Coexisting venous thromboembolism in patients with tuberculosis

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Letter to the Editors-in-Chief

Coexisting venous thromboembolism in patients with tuberculosis[1,2]

Tuberculosis (TB) is one of the most devastating curable infectious diseases. [1] TB persists as a major cause of morbidity and mortality worldwide. Respiratory infections can increase the risk of venous thromboembolism (VTE). [2] Specifically, evidence exists about the hypercoagulability state in tuberculosis. [3,4] Hypercoagulability in tuberculosis patients may be due to the increase in plasma fibrinogen and factor VIII, and reactive thrombocytosis. [3] On the other hand, stasis might occur due to local compression of veins by the enlarged reactive lymph nodes or immobility caused by severe respiratory compromise, and there is some evidence regarding endothelial dysfunction in tuberculosis patients. [3–5] Endothelial injury may be a result of bodily reactions to Koch's Bacillus, or the use of Rifampin. [6] Being able to affect all the three components of the Virchow's triad, TB could be a significant risk factor for VTE. However, few studies have addressed this potential relationship. Accordingly, this study was conducted to determine the relative frequency of VTE among TB patients in a regional referral hospital in Iran.

Methods

A retrospective review of the medical records of hospitalized patients with a diagnosis of TB at the National Research Institute of Tuberculosis and Lung Disease (NRITLD) was performed from January 2001 to December 2008. NRITLD is a World-Health-Organization (WHO)-collaborating tertiary care center for tuberculosis and lung disease, located in Tehran, Iran. NRITLD provides special care for tuberculosis patients in the region, particularly patients referred from across the country as well as referrals from neighboring countries. Using the ninth revision of the International Classification of diseases coding system (ICD-9), we selected TB patients with coexisting diagnosis of VTE (deep vein thrombosis (DVT), pulmonary embolism (PE), or both). DVT diagnosis was based on gray-scale evaluation of venous compressibility and color Doppler evaluation of venous flow. PE was diagnosed by computed tomography pulmonary angiography (CTPA). Diagnosis of TB was made only if a pathogenic species of the mycobacterium tuberculosis complex was retrieved from the smear, culture, biopsy, or body-fluid specimens. Demographic and clinical data of the patients, as well as co-morbidities and clinical course were retrieved from the medical records. Careful attention was directed toward the location of TB (pulmonary or extrapulmonary), smear results, and resistance. Onset of the VTE event and specific characteristics pertaining to each VTE event were reviewed. In January 2009, an attempt was made to contact all the patients by phone for follow-up. For survival analysis, for those who could not be contacted, the last follow-up visit was considered as the censoring time. A statistical software package (SPSS, version 16.0; SPSS Inc, Chicago, IL) was used for statistical analyses. Chi^2 test (with Fisher's correction when necessary), was used for comparison of categorical variables.

Results

From the total number of 3293 tuberculosis patients, 46 had coexisting diagnosed VTE (31 males, 15 females, mean age: 53.4 ± 19.6 years, range: 16-86 years). Twenty six patients had DVT, 13 had PE, and the remaining 7 had both DVT and PE. In-hospital VTE happened in 31 patients, with an incidence of 0.94% (95% CI: 0.63-1.25). Of the total number of 46 TB + VTE patients, 29 were primarily hospitalized due to tuberculosis and developed symptomatic VTE in the course of hospitalization; 15 were tuberculosis patients undergoing post-discharge outpatient TB treatment whom were admitted with a primary diagnosis of VTE; and the two remaining patients were hospitalized due to VTE and the diagnosis of coexisting tuberculosis was made during hospitalization. Mean length of hospital stay was 28.7 ± 14.0 days. None of the 29 patients with a primary diagnosis of TB had received VTE prophylaxis. Overall, 44 patients had pulmonary TB while 2 had pleural TB. From those with available susceptibility testing, 14 had sensitive results, 12 were culture-negative, and 3 were multi-drug resistant. Smear results were positive for 41 patients. Co-morbidities were not evenly distributed amongst the patients. While some had more than one or two risk factors, the majority of the patients (n = 28) did not have any apparent VTE risk factors (except for TB). Table 1 summarizes background information and co-morbidities.

TB-DVT Subgroup (with or without PE)

From the total of 33 patients with ultrasound-confirmed DVT, 23 had lower extremity pain and 26 patients exhibited pitting edema. Four had neither lower limb pain nor pitting edema. All patients had at least one proximal segment involved (femoral veins in 23 patients, popliteal vein in 22 patients, and other proximal segments in 3 patients). DVT was left-sided in 18, right-sided in 11; and bilateral in 4 patients. 19 DVT patients were also symptomatic for PE. Computed tomography revealed PE in 7 patients (TB + DVT + PE patients).

TB-PE SUBGROUP (with or without DVT)

Twenty patients had PE. Of those, 13 suffered from chest pain while seven did not. Eight patients with PE had hemoptysis while the remaining 12 did not develop hemoptysis.

From the total of 31 patients with in-hospital TB + VTE, four died during the hospital stay. This was significantly (P = 0.02) higher than the mortality rate in a random sample of 420 hospitalized isolated TB patients from NRITLD who had an in-hospital mortality rate of 3.5%. Of the four in-hospital mortalities in TB + VTE patients, one was due to disseminated uncontrolled HIV infection, two were caused by uncontrolled multidrug resistant tuberculosis, while one was due to PE. In-

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hospital mortality was more common in those with multidrug resistant tuberculosis. Of the 29 TB + VTE patients with available data about TB resistance, 3 had multidrug-resistant TB, two of whom died during hospitalization ($p = 0.001$). Four additional patients with TB + VTE died in the follow-up period. By Kaplan-Meier analysis, median survival time was 407 days (95% CI: 269.6- 544.4 days).

Discussion

Our results show that venous thromboembolic events are not rare in hospitalized tuberculosis patients. It is noteworthy that none of the 29 patients hospitalized with a primary diagnosis of tuberculosis alone received thromboprophylaxis. All 29 patients developed VTE in the course of hospitalization.

The Eighth Edition of the American College of Chest Physicians Guidelines on Antithrombotic and Thrombolytic Therapy states: *"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 VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, we recommend thromboprophylaxis with LMWH, LDUH , or fondaparinux"* [6].

Many of our TB patients were hospitalized to receive proper treatment and monitoring under the DOTS (Directly-Observed Treatment Short-course) strategy. [7] The majority were not severely ill or in severe respiratory distress when they were hospitalized and the few co-morbidities reported in our patients, were also unevenly distributed. Nearly half of all reported co-morbidities were found in five patients with multiple risk factors who suffered from symptomatic VTE several weeks post-discharge when they were continuing their outpatient treatment. Tuberculosis can lead to severe respiratory comprise and consequently hospitalization of acutely ill patients. On the other hand, another indication for hospitalization in TB patients is for initiation of anti-TB treatment, in order to observe the response to treatment and closely monitor the anti-tuberculous medications adverse effects. [7] None of our 29 patients with in-hospital VTE were recognized to be critically ill on admission or later during hospitalization and did not manifest with severe respiratory compromise. They were fully ambulatory until they developed VTE, and hence none received thromboprophylaxis before the VTE events. Those who developed VTE in the outpatient setting were also fully ambulatory while they developed symptomatic VTE. We believe that tuberculosis merits further assessment as a risk factor for VTE, even in cases without respiratory compromise that necessitates intensive medical care.

Rate of Venous thromboembolism in our study is lower than that reported in studies of thromboprophylaxis in medical patients, such as MEDENOX, PREVENT and ARTEMIS. [8–10] Patients in those trials had serious cardiorespiratory compromise, or an acute medical condition associated with at least one other coexisting risk factor and underwent routine venography or compression ultrasonography to detect all cases of symptomatic and asymptomatic DVT. Patients in those studies were generally older than our series of cases; however, the incidences of symptomatic VTE in those studies were comparable to our report. In MEDENOX, 10 symptomatic VTE events happened (6 cases of symptomatic DVT and 4 cases of symptomatic PE) during hospitalization which accounts for an incidence of lower than 1% (10/1102). [8] Similarly, in the PREVENT study 27 symptomatic VTE events happened (16 cases of symptomatic DVT and 11 cases of symptomatic PE) which is also below 1 % (27/3706). [9] The ARTEMIS trial, reported five cases of symptomatic VTE (all with fatal pulmonary embolism) among 849 participants. [10] We strongly believe that if routine screening for asymptomatic DVT was performed in our center, we would have found higher rates of VTE, similar to MEDENOX, PREVENT, and ARTEMIS [8–10].

Smeeth et al. reported an incidence of 1.91% (95% CI: 1.49–2.44) for DVT in the first two weeks after an acute respiratory infection. Their patient population were markedly older than our patients; however, and data were not presented about their coexisting transient VTE risk factors, such as bed-rest. [11] Studies evaluating the coexistence of TB and VTE are scant in the literature. The largest is the retrospective report by White from Cape Town, reporting 46 cases of DVT among 1366 adults (3.4%) being treated for tuberculosis. In that study, DVT diagnosis in some cases was not objectively confirmed, and also data were not available regarding other co-morbidities. [12] Authors from the same institute also reported additional 35 cases of DVT and demonstrated a hypercoagulable state among TB patients. [3] Ambrosetti et al. reported an incidence of 0.6% (5 cases of DVT and two cases of PE) among 1237 TB patients from Italy. [5] Other studies have reported smaller numbers of cases regarding this coexistence.

Given the fact that most of the hospitalized patients in our study did not have cardiorespiratory compromise or any other apparent VTE risk factors except for TB while they developed VTE, we believe thromboprophylaxis should be strongly considered in most hospitalized TB patients regardless of the presence of severe respiratory compromise. Future prospective studies can better elucidate this issue. Until then, consideration of thromboprophylaxis is important in most hospitalized TB patients.

Table 1
Background Information and Co-morbid Conditions of Patients with TB and VTE.

Gender	Male		31
	Female		15
Age (years)			53.39 ± 19.58
Nationality	Iranian	Male	29
		Female	8
		Total	37
	Afghan	Male	2
		Female	7
		Total	9
Weight (kg)			55.64 ± 12.62
Primary diagnosis	TB		29
	TB + VTE		15
	VTE		2
Final Diagnosis	TB + DVT		26
	TB + PE		13
	TB + PE + DVT		7
Hospitalization Length	TB + DVT		32.04 ± 13.06
	TB + PE		18 ± 8.21
	TB + PE + DVT		36.83 ± 16.11
	Total		28.62 ± 13.94
	Yes		25
Smoking	No		18
	N/A		3
Opium inhalation	Positive		17
	Negative		19
	N/A		10
IVDU	Yes		2
	No		44
HIV Status	Negative		39
	Positive		3
	Receiving HAART		0
	N/A		4
Co-morbidities	Renal Failure		0
	CVA		5
	HF		1
	COPD		4
	VTE History		5
	Malignancy		1
	Recent Surgery		1
	Family History of Thrombophilia		0
	Paralysis or immobilization		4
	ICU Admission during Hospitalization		3

TB: tuberculosis, VTE: venous thromboembolism, DVT: deep vein thrombosis, PE:pulmonary embolism, N/A: not available, IVDU: intravenous drug use, HIV: human immunodeficiency virus, HAART: highly active anti-retroviral therapy, CVA: cerebrovascular accident, HF: Heart failure, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit.

Our study had some limitations: The retrospective design limited extensive investigation of the patients, including echocardiographic assessment in those with PE. Also, the actual number of VTE events in the cases most possibly exceeds that we reported, partly because screening for asymptomatic VTE is not performed routinely at our center.

NRITLD is a World-Health-Organization collaborating regional referral center for tuberculosis. This report of more than 3,000 tuberculosis patients is considerable and our series of cases is one of the largest about the coexistence of TB and VTE. We suggest that VTE prophylaxis be strongly considered in most hospitalized patients with tuberculosis.

Conflict of Interest

No conflicts of interest to be disclosed.

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