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Editorial

Thromboembolism in Tuberculosis: A Neglected Comorbidity

Tuberculosis (TB) is one of the most prevalent infectious diseases worldwide. India is 17th among 22 high-burden countries. In 2011, out of the estimated global annual incidence of 9 million tuberculosis cases, 2.3 million were estimated to have occurred in India. Despite persistent and committed efforts, it continues to be a major health problem in India. TB can involve almost every organ of the human body. The most common presentation is pulmonary tuberculosis (PTB). Vascular complications associated with infection by *Mycobacterium tuberculosis* have been reported in 1.5%-3.4% of TB cases. Venous thromboembolism is considered rare in TB.

Venous thromboembolism includes the spectrum of diseases from deep vein thrombosis (DVT) to pulmonary embolism. It remains underdiagnosed universally. A multi-national report of the European Union Countries estimated that the total number of symptomatic, non-fatal venous thromboembolic events per annum was more than 465,000 cases of DVT and more than 295,000 cases of pulmonary embolism. The authors estimated more than 370,000 venous thromboembolism-related deaths, of which only 7% were diagnosed pre-mortem. Of these, 34% were cases of sudden fatal pulmonary embolism. The actual incidence is difficult to estimate because of the silent nature of the disease and its non-specific presentation. The patients who are critically ill and hospitalised are at increased risk of developing venous thrombo-embolism.

Venous thromboembolism is generally more common in post-operative patients and critically ill patients in the intensive care units. It is a rare entity outside the critical care settings and even rarer in patients with PTB. There are not many studies evaluating the coexistence of TB with venous thromboembolism. However, there are case reports suggesting a direct association between TB and venous thromboembolism, independent of other known risk factors for the disease. It may be a presenting feature of TB or may develop later during the course of the disease. The incidence of DVT in patients with PTB is about 3%-8%, confirmed by venography, and the real incidence may be close to 10%. Robson *et al*[3] observed 35 patients with PTB and DVT. In 33 of them, DVT occurred seven days after the diagnosis of TB, while only in two, DVT was the presenting feature. Ambrosetti *et al*[4] reported an incidence of 0.6% (5 cases of DVT and two cases of pulmonary embolism) among 1237 TB patients from Italy.[4] Cases of thrombosis at other sites, such as cortical venous sinus and inferior vena cava have also been reported in TB.

Various mechanisms may be responsible for the development of venous thromboembolism in patients with TB. It may act through all the three parts of Virchow's triad, i.e. hypercoagulability, venous stasis and endothelial dysfunction. The haemostatic and inflammatory changes in TB can result in hypercoagulable state. Other responsible factors may be higher levels of fibrinogen, fibrin degradation products, tissue plasminogen activator and inhibitor, decreased anti-thrombin III and reactive thrombocytosis.[3] White *et al*[5] reported that the use of rifampicin may increase the risk of DVT in patients with PTB by 4.74 times as compared to other drug regimens. Rifampicin is an enzyme inducer, and may alter the balance of anticoagulant and coagulant proteins produced by the liver. Decreased production or increased clearance of anticoagulant proteins favours hypercoagulability. Local compression of veins by enlarged reactive lymph nodes and immobility due to severe respiratory compromise can lead to venous stasis which further increases the risk of venous thromboembolism. There is also some evidence on endothelial dysfunction in TB. Endothelial injury may be a result of bodily reactions to the Koch's bacillus.

There are certain factors that may increase the risk of venous thromboembolism in patients with TB. The risk is higher in elderly patients. Those aged 70 years or older have an approximately 25-fold increased risk, compared to those of 20-29 years of age. Presence of obesity, diabetes mellitus and human immuno-deficiency virus (HIV) positivity are independent risk factors for venous throm-boembolism. The increasing incidence of TB in diabetes mellitus and HIV-positive patients further increases the risk of venous thromboembolism. Highly active anti-retroviral therapy (HAART) and possibly low CD4 cell counts may also contribute to this increased risk. Prolonged embolisation in severe forms of TB like tuberculosis meningitis, miliary TB and disseminated TB also predispose to venous thromboembolism.

Venous thromboembolism remains undiagnosed for several reasons. First, most of the patients with both DVT and pulmonary embolism are asymptomatic and when symptoms are present, these may be non-specific. DVT presenting with pedal oedema is usually taken as a consequence of malnutrition or as a sequelae of PTB, such as amyloidosis and cor-pulmonale secondary to extensive pulmonary fibrocavitatory disease. Signs and symptoms of pulmonary embolism, i.e. sudden onset of dyspnoea, and tachypnoea and chest pain are often mistaken as being secondary to generalised weakness, malnutrition, parenchymal lung destruction. The plain chest radiograph is the only readily available investigation in patients presenting with sudden onset of dyspnoea. However, in most cases of pulmonary embolism, it does not reveal any abnormality. Further under Directly Observed Treatment, Short-course (DOTS), most of the cases are treated and supervised by

peripheral health-care workers. It is beyond their skills and knowledge to suspect this condition leading to a delay in diagnosis or resulting in these cases remaining undiagnosed and eventually causing death. There is ignorance among the physicians and general practioners regarding clinical suspicion, diagnosis and prophylaxis of venous thromboembolism. Costs and limited diagnostic facilities even in tertiary care hospitals compound the problem.

It is important to suspect venous thromboembolism to make an early diagnosis and initiate prompt treatment. Patients who respond poorly to anti-tuberculosis drugs, those who have other predisposing factors and those in need of a prolonged stay in hospital should be carefully monitored and investigated for an early diagnosis of the condition. The patients with multiple risk factors should be considered for prophylactic anticoagulant therapy.

Importance of D-dimer estimation lies in the low risk patients to rule out venous thromboembolism. Positive values are not of much significance in high risk patients. Diagnostic tests include doppler ultrasonography for DVT and computed tomography pulmonary angiography for pulmonary embolism.

Venous thromboembolism is an easily preventable disease by prophylactically starting anticoagulants in high risk patients. The latest edition of the American College of Chest Physicians Guidelines on Antithrombotic and Thrombolytic Therapy state that "For acutely ill medical patients admitted to hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous venous thromboembolism, sepsis, acute neurologic disease, or inflammatory bowel disease, thrombo-prophylaxis with low molecular weight heparin (LMWH), low dose unfractionated heparin (LDUH), or fondaparinux is recommended.[6] Inferior vena cava filters may be used for prevention of pulmonary embolism in addition of heparin therapy. Antituberculosis treatment should be started at the earliest as the haematological changes improve during the first month of treatment. Frequently, a higher dose of warfarin is necessary to achieve the therapeutic INR values, because of the enzyme-inducing effect of rifampicin on cytochrome P450. The probable association between rifampicin and DVT does not contraindicate its use. However, measures should be taken to prevent DVT in patients receiving rifampicin.

Tuberculosis is, thus, an independent risk factor for the development of venous thromboembolism irrespective of the presence of other risk factors. Studies are required to further understand the mechanism involved. In the Indian perspective, it may not be easy to diagnose and treat this complication, as the required investigations and treatment are not readily available everywhere. Emphasis is laid on high index of suspicion, early referral to better-equipped centre, early diagnosis, and institution of prompt treatment for deep venous thrombosis while continuing the antituberculosis treatment.

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