing factors for DVT should be carefully monitored and investigated for an early diagnosis and treatment.

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Conflicts of interest
There are no conflicts of interest.

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