Case Report

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

Amitesh Gupta, Parul Mrigpuri, Abhishek Faye, Debdutta Bandyopadhyay, Rupak Singla
Department of TB and Respiratory Diseases, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India

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, with 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

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.

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...
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'
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.[28,29]

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.[5]

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[7]        | Case series   | 1989                | 46           | Not mentioned                      | Not mentioned                                 | Not mentioned                          |
| Ambrosetti et al.[8] | Case series   | 2006                | 5            | Not mentioned                      | Not mentioned                                 | Not mentioned                          |
| El Bekh et al.[7] | Case series   | 2009                | 14           | Not mentioned                      | Not mentioned                                 | Not mentioned                          |
| Bikkeli[9]      | Case series   | 2010                | 46           | Color Doppler and CT pulmonary angiography | 17 days                                       | Venous Doppler and D-dimer             |
| Shitrit et al.[10] | Case series   | 2012                | 5            | Not mentioned                      | 14 days                                       | Venous Doppler USG                      |
| Mariani et al.[11] | Case series   | 2012                | 23           | Venous Doppler and CT of chest     |                                              | Enoxaparin                             |
| Kouismi et al.[12] | Case report  | 2013                | 30           | Venous Doppler and D-dimer         |                                              | Enoxaparin + warfarin                   |
| Sharma et al.[13] | Case report  | 2007                | 1            | Venous Doppler USG                 |                                              | Enoxaparin + warfarin                   |
| Goncalves et al.[14] | Case report  | 2009                | 2            | Venous Doppler and CT angiography  | 0 day and 13 days                            | Enoxaparin + warfarin                   |
| Kumar et al.[15] | Case report   | 2011                | 1            | Venous Doppler                     | 4 days                                        | Unfractionated heparin + warfarin      |
| Shah et al.[16] | Case report   | 2011                | 2            | Venous Doppler                     | 2 months                                      | Unfractionated heparin + warfarin      |
| Sarkar et al.[17] | Case report   | 2012                | 2            | Venous Doppler and CT angiography  | 18 days and 14 days                          | Unfractionated heparin + warfarin      |
| Ramurthy et al.[18] | Case report  | 2014                | 1            | Venous Doppler                     | 0 day                                         | Unfractionated heparin + acenocoumarol|
| Muley et al.[19] | Case report   | 2014                | 2            | Venous Doppler USG                 | 0 day and 2 days                             | Unfractionated Heparin + acenocoumarol|
| Kumar et al.[20] | 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                   |
| Koop 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. 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%.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. World Health Organization. Report on the Tuberculosis Epidemic. Geneva: World Health Organization; 2014.
2. White NW. Venous thrombosis and rifampicin. Lancet 1989;2:434-5.
3. Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, et al. The long‑term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125:1-7.
4. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: A population‑based study. Arch Intern Med 2002;162:1245-8.
5. Mark PL, Ashok PP, Deshpande RB, Mahashur AA. A patient with hypercoagulable state due to tuberculosis. Indian J Chest Dis Allied Sci 2009;51:49-51.
6. Ambrosetti M, Ferrarese M, Codecasa LR, Besozzi G, Sarassi A, Viggiani P, et al. Incidence of venous thromboembolism in tuberculosis patients. Respiration 2006;73:396.
7. El Fekih I, Oueslati I, Hassene H, Fenniche S, Belhabib D, Megdiche ML. Association deep venous thrombosis with pulmonary tuberculosis. Tunis Med 2009;87:328-9.
8. Bikdeli B. Venous thromboembolism in tuberculosis patients: A neglected co-morbidity; May, 2010. Available from: http://www.NATFonline.org/ethrombosis.php. [Last accessed on 2015 Jul 15].
9. Shitrit D, Fox I, Preiss R, Raz M, Mitzelsak A. Incidence of venous thromboembolism in 700 patients with acute tuberculosis. Harefuah 2012;151:208-10, 254.
10. Marjani M, Taharsi P, Baghaei P, Shamani M, Biani PG, Mansouri D, et al. Incidence of thromboembolism in hospitalized patients with tuberculosis and associated risk factors. Arch Clin Infect Dis 2012;7:56-9.
11. Kouissi H, Laine M, Bourkade J, Iriqi G. Association deep venous thrombosis with pulmonary tuberculosis. Egypt J Chest Dis Tuberc 2013;62:541-3.
12. Sharma RR, Acharya KV, Poornima V. A rare complication of pulmonary tuberculosis. J Indian Acad Clin Med 2007;8:179-81.
13. Goncalves IM, Alves DC, Carvalho A, do Ceu Brito M, Calvario F, Duarte R. Thrombosis and venous thromboembolism: A case series. Cases J 2009;2:9333.
14. Kumar V, Gupta KB, Aggarwal R. Deep vein thrombosis in tuberculosis. J Infect Dis Antimicrob Agents 2011;28:63-7.
15. Shah PA, Yaseen Y, Malik AH. Pulmonary tuberculosis with deep venous thrombosis. Webmedcentral Gen Med 2011;2:WMC002093.
16. Sarkar S, Saha K, Maikap MK, Jash D. Deep vein thrombosis: A rare association with tuberculosis. J Med 2012;13:106-8.
17. Rammurthy P, Sunil Kumar N, Aradhya D, Vishwanatha H. Deep vein thrombosis in pulmonary tuberculosis: A rare case report. Int J Clin Cases Investig 2014;6:46-9.
18. Muley P, Shah U, Shah V, Gandhi D. Deep vein thrombosis with tuberculosis: A rare presentation of common disease. Global J Med Public Health 2014;3:1-4.
19. Kumarahamy KW, Ratapanam DM, Jayalaht WA. A rare complication of pulmonary tuberculosis: A case report. BMC Res Notes 2015;8:39.
20. Sangani J, Mukherjee S, Biswas S, Chaudhuri T, Ghosh G. Tuberculosis and acute deep vein thrombosis in a paediatric case. J Clin Diagn Res 2015;9:SD01-2.
21. Koç İ, Doğan S, Doğan Y, Ulusan A. Co-existence of lymph node tuberculosis and pulmonary embolism: A case report. J Clin Anal Med 2015;6(suppl 5):650-2. [DOI: 10.4328/JCAM.3758].
22. Dantan C, Epaulard O, Seynaeve D, Genty C, Bosson JL. Active tuberculosis and venous thromboembolism: Association according to international classification of diseases, ninth revision hospital discharge diagnosis codes. Clin Infect Dis 2014;58:495-501.
23. Suárez Ortega S, Artiles Vizcaino J, Balda Aguirre I, Melado Sánchez P, Arkuch Saade ME, Ayala Galán E, et al. Tuberculosis as risk factor for venous thrombosis. An Med Interna 1993;10:398-400.
24. Andus T, Bauer J, Gerok W. Effects of cytokines on the liver. Hepatology 1991;13:364-75.
25. Robson SC, White NW, Aronson I, Woolgar R, Goodman H, Jacobs P. Acute-phase response and the hypercoagulable state in pulmonary tuberculosis. Br J Haematol 1996;93:943-9.
26. Turken O, Epaulard O, Seynaeve D, Genty C, Bosson JL. Active tuberculosis and venous thromboembolism: Association according to international classification of diseases, ninth revision hospital discharge diagnosis codes. Clin Infect Dis 2014;58:495-501.
27. Gupta, et al.: Deep venous thrombosis in tuberculosis

Lung India • Vol 34 • Issue 1 • Jan - Feb 2017

69