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Original Research Article

Tuberculosis as An Emerging Risk Factor for Hypercoagulability: A Study from A Tertiary Care Centre in Central India

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Abstract:

Introduction: Pulmonary tuberculosis (PTB) is increasingly recognized as a risk factor for venous thromboembolism due to inflammation-induced hypercoagulability. Venous thromboembolism, including deep vein thrombosis (DVT) and pulmonary embolism (PE), contributes significantly to morbidity and mortality.

Materials and Methods: This descriptive observational case series was conducted at a tertiary care centre in Central India from 2022 to 2024. Ten patients diagnosed with PTB and clinical features suggestive of DVT were included. Diagnosis was confirmed using Doppler ultrasonography and relevant imaging. Clinical details including presentation, investigations, treatment, and outcomes were documented.

Results: The mean age of patients was 34.6 years. Lower limb DVT was observed in 60% of cases, upper limb DVT in 30%, and both in 10%. Pulmonary artery thrombosis was seen in 20% of patients. All patients had high clinical probability scores for DVT. Anticoagulation included warfarin (60%), rivaroxaban (30%), and dabigatran (10%). Three patients died due to complications.

Conclusion: PTB is associated with an increased risk of thromboembolic events. Early recognition and prompt initiation of anti-tubercular therapy along with anticoagulation can reduce morbidity and mortality.

Keywords: Deep-Vein Thrombosis, Anticoagulant, Venous Thromboses, Tuberculosis, Pulmonary thromboembolism

Introduction

Venous thrombo-embolism that is, deep vein thrombosis (DVT) and pulmonary thrombo-embolism (PTE) is prevalent among both hospitalised and non-hospitalised patients leading to increased risk of morbidity and mortality. [1] Amongst the top three leading causes of cardiovascular deaths worldwide are Myocardial infarction, stroke followed by pulmonary embolism. [1]

Lower limb Deep vein thrombosis is a more common phenomenon. The risk factors for DVT in the lower limbs are depicted by Virchow's triad: venous stasis, hypercoagulability, and injury to the intima of veins. Upper limb deep vein thromboses accounts for 1% to 4% of all DVT cases. Venous catheters; central or peripheral, pacemakers, are usually the more common causes of UEDVT. The predisposing factors for upper limb DVT are both endogenous factors such as thrombophilia and pregnancy, as well as exogenous factors like external vein compression due to cervical rib or solid tumors. [2]

The association between DVT and tuberculosis (TB) infection is well-established. Active PTB can lead to DVT due to a hypercoagulable state stemming from the inflammatory response. Furthermore, anti-TB medications can contribute to this hypercoagulable disposition. Deep venous thrombosis is present in around 1.5% to 3.4% of TB cases. [3]

Tuberculosis is a chronic infectious disease hence it also shares an association with PTE in both hospitalized and non-hospitalized individuals, carrying substantial morbidity and mortality [5].

Initiating anti-TB treatment early, alongside anticoagulant therapy, has demonstrated efficacy in

reducing the overall morbidity and mortality associated with this condition. [3] Moreover, certain instances of PTE in TB patients can be subtle, emerging without risk factors or clinical symptoms. Delay in diagnosis of PTE can lead to increased mortality hence there is a need to explore indicators of DVT and PTE in TB patients and require more comprehensive clinical studies.

Materials and Methods

This study is a descriptive observational case series conducted in the Department of Respiratory Medicine, Gandhi Medical College, Bhopal, from 2022 to 2024. Ten patients diagnosed with pulmonary tuberculosis (PTB) presenting with clinical features suggestive of deep vein thrombosis (DVT) were included.

Diagnosis of PTB was established microbiologically or clinically as per NTEP guidelines. DVT was confirmed using Doppler ultrasonography, and additional imaging such as CT pulmonary angiography was performed where indicated.

Detailed clinical data including demographic profile, clinical presentation, risk factors, diagnostic workup, treatment details, and outcomes were recorded. Each case was evaluated systematically, and relevant investigations and timelines were documented in accordance with CARE guidelines to improve clarity and completeness.

Results:

The mean age of the study population was 34.6 years, with patients predominantly in the young adult age group.

Lower limb deep vein thrombosis was the most common presentation, seen in 6 patients (60%). Upper limb thrombosis was observed in 3 patients (30%), while 1 patient (10%) had involvement of both upper and lower limbs. Pulmonary artery thrombosis was identified in 2 patients (20%) and occurred independently without peripheral venous involvement.

All patients had a high clinical probability of DVT based on scoring systems. Eight patients had a high probability of pulmonary embolism, while two had intermediate probability.

Anticoagulation therapy included warfarin in 6 patients (60%), rivaroxaban in 3 patients (30%), and dabigatran in 1 patient (10%). Low molecular weight heparin (LMWH) was used as initial therapy in most cases.

Clinical outcomes were favorable in the majority of patients; however, 3 patients died during hospitalization due to complications likely related to pulmonary thromboembolism and severe disease.

Table 1: Clinical profile and outcome of cases

Case	Age/ Sex	Duration of ATT intake/ no. of times	Diagnosis	Extremity involved	Deep Veins involved	Pulmonary thrombosis	Relevant investigations	Treatment started	Outcome
1	49/ M	Started on ATT post admission, h/o incomplete ATT intake once 2 years back	Smear Positive PTB	None	None	Right pulmonary artery thrombosis	CECT Chest: patchy area of wedge-shaped consolidation with central ground glass attenuation in lateral basal segment of right lower lobe. Focal areas of hypodense filling	LMWH and Warfarin	Healthy and Discharged

							defect in B/L ventricles, right main pulmonary artery and segmental branches of right upper and lower lobes suggestive of thrombus.		
2	46/F	Defaulter, Multiple times (25 years and 1 year back)	CTEPH (Chronic thromboembolic Pulmonary Hypertension)	None		Right and left main pulmonary artery thrombosis.	CT Pulmonary Angiogram: long segment hypodense filling defect suggestive of thrombosis in right and left main pulmonary artery. Reversal of aorta pulmonary ratio present. Whole Body PET Scan: Thrombus noted in right and left pulmonary arteries, extending into segmental arteries. Also, thrombus noted in IVC from right atrium extending into the	LMWH and Warfarin	Referred for surgical intervention to higher centre (loss to follow up)

							abdominal IVC. 2D ECHO: dilated RA/RV, severe TR/PAH, normal LA/LV, no RWMA at rest, LVEF: 60%		
3	36/M	1 month	Smear Positive PTB	Left lower limb	Left SFV, DFV, POPV		Chest x ray - B/L infiltrates with fibro - cavitary changes	LMWH Rivoroxaban	Healthy and Discharged
4	23/F	2 months	DSTB	Left lower limb	Left CFV, FV, PV		Chest x ray- of B/L infiltrates with cavitations	LMWH Rivoroxaban	Healthy and Discharged
5	23/F	Started	EPTB	Right upper limb	Brachiocephalic, subclavian, axillary vein. Lower 1/3rd of right IJV		CECT chest: gross right sided empyema causing near complete collapse of right lung with C/L shift of mediastinum. Thoracoscopy: granulomatous lesions. Negative for malignant cells.	LMWH Rivoroxaban	Healthy and Discharged

6	17/ F	Started	Clinically diagnosed PTB	Left upper limb, Left lower limb	left brachial vein, left common femoral vein, superficial femoral vein, popliteal vein, tibial vein.		Chest X ray: s/o right destroyed lung	Dabigatran	Healthy and Discharged
7	55/ M	Defaulter Multiple times (twice)		B/L lower limb, Right upper limb	Right basilic and axillary vein		CECT chest: tree in bud appearance in right middle, lower lobe and left Lowe lobe with fibrocavitary changes in right and left upper lobes.	LMWH, Warfarin	Died (? pulmonary thromboembolism)
8	42/ M	Started	EPTB	B/L lower limb	left tibial vein and right popliteal vein		Chest Xray - right effusion with collapse. 2DECHO - gross pericardial effusion (21.4 mm on RV side, 12.1 mm on LV side) without tamponade D - Dimer - 10000, PT- 19, INR - 1.4. Pleural fluid: hemorrhagic appearance, AFB, cbnaat -	Heparin, Warfarin	Died (? pulmonary thromboembolism? cardiac tamponade)

							negative, ADA - 70, R/M - glucose - 60 mg/dL, protein - 3.40 g/dL, cells- 130 (N -8%, L - 89%), cytology - s/o hemorrhagic smears.		
9	17/F	2 months	Smear Positive PTB	Right lower limb	Iliac vein, common femoral vein, SFJ, saphenous vein and superficial femoral vein		Chest Xray - B/L non homogenous opacities (R>L) with cystic changes in. Rt side PT/INR: 15/1.09, aPTT: 39, TLC: 22000. USG abdomen - short segment circumferential wall thickening of bowel (3.5mm) noted in right hypochondriac, lumbar region ECG: sinus tachycardia	Heparin, Warfarin	Died (Respiratory failure, sepsis? pulmonary thromboembolism, disseminated TB)
10	38/M	1.5 months, defaulter, multiple times	DSTB	Left leg	External iliac vein, common femoral vein, superficial femoral vein		Chest X ray - right middle zone consolidation with B/L fibrocavitary changes	Heparin, Warfarin	Healthy and Discharged

							with left destroyed lung PT/INR: 15/1.09, aPTT: 39		

Table 2: Scoring systems of thromboses

Case	Well's criteria score	Modified Geneva Score	Constans score
1	7.5	12	0
2	8.5	14	0
3	6	10	0
4	7	12	0
5	6	10	2
6	7.5	12	2
7	8.5	14	2
8	7.5	12	0
9	7.5	12	0
10	8.5	12	0

Discussion:

Tuberculosis (both pulmonary and extra-pulmonary) has been identified as standalone risk factors for venous thromboembolism (VTE). Three main causes are suggested by the literature to be responsible for thrombosis in TB patients: venous compression, local invasion of lesions, and hypercoagulability [9]

Chronic infection in conjunction with hypoxemia causes erythrocyte aggregation, damages vascular endothelial cells, and activates coagulation factors. This cascade leads to increased blood viscosity and coagulation factors, which ultimately contribute to a hypercoagulable state. Furthermore, the vascular endothelium is harmed by the release of pro-inflammatory cytokines throughout the illness, which increases thrombotic potential. In active tuberculosis, Turken et al. described a hypercoagulable condition caused by an unbalanced combination of pro- and anticoagulant agents. Protein C and anti-thrombin III levels fall during the first month of treatment, whereas fibrinogen and factor VIII plasminogen activator inhibitor 1 levels rise in plasma. [10]

Few studies have also shown a potential link between deep vein thrombosis (DVT) and the use of rifampicin, with patients under rifampicin-containing regimens exhibiting a relative risk of 4.74 (11). A study by Marcin S. et al. suggests that all PTB should begin anti-tuberculosis treatment (ATT) immediately and combine it with anticoagulant therapy. This will enhance hemostatic changes during the first month of treatment. [12].

However, administering anticoagulant therapy to these patients presents concerns due to potential interactions between ATT and substances like rifampicin, particularly with warfarin analogs. These interactions can lead to reduced efficacy due to enzyme induction. Notably, more recent Xa inhibitors provide benefits over traditional parenteral anticoagulant medication, such as a faster onset of action, no requirement for a heparin lead-in phase, and a lower incidence of bleeding than with normal therapy. It is significant to remember that these more recent Xa inhibitor medications can have a 50% to 54% decrease in plasma levels when used in conjunction with rifampicin [13, 14].

Of these 10 cases, 6 (60%) occurred in deep vein of lower extremities, with distal vein involvement 50%, popliteal, femoral and common femoral vein involvement in 83% cases and iliac vein involvement in 4% cases. According to a study, the lower leg is frequently affected by deep vein thrombosis (DVT), which occurs at a rate of approximately 1.6 per 1000 people annually. The rate of involvement of particular sites vary: distal veins 40 %, popliteal 16 %, femoral 20 %, common femoral 20 % and iliac veins 4 % [15]

In our study, 3 out of 10 patients of VTE (30%) had thrombosis in deep vein of upper extremities. 66% of patients had involvement in the axillary vein, 33% had subclavian and IJV involvement, and 33% had brachial involvement. About 5–10% of DVT cases are upper extremity deep vein thrombosis (UEDVT), a percentage that has been increasing as a result of an increase in the use of intravenous catheters. The axillary and subclavian veins are frequently affected in UEDVT cases. [16]

2 out of 10 patients had pulmonary artery involvement which were isolated, had no upper and lower limb involvement. 1 of the patients had past h/o pulmonary artery thrombus 1 year back. According to literature, CTEPH is a one of the life-threatening complications of acute pulmonary embolism. It occurs when blood clots that cause PE do not dissolve completely and instead become scar

like tissue that narrows and obstructs pulmonary arteries. [17]

Although incidence of UEDVT and LEDVT occurring in same patient is rare, 1 of our patients had both upper and lower limb involvement of same side. 3 out of 10 patients died during the course of hospitalization. Globally, VTE is a major source of morbidity and mortality, with an estimated incidence of 1-2 cases per 1000 people per year. [17]

One of the cases had IVC thrombus along with pulmonary artery thrombosis without lower limb involvement - inferior vena cava (IVC) thrombosis is a rare condition that can lead to pulmonary embolism (PE). The article states that the causes of isolated IVC thrombus are not well understood, but several risk factors have been identified, including malignancy, hypercoagulable states, and prior abdominal surgery.[18]

In our study, out of 10, 6 (60%) patients were on Warfarin, 3(30%) on Rivaroxaban and 1(10%) on Dabigatran. As per literature, direct oral anticoagulants (DOACs) are a newer class of anticoagulants that have been shown to be effective in the treatment of deep vein thrombosis (DVT). Compared to conventional anticoagulants, they offer a number of benefits, such as a decreased risk of bleeding and fewer medication interactions. Nonetheless, patients with severe renal impairment, antiphospholipid syndrome, and artificial heart valves still prefer warfarin over other anticoagulants. The recommended anticoagulant for the first management of pulmonary embolism (PE) and deep vein thrombosis (DVT) is low-molecular-weight heparin (LMWH). Compared to unfractionated heparin (UFH), it offers a number of benefits, such as a more consistent dose-response relationship and a decreased risk of bleeding. [18]

Wells scoring is able to rule out the possibility of DVT with a sensitivity of 100% and an NPV of 100% in low risk patients (scores<1), while it was able to predict DVT with a specificity of 90% in moderate-high risk patients (scores >/=2). In our study, all 10 patients had scores >6, suggesting a high risk of DVT. [6]

In our study, 8 patients had a score >12, indicating high risk, and 2 patients had a Geneva score of 10, indicating moderate risk. Based on a patient's risk variables and clinical findings, the Geneva score is a clinical prediction algorithm that calculates the pre-test probability of pulmonary embolism (PE). Patients are categorized into low, intermediate, and high risk groups for PE according to the updated Geneva score [3]. Based on pretest probability, the estimated percentages of PE confirmation are 10% in low, 30% in moderate, and 65% in high pretest likelihood 4. Pretest likelihood assessment of pulmonary embolism (PE) is made easier with the help of the simplified Geneva score [7].

Three of the patients in our study had Constans scores of 2, which indicates a significant likelihood of DVT. Based on clinical criteria, the Constans score is a clinical measure that determines the likelihood of upper limb deep vein thrombosis (DVT). Patients with upper limb DVT are divided into low, middle, and high probability groups based on the Constans score. With a specificity of 45%, the Constans score has a 100% sensitivity for identifying upper limb DVT. Although the D-dimer test is advised for the diagnosis of upper limb DVT, we were unable to get D-dimer readings due to resource constraints. [8]

Management of thromboembolism in patients with tuberculosis presents unique challenges due to drug–drug interactions. Rifampicin, a key component of anti-tubercular therapy, is a potent inducer of cytochrome P450 enzymes and significantly reduces the efficacy of oral anticoagulants such as warfarin and direct oral anticoagulants (DOACs). This necessitates careful dose adjustment and close monitoring.

Low molecular weight heparin (LMWH) remains the preferred initial anticoagulant due to its predictable pharmacokinetics and minimal interaction with anti-tubercular drugs. Although DOACs offer advantages such as ease of use, their plasma levels may be reduced when co-administered with rifampicin.

Early recognition and combined management of tuberculosis and thromboembolism are crucial in reducing morbidity and mortality. Clinicians should maintain a high index of suspicion for thromboembolic complications, especially in patients with advanced disease.

Conclusion: Pulmonary tuberculosis is an important risk factor for venous thromboembolism. Early recognition and timely initiation of anti-tubercular therapy along with appropriate anticoagulation are essential to reduce morbidity and mortality.

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