

Case series

Coagulation abnormalities in pediatric patients with Tuberculosis: Case series and review of literature

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Abstract

Tuberculosis is one of the chronic infectious diseases affecting the population in all regions of the world. This disease is more common in low-middle-income countries (LMIC), especially India. This affects almost all organs of our body. One of the serious complications of TB is venous thromboembolism (VTE). This complication is relatively rare and more common in adults than in children. High index of suspicion and early management with low molecular weight heparin will help in preventing mortality and morbidity due to this complication. We present here a case series of 2 pediatric patients who had coagulation abnormalities in association with various severe forms of tuberculosis.

Keywords: Deep vein thrombosis, Low molecular weight heparin, Thromboembolism, Tuberculosis

Introduction

Tuberculosis (TB) caused by Mycobacterium tuberculosis affects almost all organs of our body and is one of the most common chronic infectious diseases in LMIC, especially in India. It is also one of the global health problems that causes a phenomenal public health burden. The incidence of TB in the Southeast Asia region is 324 per million as per the WHO data 2024 [1]. With appropriate treatment as prescribed by the National Tuberculosis Elimina-

tion Program (NTEP), the vast majority of patients are being treated and getting cured. Tuberculosis infection, which is a chronic inflammatory state, causes a procoagulative condition in our body, causing venous thromboembolism (VTE), which is more common in adults [2]. But the incidence of VTE in children secondary to Tuberculosis is rare [3].

Here, we report a case series of 2 pediatric patients who presented various patterns of tuberculosis associated with hypercoagulable states.

Citation : Saroja C. N., Gopalakrishnan S., Mohammad U., Gupta I., Sharma S., Coagulation abnormalities in pediatric patients with Tuberculosis: Case series and review of literature. *Ethiop J Pediatr Child Health.* 2026;21 (1): 117-125 **Submission date:** 11 July 2025 **Accepted:** 16 December 2025 **Published:** 1 January 2026

Case 1

A 15-year-old adolescent girl presented to the pediatric OPD in Teerthankar Mahaveer Medical College, Moradabad, with a history of fever and generalized weakness since 1.5 months and cough since 15-20 days. She was a known case of microbiologically positive pulmonary tuberculosis, RIF sensitive detected 4 months back, and took anti-TB Treatment (ATT) for 1.5 months and stopped the ATT on her own. Both her parents had tuberculosis; father was treated for pulmonary tuberculosis and mother is being treated for disseminated tuberculosis. On arrival, the patient was conscious and well oriented to time, place and person. She was febrile (101.2°F), pulse rate 120/min, respiratory rate 24/min, SpO₂ was 98% in room air. She was having severe pallor, but no clubbing and no lymphadenopathy. Her weight was 26 kgs. She looked emaciated and cachectic, had dry scaly skin with bipedal edema. The BCG scar was absent. On systemic examination, in the respiratory system, breath sounds were reduced over

the infra-mammary and infra-axillary areas with a hyper-resonant note on percussion in the above areas on the left thorax. She was suspected to be having drug-resistant tuberculosis and evaluated further.

Her hemoglobin was 10.6 g/dL, total leukocyte count was 10800 / cmm (P86, L10, E01, M03), platelets 3.67 Lakh/ cmm and CRP was 62.54 mg/L. Sputum CBNAAT was positive for Mycobacterium Tuberculosis with RIF sensitive. LFT was normal except for hypoalbuminemia (2.3 gm/dl), and her renal functions were normal. HIV status was negative. Sputum for KOH was negative, and Gram's stain showed Gram-positive cocci in pairs, but sputum culture was sterile. Chest X Ray showed cavitary lesions on the right lower lobe with collapse of the left upper lobe with moderate pneumothorax on the left side [Figure 1]. Ultrasound abdomen showed borderline hepatomegaly with grade I fatty changes with mild left-sided pleural effusion. X-ray of the spine was normal.



Figure 1. Chest X Ray showing cavitary lesions on right lower lobe with collapse of left upper lobe with moderate pneumothorax on the left side

CECT Thorax showed bronchiectatic changes, centrilobular ground glass nodules, parenchymal destruction, consolidation, mediastinal and axillary lymph nodes with some calcifications, gross left hydropneumothorax, large filling defect causing complete luminal occlusion in right subclavian vein extending into right brachiocephalic vein causing its near complete luminal occlusion of right subclavian vein

(likely thrombus) and partial filling defect in pulmonary artery supplying right upper and lower lobes along with its segment branches. A partial filling defect in the segmental branch supplying the medial segment of the right middle lobe was also noted, with the possibility of pulmonary thromboembolism [Figure 2].

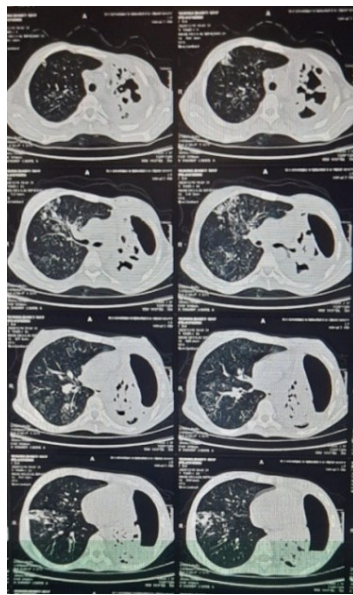


Figure 2. CECT Thorax showing bronchiectatic changes, calcified mediastinal nodes, gross hydropneumothorax

In view of the above findings, pulmonary angiography was done which showed partial filling defects in most of the segmental branches of right lung (likely pulmonary thromboembolism) and large filling defect causing complete luminal occlusion in right subclavian vein ex-

tending into right brachiocephalic vein and right internal jugular vein causing complete luminal occlusion of right subclavian vein and partial occlusion of right brachiocephalic vein (likely thrombus) [Figure 3].

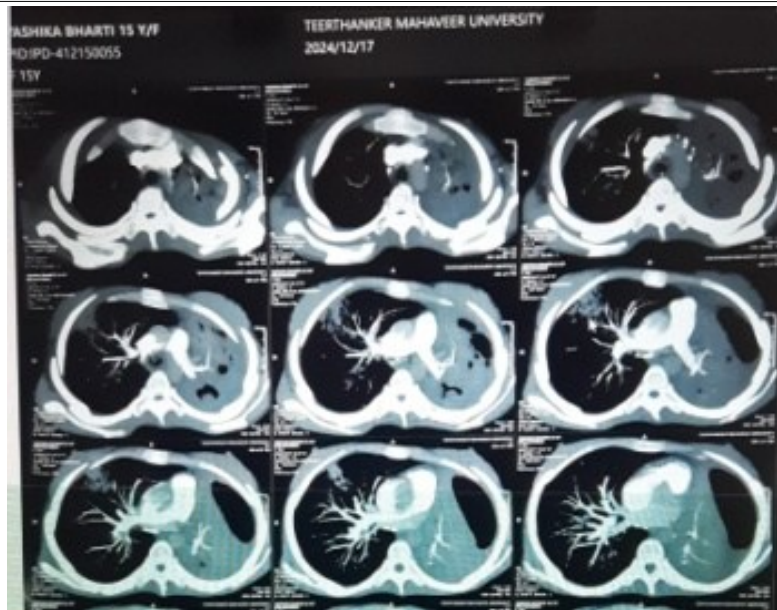


Figure 3 CT Pulmonary angiogram showing partial filling defects in most of the segmental branches of right lung

The patient was started on ATT from NTEP center as a fresh case. She was also started on Inj Enaxoparin initially followed by oral Tab Nicoumalone for pulmonary thromboembolism with PT / INR titrated to be in the range INR 2-3. In the meanwhile, she was given protein supplements along with good nutrition and psychiatric counseling to the family. Patient gradually improved and became afebrile and discharged on ATT with oral anticoagulant with regular follow-up.

Case 2

14 years 14-year-old adolescent female presented with fever, generalized weakness for 1 month, and acute onset of respiratory distress for 3 days. The fever was moderate degree, not with chills and rigors. She had a mild cough with no expectoration. There was no history of contact with an open case of TB. On examination, she was conscious, anxious, pulse rate

was 140/min, resp rate was 44/min, SpO₂ was 80 % in room air, BP was 124/66 mmHg, CRT was < 3 sec. Her weight was 36 kg (10th-50th centile), height was 146 cm (10th-50th centile). The BCG scar was absent. She was pale; no clubbing or lymphadenopathy was noted. On examination of the respiratory system, the chest was symmetrical, a dull note on percussion was noticed in all areas of both lungs, and breath sounds were decreased in all areas of the left chest compared to the right side.

There were fine crackles in both lung fields. Her cardiovascular, abdominal, and CNS examination were normal. She was clinically diagnosed with ARDS and was investigated further. She was started on O₂ by NRBM, low-dose lasix infusion, IV fluids, antibiotics, and antivirals.

Investigations showed Hb 8.3 gm/dl, total leucocyte count 10800 cells/dl (N73, L21, E02, M04), platelet 1.47 Lakh /dl, ESR 20 mm/hr, CRP 45.22 mg/L, AST 200.6 IU/l, ALT 176.5 IU/l, Albumin 2.8 gm/dl, rapid diagnostic tests for malaria, dengue, typhoid – negative, HbsAg, Anti HCV and HIV rapid test were negative. Sputum for CBNAAT was negative. The tuberculin test showed more than 20 mm induration. USG abdomen showed borderline hepatomegaly and mild splenomegaly. ECHO was normal. CT chest showed symmetric infiltrations in both lung fields, suggestive of pulmonary edema, along with minimal bilateral pleural effusion. A lytic lesion was noticed in

the L1 vertebra. MRI Dorsal spine showed anterior wedging of the L1 vertebral body with reduced intervertebral space at the D12–L1 level. Her D-dimer level was 3068.6 ng/mL. Patient was started on injection enoxaparin. The patient was started on ATT as per NTEP. Patients gradually responded to treatment, and orthopedic consultation was done, and vertebral braces were advised, and discharged with braces after 15 days. After 2 weeks, she developed having headache and her MRI brain showed a tuberculoma with perilesional edema. Steroids were added to ATT and is being followed regularly in OPD.

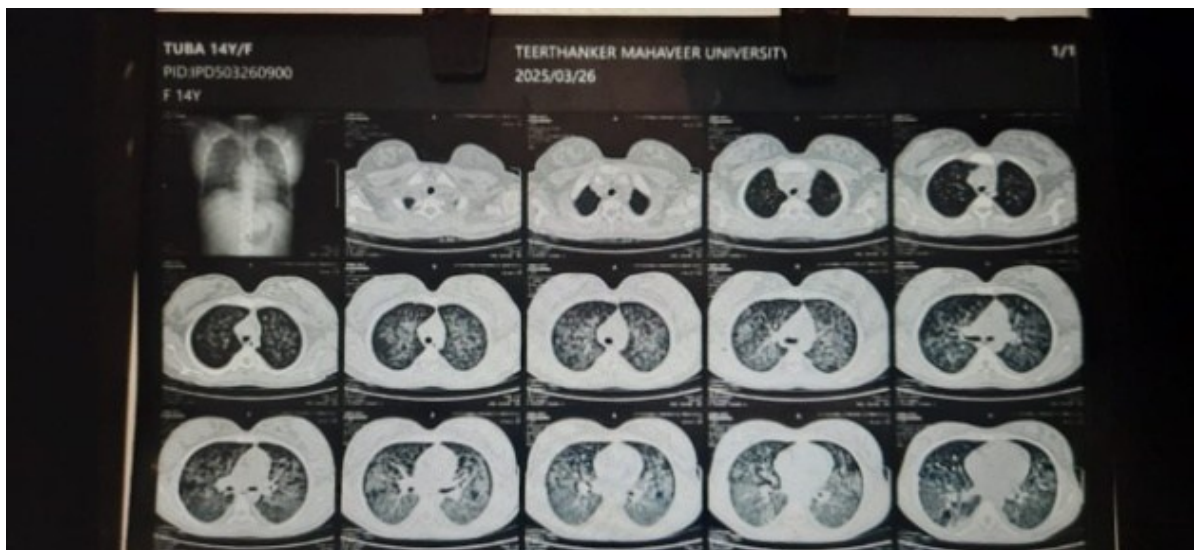


Figure 4. CT chest showing symmetric infiltrations in both lung fields suggestive features of pulmonary edema along with minimal bilateral pleural effusion

Discussion

Pulmonary thromboembolism in children is associated with a high mortality of around 10%. The presentation of VTE has a bimodal distribution, i.e., more in neonates and adolescents [4]. Various risk factors of pulmonary

thromboembolism are the presence of a central line, septicemia, congenital heart diseases, nephritic syndrome, dehydration, trauma, malignancy, systemic lupus erythematosus, congenital prothrombotic conditions (protein C, protein S or prothrombin deficiency,

Leiden factor V mutation, G20210A mutation prothrombin gene, and hyperhomocysteinemia), etc [5,6,7]. However, there are very few reports documenting the occurrence of VTE in pediatric patients with TB [8].

Coagulation abnormalities can present as a complication of TB, which manifests as VTE such as deep vein thrombosis, pulmonary embolism etc. Venous thromboses involving other veins have also been reported such as hepatic vein thrombosis [9], portal vein thrombosis [10], superior sagittal vein thrombosis [11], Central retinal vein obstruction [12], etc. These complications are commonly seen in adult patients whereas the occurrence of these in children is rare[13,14,15]. These occur due to the hypercoagulable state, which happens in Tb. Various reasons for this hypercoagulable state are an increase in plasma fibrinogen levels, factor VIII, and reactive thrombocytosis. Pro-inflammatory mediators which occur during the disease process, make the vascular endothelium more thrombogenic and also synthesize more coagulation proteins in the liver. There is also reduced antithrombin III, protein C levels and reactive thrombocytosis. Moreover, the patients are immobilized in serious disease which also predisposes to thromboembolic state [2]. It has also been found that anti-tuberculous drugs like Isoniazid and rifampicin aggravate hypercoagulability by increasing the release of interleukin-6 by mononuclear cells [16,17, 18,19]. The possible association between DVT and rifampicin use has also been documented. Other

causes could be prolonged immobilization during hospital stay and lymphadenopathy causing mechanical venous obstruction[20].

The investigations for diagnosing coagulation abnormalities, especially VTE include CT Angiogram of the chest, which may not be possible in all classes of patients. Estimation of D – D-dimer levels is very sensitive for diagnosing VTE, even though their specificity is not good, especially in children[21]. The management of these patients with VTE are low molecular weight heparin injection initially for 7 – 10 days. Since medical management is for long duration, oral anticoagulants are recommended after discharge. Frequent monitoring of PT/INR should be done and the target INR should be between 2 – 3[22].

In a retrospective study by Kouismi et al in 2013, the authors documented 30 cases of confirmed pulmonary tuberculosis associated with deep vein thrombosis in a 3 year period from 2010-2013 in adult population and discussed about various mechanisms of hypercoagulable state in tuberculosis due to high plasminogen level, decreased antithrombin III, protein C and platelet aggregation[23].

Our first case, a defaulter of pulmonary TB, presented with high fever and was found to have pulmonary thromboembolism on CT Angiogram, who also had a very high level of D –D-dimer. Our second case, presented with ARDS with pulmonary edema with disseminated TB (LUNG, skeletal, AND CNS) did not have frank VTE but had a significant

elevation of D-Dimer indicating a potential risk of developing VTE. Both cases were managed with parenteral low molecular weight heparin. For one case with pulmonary thromboembolism, the patient was discharged on oral anticoagulants for 6 months and for another case, low molecular weight heparin was given for 14 days and no anticoagulant was advised on discharge since the last D – Dimer level was normalized.

Conclusion

VTE in association with Tb is one of the rare entity especially in adults but there are few reports of VTE in pediatric population. This condition can be diagnosed early in the course of illness especially when there is severe form of Tb so that early initiation of anticoagulants can help in better outcome. Hence physicians should have a high index of suspicion of this rare condition in Tb.

Declarations

Ethical consideration

Written informed consent was taken from the caregivers of the patients.

Conflict of interest

We declare no conflict of interest in the manuscript.

Authors contribution

CNS made substantial contributions in admitting, managing the patients, writing the draft, and interpreting the investigations. He will act as the guarantor. SG contributed to the man-

agement, reviewing the draft and manuscript writing. UM contributed to acquiring the data, writing, and also in managing the patients. IG is actively involved in the management of the patient and is involved in image acquisition. SS also contributed to managing the patients and draft writing.

Funding: None

Acknowledgments: Not applicable

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