

Original Article



Thromboembolism in *Mycobacterium tuberculosis* Infection: Analysis and Literature Review

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ABSTRACT

Background: Tuberculosis is associated with hypercoagulation; however, there are few reports of cases thromboembolism and tuberculosis at the same time in the real world. The purpose of this study was to report the incidence and clinical course of thromboembolism in patients diagnosed with tuberculosis.

Materials and Methods: We retrospectively analyzed the data of patients who were diagnosed with both tuberculosis and thromboembolism including pulmonary thromboembolism (PTE) or deep vein thrombosis (DVT) at Seoul National University Boramae Medical Center from January 2000 through March 2015.


Results: Among the 7905 tuberculosis patients, 49 (0.6%) exhibited PTE, DVT, or both at or after the time of tuberculosis diagnosis. All patients treated for tuberculosis started with isoniazid, ethambutol, rifampicin, and pyrazinamide. Eight patients were switched to treatment with second-line medication because of resistance or adverse events. About half of the patients (n = 21, 44.7%) had thrombosis at the time of tuberculosis diagnosis. Of 48 patients treated for thromboembolism, 36 received warfarin. A total of 20 patients improved symptom caused by thrombosis, and 10 patients were confirmed cure by image study such as computed tomography or doppler ultrasonography. Eight patients who were treated with warfarin had persistent thrombosis. Five patients (10.2%) experienced major bleeding that required hospitalization. All of these bleeding events were associated with warfarin therapy.

Conclusions: Careful attention to PTE/DVT is needed at the time of diagnosis of tuberculosis and during anti-tuberculosis therapy. Warfarin therapy administered with anti-tuberculosis medication requires frequent monitoring to prevent major bleeding.


Keywords: Tuberculosis; Thromboembolism; Pulmonary embolism; Deep vein thrombosis

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Conflict of Interest

No conflict of interest.

Author Contributions

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INTRODUCTION

Tuberculosis is defined as an infectious disease caused by *Mycobacterium tuberculosis*. It is estimated that one-third of the population worldwide is infected with the tuberculosis pathogen. In the Republic of Korea, the incidence and prevalence of tuberculosis have been reported as 143 and 97 patients per 100,000, respectively [1]. Tuberculosis leads to diverse symptoms and signs according to infected organs. The lungs are involved in approximately 90% of cases, while the gastrointestinal tract, genitourinary tract, lymph nodes, bone, muscle, and central nervous system can also be involved in so-called extrapulmonary tuberculosis. In addition, it is well known that a hypercoagulable state associated with tuberculosis may provoke thromboembolism, and this complication occurs in 0.6–1.0 of patients with tuberculosis [2]. Further, drug interactions may occur between rifampicin, the mainstay of tuberculosis treatment, and warfarin, which is widely used to manage thromboembolism [3]. However, to the best of our knowledge, few cases have been reported about thromboembolism in tuberculosis patients [4–6].

The purpose of this study was to analyze the incidence and clinical course of thromboembolism in patients with tuberculosis.

MATERIALS AND METHODS

1. Patient population

Patients who were diagnosed with tuberculosis at Seoul National University Boramae Medical Center from January 2000 through March 2015 were enrolled in the study. We retrospectively analyzed the data of the patients diagnosed with pulmonary thromboembolism (PTE) or deep vein thrombosis (DVT). Diagnosis of tuberculosis was confirmed by growth of *M. tuberculosis* from specimens such as sputum, fluid collected by bronchoscopy, aspirated pus, and infected-organ biopsy samples. PTE or DVT was diagnosed using imaging modalities such as computed tomography angiography and doppler ultrasonography of the extremities.

Adult patients aged 18 years or older with tuberculosis were included for analysis.

2. Analysis

Demographic information including gender, age at the time of diagnosis, laboratory results, and risk factors for thromboembolism was obtained by searching the electronic medical record system. The recorded laboratory results included parameters associated with coagulation state, such as protein C, protein S, and autoantibodies values. In addition, the treatment history for tuberculosis and PTE/DVT was obtained.

3. Ethics statement

The study protocol was approved by the Institutional Review Board (IRB) of the Seoul National University Boramae Medical Center (IRB no. 26-2015-101). The study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Of the 7,905 patients who were diagnosed with tuberculosis, 49 (0.6%) exhibited PTE or DVT or both at or after the time of tuberculosis diagnosis. The mean age at the time of diagnosis

of tuberculosis was 65.5 (standard deviation, 16.3), and there were 31 male patients (63.3%). Twelve patients had cardiovascular disease and 6 patients had malignancy or stayed under immobilization, respectively. The patients with risk factors for thromboembolism are shown in **Table 1**.

With regard to infection site, 45 of the 49 patients (92.9%) exhibited pulmonary tuberculosis. Of the 49 tuberculosis patients, 47 received anti-tuberculosis medication, including 1 who underwent pneumonectomy after concluding the medical therapy. The precise tuberculosis treatment history was not available for the remaining 2 patients. The 47 treated patients all started treatment with isoniazid (H), ethambutol (E), rifampicin (R), and pyrazinamide (Z) (HERZ), but 8 of these patients were changed to a different regimen because of resistance (N = 5) or toxicity (N = 3). Most patients (63.3%) treated with medication were cured. Seventeen patients were not evaluated for the response to tuberculosis treatment; of these, 8 died during the treatment of tuberculosis and PTE/DVT (**Table 1**).

Among the 49 patients, 21 had PTE alone, 13 had DVT alone, and the remaining 15 had both PTE and DVT (**Fig. 1**). Twenty-one patients (42.3%) exhibited PTE/DVT at the time of diagnosis with tuberculosis. In most patients (n = 36, 76.6%), thromboembolism was treated with low molecular weight heparin (LMWH) followed by warfarin. Treatment with LMWH

Table 1. Baseline characteristics

	Patients (N = 49)
Age (mean ± standard deviation)	65.5 ± 16.3
Gender	
Male	31 (63.3 %)
Female	18 (36.7 %)
BMI (kg/m ²)	
<18.5	17 (34.7%)
18.5 ≤ BMI <22.9	17 (34.7%)
23 ≤ BMI <24.9	3 (6.1%)
25 ≤ BMI	8 (16.3%)
Not applicable	4 (8.2%)
Risk factor	
Major surgery	2
Immobilization	6
Malignancy	6
Cardiovascular disease	12
Cerebrovascular disease	4
Chronic alcoholics	4
COPD/asthma	5
No comorbidity	8
Infection site	
Pulmonary Tb	45
Extrapulmonary Tb	4
Tb treatment	
Yes	47
No	2
Anti-Tb medication regimen	
HERZ	39
2nd line therapy	8
Unknown	2
Response to anti-Tb medication	
Cured	31
Failed	1
Not evaluated	17

BMI, body mass index; COPD, chronic obstructive pulmonary disease; Tb, tuberculosis; HERZ, isoniazid (H), ethambutol (E), rifampin (R), pyrazinamide (Z).

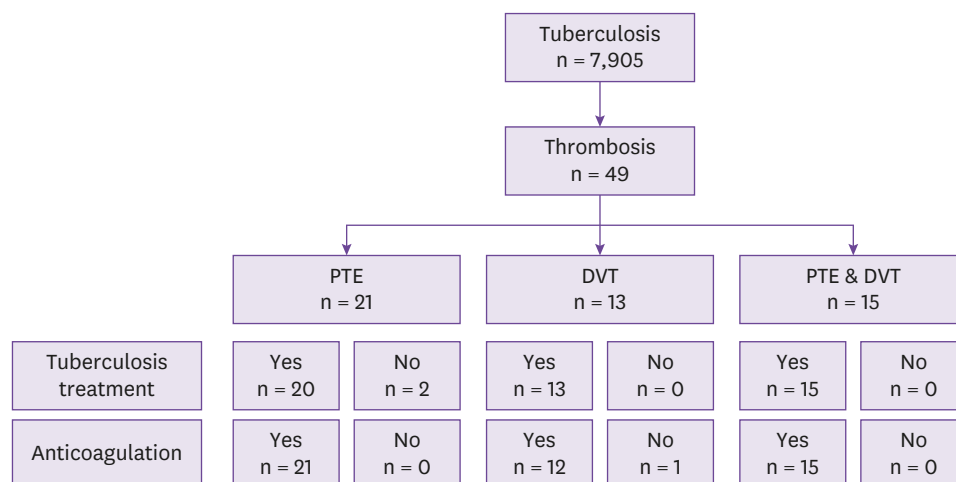


Figure 1. Pulmonary thromboembolism/deep vein thrombosis incidence of tuberculosis and treatment. The incidence of PTE/DVT and treatment pattern of tuberculosis and thromboembolism was visualized in this figure. PTE, pulmonary thromboembolism; DVT, deep vein thrombosis.

alone or novel oral anticoagulant (NOAC) agents was used in an equal but smaller number of patients. During treatment, 5 out of 8 patients were experienced major bleeding. Major bleeding was defined as bleeding requiring hospitalization. There are severe hemorrhagic manifestations such as hemoperitoneum (N = 1), hematuria (N = 1), hemoptysis (N = 2), and subdural hemorrhage (N = 1). All of these major bleeding events were associated with warfarin use, and 3 of these patients had both PTE and DVT. A total of 10 patients were confirmed cure by image study such as CT or Doppler ultrasonography and another 10

Table 2. Treatment of pulmonary thromboembolism/deep vein thrombosis

	Patient (N=49)	Percent (%)
Location of thromboembolism		
PTE	21	42.9
DVT	13	26.5
Both	15	30.6
Diagnosis time of PTE/DVT		
At diagnosis of Tb	21	44.7
During treatment	17	36.2
After treatment	9	19.1
PTE/DVT treatment		
Yes	48	98.0
No	1	2.0
Management of PTE/DVT		
Warfarin	36	72.5
LMWH	6	12.2
NOAC	6	12.2
Intervention + medical treatment	6	
Response to treatment		
Cure (image confirm)	10	24.4
Clinically improved symptom	10	24.4
Chronic state	8	19.5
No evaluation	13	31.7
Bleeding complication		
None	41	83.7
Minor bleeding	3	6.1
Major bleeding	5	10.2

PTE, pulmonary thromboembolism; DVT, deep vein thrombosis; Tb, tuberculosis; LMWH, low molecular weight heparin; NOAC, novel oral anticoagulant.

patients improved symptom clinically. Eight patients who were treated with warfarin had chronic thrombus (Table 2).

The parameters associated with coagulation state, including D-dimer, protein C, protein S, fibrinogen, antithrombin III, anti-cardiolipin antibody, lupus anticoagulant, rheumatoid factor, and anti-nuclear antibody values, were examined in the 49 patients. There was no difference among patients with PTE, DVT, and both PTE and DVT in the values of these parameters, except for rheumatoid factor (Table 3). Three out of the 8 patients with persistent thromboembolism in spite of anticoagulation treatment showed hyperfibrinogenemia before treatment.

Table 3. Factors related to coagulation by thrombosis site

	PTE (N = 21)	DVT (N = 13)	Both (N = 15)	Total (N = 49)
D-dimer				
Normal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Increased	10 (47.6%)	5 (38.5%)	8 (53.3%)	23 (46.9%)
NA	11 (52.4%)	8 (61.5%)	7 (46.7%)	26 (53.1%)
Platelet				
Normal	11 (52.4%)	12 (92.3%)	10 (66.7%)	33 (67.3%)
Increased	7 (33.3%)	0 (0.0%)	2 (13.3%)	9 (18.4%)
NA	3 (14.3%)	1 (7.7%)	3 (20.0%)	7 (14.3%)
Fibrinogen				
Normal	3 (14.3%)	5 (38.5%)	2 (13.3%)	10 (20.4%)
Increased	7 (33.3%)	5 (38.5%)	7 (46.7%)	19 (38.8%)
NA	11 (52.4%)	3 (23.1%)	6 (40.0%)	20 (40.8%)
Protein C activity				
Decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Normal	4 (19.0%)	5 (38.5%)	5 (33.3%)	14 (28.5%)
NA	17 (81.0%)	8 (61.5%)	10 (66.7%)	35 (71.4%)
Protein S activity				
Decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Normal	4 (19.0%)	5 (38.5%)	5 (33.3%)	14 (28.5%)
NA	17 (81.0%)	8 (61.5%)	10 (66.7%)	35 (71.4%)
AT III				
Decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Normal	3 (14.3%)	6 (46.2%)	5 (33.3%)	14 (28.6%)
NA	18 (85.7%)	7 (53.8%)	10 (66.7%)	35 (71.4%)
ACA IgM				
Negative	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Positive	1 (4.8%)	0 (0.0%)	1 (6.7%)	2 (4.1%)
NA	20 (95.2%)	13 (100.0%)	14 (93.3%)	47 (95.9%)
LAC				
Negative	3 (14.3%)	1 (7.7%)	0 (0.0%)	4 (8.2%)
Positive	0 (0.0%)	4 (30.8%)	4 (26.7%)	8 (16.3%)
NA	18 (85.7%)	8 (61.5%)	11 (73.3%)	37 (75.5%)
RF				
Negative	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Positive	1 (4.8%)	6 (46.2%)	0 (0.0%)	7 (14.3%)
NA	20 (95.2%)	7 (53.8%)	15 (100.0%)	42 (85.7%)
ANA				
Negative	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Positive	1 (4.8%)	3 (23.1%)	0 (0.0%)	4 (8.2%)
NA	20 (95.2%)	10 (76.9%)	15 (100.0%)	45 (91.8%)
RPR				
Negative	1 (4.8%)	1 (7.7%)	0 (0.0%)	2 (4.1%)
Positive	16 (76.2%)	12 (92.3%)	12 (80.0%)	40 (81.6%)
NA	4 (19.0%)	0 (0.0%)	3 (20.0%)	7 (14.3%)

PTE, pulmonary thromboembolism; DVT, deep vein thrombosis, NA, not available; AT III, antithrombin III; ACA, anti-cardiolipin antibody; LAC, lupus anticoagulant; RF, rheumatoid factor; ANA, anti-nuclear antibody; RPR, rapid plasma reagin test.

DISCUSSION

This retrospective study investigated the incidence of PTE/DVT in patients diagnosed with tuberculosis at a single institution, together with the therapeutic regimens, responses to treatment, and treatment complications. This incidence of thromboembolism is higher than that in the general population of approximately 0.1% [7]. Thus, patients with tuberculosis are predisposed to the development of thromboembolism, and careful monitoring and appropriate treatment for thromboembolism are required in these patients.

Inflammation activates the coagulation cascade while decreasing the activity of the anti-coagulant mechanism [8]. Inflammation in the lower respiratory tract leads to fibrin deposition - a hallmark of conditions such as pneumonia and acute respiratory distress syndrome - and resultant pulmonary and systemic thrombin generation [9, 10]. This phenomenon is thought to occur also in tuberculosis, and analysis of laboratory test results has revealed elevated fibrinogen and fibrin degradation product levels due to impaired fibrinolysis and decreased anti-thrombin III levels in these cases. In addition, the hypercoagulable state persists for 2 weeks after the initiation of anti-tuberculosis medication and improves while continuing the treatment [11-13]. The high incidence of PTE/DVT in this study is consistent with previous studies showing that inflammation caused by tuberculosis infection causes hypercoagulability resulting in thromboembolism.

The standard treatment for tuberculosis has been 2 months of HERZ followed by 4 months of HER maintenance [14], and most patients of this study are treated initially with HERZ according to current guidelines. However, resistance has been encountered recently to certain anti-tuberculosis medications, particularly isoniazid and rifampicin. In this study, the therapeutic regimen had to be changed in 5 patients because of resistance; 3 patients showed resistance to isoniazid and 2 to isoniazid and rifampicin.

It is interesting that previous research has suggested a possible association between rifampicin use and thromboembolic complications [15]. In this study, approximately 65% of patients were diagnosed with PTE/DVT at the same time as the tuberculosis diagnosis or during treatment. Thus, thromboembolic complications may be due to tuberculosis itself or certain treatment agents including rifampicin. All treated patients took rifampicin for at least 2 weeks.

Although most patients receive warfarin to control PTE/DVT, administration of NOAC agents has been increasing recently. NOAC agents have been shown to possess similar efficacy and safety to warfarin in thromboembolism prevention and treatment [16, 17]. This shift toward NOAC use is expected to increase in tuberculosis patients with PTE/DVT because of the interaction between warfarin and rifampicin. Rifampicin acts as a non-specific inducer of hepatic cytochrome P450 and thereby affects the metabolism of multiple drugs. The metabolism of warfarin increases in the presence of rifampicin, and the dose of warfarin sometimes has to be increased to more than double the recommended level [18, 19]. Careful monitoring of prothrombin time is necessary to monitor bleeding risk in cases of co-administration of rifampicin and warfarin. Although massive bleeding requiring hospitalization or intervention occurred in only about 10% of the patients in this study, this could be a major factor in the decision to discontinue treatment of tuberculosis or thromboembolism. All the patients with bleeding were treated with warfarin. Although warfarin is very effective for treating thromboembolism, bleeding is common and sometimes fatal. For this reason, NOAC

agents or LMWH may be worth considering for control of PTE/DVT in patients receiving anti-tuberculosis medication. However, caution is also needed when using NOAC agents in patients receiving anti-tuberculosis medication, because rifampicin is a CYP3A4 and P-glycoprotein/ABCB1 inducer, and could lead to decreased serum concentration of NOAC agents such as rivaroxaban, apixaban, and dabigatran. In this study, 4 of 5 patients with major bleeding had pulmonary tuberculosis; however, serious bleeding occurred in other sites such as the abdomen and brain, and not the lung. For this reason, full physical examination should be carried out to monitor for bleeding not only in the diseased site but the whole body.

The risk factor of thromboembolism such as old age, obesity, malignancy, major surgery and bedridden state is well-known [20, 21]. In this study, we evaluate the risk factor of thromboembolism. Median age of this study was 65 years old and the patients of 83.7% had one or more risk factors. This may have affected the increased incidence of thromboembolism compared to the general population.

Our study had some limitations. The patient sample was small and comprised a single-center cohort. Also, this study was retrospective study not prospective observational study. Although Korea has a relatively high incidence of tuberculosis, the incidence of tuberculosis is decreasing due to improvement of hygiene environment and nutrition. Thromboembolism is reported to occur acutely within 2 weeks after the administration of the anti-Tb medication, however, long term follow-up is necessary due to it occurs chronically, also. For this reason, it was difficult to conduct prospective studies. Nonetheless, this study has value in providing well-described information about tuberculosis patients diagnosed with PTE/DVT.

In conclusion, tuberculosis patients exhibit PTE/DVT more than do the general population due to a hypercoagulable state likely associated with the tuberculosis infection. Careful monitoring for PTE/DVT is needed at the time of tuberculosis diagnosis and during anti-tuberculosis therapy.

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