Deep Vein Thrombosis in a Patient with Disseminated Tuberculosis

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ABSTRACT

Severe pulmonary tuberculosis (PTB) is sometimes complicated with deep venous thrombosis (DVT). We report a case of PTB and lower leg DVT in a young patient without any risk factors. Wide derangement of coagulation parameters was found, indicating a pro-coagulant state. The cause-effect relationship between PTB and DVT which has significant therapeutic implications is discussed. (J Infect Dis Antimicrob Agents 2011;28:63-7.)

INTRODUCTION

India accounts for almost one-third of the global burden of tuberculosis (TB).¹ Deep vein thrombosis (DVT) is clinically observed and can be confirmed with laboratory methods in 3 percent-4 percent of patients with pulmonary tuberculosis (PTB). The real incidence may be closer to 10 percent because most of the patients are thought to be clinically inapparent.² It is possible that large amounts of interleukins synthesized by monocyte-macrophage system during inflammation induce hepatic dysfunction and hemostatic abnormalities. Hemostatic changes in PTB may favor the development of hyper-coagulable states.³ The lack of awareness regarding the association is possibly responsible for the condition not being recognized and hence screening and treatment strategies have not been standardized. Our case highlights the occurrence of DVT, a significant but rare association, in a patient with severe PTB and poses a diagnostic dilemma.

CASE REPORT

A 17-year-old female was admitted to the hospital with a history of cough with expectoration, chest and abdominal pain, low grade fever, loss of appetite and dyspnea for the past month. She was a known case of epilepsy for the last three years. There was no recent pelvic or orthopaedic surgery, no recent long journey and no trauma. There was no history of leg swelling, diabetes mellitus or thrombotic stroke. She was unmarried and was non smoker and non alcoholic. On examination, she was febrile with pallor but no icterus.
On auscultation, there were bilateral basal inspiratory crackles. Examination of other systems revealed no abnormality. Her two sputum samples were negative for acid fast bacilli (AFB) by direct smear examination. A complete blood count revealed a hemoglobin of 8.1 g/dL (normal 13-18 g/dL), white blood cell (WBC) count of $14 \times 10^3$/mm$^3$ (normal 4.5-11 $\times 10^3$/mm$^3$) and platelet count of $260 \times 10^3$/mL (normal 130-400 $\times 10^3$/mL). Liver function test results showed aspartate transaminase (AST) of 96 units/L (normal 10-40 units/L), alanine transaminase (ALT) of 82 units/L (normal 10-55 units/L) and serum bilirubin of 0.8 mg/dL (normal 0-1 mg/dL). The erythrocyte sedimentation rate (ESR) was 86 mm/hr. Human immunodeficiency virus (HIV) serology was negative. Cerebrospinal fluid (CSF) was examined with the suspicion of disseminated TB. The CSF analysis revealed glucose of 70 mg/dL and protein of 20 mg/dL. Mantoux test was positive with an induration of 14 mm $\times$ 16 mm. Chest radiograph (Figure 1) revealed cavity in left upper zone and infiltration in right upper, middle and lower zones. Computed tomography (CT) of the chest revealed nodular opacities in both the lungs and cavitary lesions in left upper lobe (Figure 2) with necrotic lymph nodes. CT abdomen showed gut thickening of jejunal loops and CT head showed multiple calcified lesions in both cerebral hemispheres suggestive of old healed granulomas.

She was started on a four drug anti-TB therapy with isoniazid (300 mg/day), rifampicin (450 mg/day), pyrizinamide (1,500 mg/day) and ethambutol (1,200 mg/day). After 3-4 days of treatment, she complained of swelling and pain in her left lower limb. Upon examination signs of deep venous thrombosis were present. Colored venous doppler of the lower limbs showed an echogenic thrombus with minimal flow on CD in lumen of left external iliac, femoral, popliteal and posterior tibial vein (Figure 3). Venous system of the right leg was normal. A detailed coagulation profile was sent for and was found to be deranged: D-dimer 7.1 mg/mL (normal 0-0.35 mg/mL), aPTT 34.6 seconds (control 28 seconds), FDP > 320 mg/mL (normal 0-5 mg/mL), bleeding time 3.2 minutes (control 3.4 minutes), thrombin time 20.1 seconds.
(control 14.6 seconds) and INR 0.97 (normal 1-1.4). Tumor-markers were investigated to rule out an occult malignancy as a cause of the hypercoagulable state and were not contributory. Patient was treated with subcutaneous unfractionated Heparin along with supportive measures. Heparin was stopped after 10 days and oral anticoagulants were continued. The patient showed a significant clinical improvement with resolution of fever, gain of weight and an overall feeling of well-being. Repeat ultrasound at 6 weeks showed residual thrombus, partial re-canalization and flow around the thrombus. Patient was lost to follow-up as she returned to her village.

**DISCUSSION**

Causes of DVT include obstruction of blood stream due to prolonged bed rest, long air journeys, cardiac failure, malignant pelvic masses, injury to pelvic veins due to trauma, pelvic surgery, childbirth and increased coagulability of blood due to oral contraceptives, malignancies, hereditary thrombophilia (factor V Leiden defect, protein C, protein S and antithrombin III deficiency states), dysfibrinogenaemia, and acquired thrombophilias found in systemic lupus erythematosus and anti-phospholipid syndrome. The thrombogenic potential of TB is not well known but can have serious consequences. Activation of endothelial cells occurs in response to numerous physiological stimuli and results in the expression of endothelial proteins that change the normally non-thrombogenic internal surface of the vessel into a thrombogenic surface with subsequent development of local thrombosis. Priming of vascular endothelium as a result of interaction between mycobacterial products and the host monocyte-macrophage system, which then synthesizes large amounts of TNF-α and interleukin-6, has been postulated. Widespread disturbance in homoeostasis could focus on vascular intima that is activated and rendered more thrombogenic by pro-inflammatory cytokines. Additionally, these cytokines induce hepatic acute phase responses that alter the levels of coagulation proteins. It is also postulated that these changes result in hypercoagulable state which may predispose to DVT. Sequential analysis in a central group with active PTB showed anaemia, reactive thrombocytosis, elevations in plasma fibrinogen degradation products (FDP), tissue plasminogen activator and inhibitors with depressed antithrombin III levels which appear to favour the development of deep vein thrombosis in disseminated TB. Muzaffer Sezer et al reported anaemia, thrombocytosis, increased ESR, C-reactive protein, fibrinogen and decreased anti thrombin III levels in army members with active PTB. The levels became normal with in 4 weeks of anti-TB therapy. The return of these haematological parameters to a normal level is a good indicator of disease control and they correlate with sputum conversion in sputum positive TB patients.

There have been few reported associations between PTB and disseminated intravascular
coagulation. Studies have shown subtle changes in blood rheologic properties and in the haemostatic system in patients with PTB. A study by Kaminiskia et al showed erythrocyte edema, more rapid depletion, lower resistance, and higher aggregation which is accompanied by increased haematocrit and normal erythrocyte count. There was also an increase in the prothrombin indices and antithrombinIII activity. The fibrinogen levels were within normal limits or reduced despite an increase in other acute phase reactants, followed by the appearance of large amounts of blocked fibrinogen in the blood. Cases of DVT have been reported in patients with intraabdominal lymphadenopathy of tubercular aetiology. To summarize we can say that hypercoagulable state, DVT, DIC can all be associated with TB whether it is disseminated, miliary, pulmonary and even lymphadenopathy. Therefore, it is possible that one of the causes for sudden unexplained deaths in patients with TB may be undiagnosed pulmonary thromboembolism secondary to clinically asymptomatic DVT.

The coexistence of DVT and PTB has implications for treatment since rifampicin is a potent inducer of cytochrome p450 system which is responsible for metabolism of large number of drugs including oral anti-coagulants such as coumadins. The dosage of coumadins has to be increased to maintain therapeutic efficacy and has to be monitored regularly by coagulation tests.

In our case, association between DVT and PTB is plausible as the patient was a young female with no specific risk factors for DVT; other causes for DVT were ruled out systematically. Occurrence of DVT coincided with development of extensive PTB and DVT resolved along with improvement in PTB. The limitations of this report are that sputum and CSF culture for mycobacteria were not done. Nevertheless, the patients had a history consistent with TB; the presence of cavity in left upper zone, infiltration in right upper, middle and lower zones on chest radiograph, CT showing nodular opacities in both lungs with necrotic lymph nodes, gut thickening in jejunal loops, multiple calcified lesions in both cerebral hemispheres suggestive of old healed granulomas, elevated ESR, positive Mantoux test and the clinical response to antituberculosis drugs makes the diagnosis of TB very likely. Our case highlights the risk of DVT developing in patients with severe PTB even in the absence of specific risk factors. We emphasize the potential seriousness of this under reported phenomenon, the need for establishing an early diagnosis and institution of prompt treatment for DVT while continuing the anti-TB treatment.

References

