*International Journal of Medicine*, 12 (1) (202) 1-3

**International Journal of Medicine**

*Website: www.sciencepubco.com/index.php/IJM*

***Research paper***

# Pulmonary tuberculosis and venous thromboembolism

**Faouzia Kambouche [1] *, Labdouni Mohamed El Habib [2]**

[1] *Department of Pulmonology, university hospital center of Mostaganem, faculty of medicine of Mostaganem -Algeria*
[2] *Department of infectious diseases, university hospital center of Oran, faculty of medicine of Oran- Algeria*
**Corresponding author E-mail: ryadouzlifi@yahoo.fr*

## Abstract

***Context:***
Acute infections are among the risk factors for venous thromboembolism (VTE). The role of chronic infections such as active tuberculosis is poorly defined, although several case reports and case series have suggested a link association between tuberculosis and VTE. The unexpected resurgence of tuberculosis (TB) in developed countries provided the rationale for evaluating VTE as a possible complication of TB; never theless, the topic has received little attention in the literature.
***Patient and Method:*** This is a prospective multicenter study done between January 2016 and January 2018. It is about 17 cases of confirmed pulmonary tuberculosis associated with deep vein thrombosis.
***Results:*** It is about fifteen men and two women, their average age is 44,88 years. The thromboembolic complication revealed tuberculosis among 2patients, appearing during the hospitalization of 15 patients among which 11of them receiving antituberculosis drug. We have listed 3 cases of immediate pulmonary embolism and 14cases of deep vein thrombosis complicated with pulmonary embolism in 7 cases. These patients received anti-tuberculosis treatment according to the 2RHZE / 4RH protocol and a curative anticoagulant treatment based on low molecular weight heparin. A relay by vitamin K antagonists was instituted after a satisfactory INR control. The average time to effective anticoagulation was 15.12 days with extremes between 08 and 50 days.
There was favorable evolution among 14 patients, 1of them was lost to follow-up. Sight and the evolution has been fatal in two case.
***Conclusion:*** Thromboembolic (DVT) disease must be sought systematically in the TB patients because of the risk of this complication particularly in extensive and severe forms. Prophylactic anticoagulation therapy finds its indications in these forms.

***Keywords***: *Pulmonary Tuberculosis; Venous Thromboembolism; Pulmonary Embolism.*

## 1. Introduction

Tuberculosis continues to cause significant morbidity and mortality in developing countries, and remains a public health problem. Tuberculosis has been described as a risk factor for thromboembolic complications. Thromboembolic complications are generally secondary to hypercoagulability and prolonged bed rest in bedridden patients. The coexistence of thromboembolic disease and tuberculosis is uncommon, but remains frightening. However, it has been reported in the literature in 1.5% to 3.4% of cases [1,2]. While the association of venous thrombosis and tuberculosis has sometimes been described, the association of arterial thrombosis appears to be very rare. The aim of this study was to investigate the pathophysiological, clinical and therapeutic features of thromboembolic events complicating pulmonary tuberculosis.

## 2. Patients and methods

This was a prospective multicenter study done between January 2016 and January 2018. It focused on the records of patients hospitalized for pulmonary tuberculosis complicated by Thromboembolic disease. Patients with obvious risk factors for thrombosis [3] were not included.
We recorded 17 cases of thromboembolic disease (VTE) associated with pulmonary tuberculosis admitted during this period. 07 cases were exclusively deep-vein thrombosis (DVT) of the lower limbs, 07 cases were deep-vein thrombosis of the lower limbs complicated by pulmonary embolism and 03 cases were exclusively pulmonary embolism (PE). The median age was 44.88 years, with a sex ratio of 2 women to 15 men. No estrogen-progestin was found in any of the women.
Clinically, symptomatology was dominated in all our patients by an altered general condition, productive cough, fever and paleness of the mucous membranes. The thromboembolic event was deep vein thrombosis of the lower limbs. This was confirmed by venous Doppler

**Copyright © Faouzia Kambouche, Labdouni Mohamed El Habib. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**

ultrasound of the lower limbs. Pulmonary tuberculosis was confirmed by the presence of acid-fast bacilli on direct sputum examination in 13 patients. In 7 patients, the thromboembolic event occurred on the fourth day and 10 days respectively after initiation of anti-tuberculosis treatment. The diagnosis of thromboembolic disease preceded that of tuberculosis in 2 cases.
Biological investigations revealed a median haemoglobin level of 6.75g/dl. Sedimentation rate (ESR) and CRP values were elevated in all our patients. All HIV retroviral serologies were negative. Due to a lack of resources, the patients did not benefit from immunological testing for anti-phospholipid antibodies or anti-protein S antibodies. In one case, Biermer's disease was identified, with a collapse in serum vitamin B12 levels and a defect in intrinsic factor secretion.
Venous Doppler ultrasound showed expansive thrombophlebitis of the left popliteal and sural veins (1 case), expansive thrombosis of the superficial femoral, popliteal and right sural veins (1 case), and left sural thrombosis (1 case).
All our patients received supervised anti-tuberculosis treatment according to the national standard protocol: combination of Rifampicin (R), Isoniazid (H), Pyrazinamide (Z), Ethambutol (E) for 2 months, followed by Rifampicin and Isoniazid for 4 months.
As a result, curative anticoagulant treatment with low-molecular-weight heparin (Enoxaparin sodium) was initiated at a dosage of 100 IU/Kg morning and evening subcutaneously. Antivitamin K treatment was started concomitantly with low-molecular-weight heparin at a dose of 1 tablet per day. Relief with antivitamin K alone (Acenocoumarol) was maintained after satisfactory INR control (between 2 and 3).
Immediate evolution was favorable in 15 patients, with complete regression of swelling in the lower limbs and improvement in general condition 03 weeks after initiation of anticoagulant treatment. On the other hand, the evolution was unfavorable, with death occurring 1 week after initiation of anti-tuberculosis treatment in 2 cases. However, we encountered some difficulties in achieving a good PT/INR balance in these two patients, probably due to the concomitant use of Rifampicin.

## 3. Discussion

Infectious processes can disrupt the hemostatic balance through multiple mechanisms [4]. Respiratory infections, notably tuberculosis, have been described as a risk factor for thromboembolic complications. These are secondary to several mechanisms inducing a state of hypercoagulability [5].
The association between thromboembolic disease and tuberculosis (TB) is uncommon, but remains formidable. However, several studies have demonstrated this association [6,7]. In Senegal, Toure [8] and Fall [9] each reported 6 cases in their series. Deep vein thrombosis is seen in 3% to 4% of patients with pulmonary tuberculosis [6, 9,10]. However, this incidence is probably underestimated, since it is unrecognized in 2/3 of cases [11]. In our study, we identified 17 cases of venous thromboembolism among patients hospitalized for tuberculosis pulmonary tuberculosis. This complication occurred on average 10 days after initiation of anti-tuberculosis treatment in 05 patients.
Venous thromboembolism is generally caused by hyperfibrinemia (in our series, all patients had elevated CRP levels), direct endothelial damage by BAAR and also to rifampicin treatment. Thus, hypercoagulability is attributed to various more or less associated factors: the biological inflammatory syndrome, haemostasis disorders (protein C deficiency, protein S deficiency, antithrombin III deficiency) and chronic hypoxia.
Disseminated tuberculosis can induce mononuclear cell activation in the peripheral blood, and the interaction of these activated cells with mycobacterial products induces increased synthesis of tumor necrosis factor-alpha and interleukin-6 [12].
Various studies have concluded that elevated plasma fibrinogen levels, with impaired fibrinolysis associated with decreased thrombin III, protein C and platelet aggregation, appear to induce this state of hypercoagulability favoring the development of thromboembolic in pulmonary tuberculosis [1, 10,11].
Autoimmune phenomena may also explain coagulation abnormalities through the production of antibodies with thrombogenic properties (anti-phospholipid bodies or anti-protein S antibodies) [13]. However, some authors have mentioned the high frequency of antiphospholipid antibodies detected in tuberculosis, and the possible relationship between these and protein S. Although studies on prothrombin activity in tuberculosis are not numerous, it seems that hypoprothrombinemia rather than prothrombin hyperactivity exists in an appreciable number of cases. Various studies indicate that prothrombin deficiency occurs in around one-third of patients with tuberculosis [1,14].
The pro-inflammatory nature of cytokines activates the vascular intima and renders the endothelium thrombogenic. They also stimulate hepatic synthesis of coagulation proteins [12]. These risks of hypercoagulability are increased by immobility and bed rest, due to the morbidity caused by the disease.
Although several factors are incriminated, the pathophysiology of thromboembolic disease in tuberculosis has not been fully elucidated.
The therapeutic management of this association is complicated by interactions between anti-vitamin K-type anticoagulants (AVK) and anti-tuberculosis drugs, particularly rifampin. Rifampicin is a powerful cytochrome P450 enzyme inducer. Induction of cytochrome P450 isoenzymes (CYP2C9, 2C19, 1A2 and 3A4) would therefore lead to increased degradation of administered anticoagulants and a significant reduction in their activity.
their activity. Another mechanism may be involved: induction of P-glycoprotein by rifampin, leading to reduced concentrations of associated drugs [17].
Drug interactions lead to a reduction in anticoagulant efficacy. As a result, they are responsible for difficulties in maintaining proper PT/INR balance, as well as prolonged hospitalization [11], as in the case of our two deceased patients. To manage the consequences of this interaction in two patients, it was decided to discontinue anticoagulant therapy and continue treatment with low-molecular-weight heparin.
Thromboembolic events in the medical setting vary according to the nature of the acute medical condition involved. This association raises a number of questions for clinicians: should thromboembolic disease be suspected in patients hospitalized with bacilliferous pulmonary tuberculosis? Is it possible to systematically propose preventive anticoagulation to avoid this risk? However, in many medical circumstances, and particularly in pneumology, the value of prophylaxis does not appear to be established [18].
According to the results of a case-control study of venous thromboembolic risk in the aftermath of acute respiratory infectious disease [19], this risk appears to double in the first few weeks, then gradually decrease, returning to baseline one year after the infectious episode.

## 4. Conclusion

The association of pulmonary tuberculosis and thromboembolic disease is rare, but remains formidable. It would be important to implement appropriate prophylaxis strategies to avoid its occurrence in patients hospitalized for severe pulmonary tuberculosis, especially when risk factors are present.

## References


[1] Irene M., Mackman N., Kriett J. et al Prothrombotic activation of pulmonary arterial endothelial cells in patient with tuberculosis.Hum Pathol. 1996, 27:423-27. https://doi.org/10.1016/S0046-8177(96)90118-5.

[2] Fekih L., Oueslati I., Fenniche S. et al Association of deep vein thrombosis with pulmonary tuberculosis.Tunis Med. 2009, 87(5):328-9.

[3] Delluc A., Le Ven F., Mottier D. et al Epidemiology and risk factors of throm-boembolic venous disease Journal of Respiratory Diseases, 2012, 29: 254-266. https://doi.org/10.1016/j.rmr.2011.12.001.

[4] Fourrier F. Hemostasis disorders and serious infectious conditions. Med Infection Diseases, 2006, 36:524-33. https://doi.org/10.1016/j.med-mal.2006.10.003.

[5] Sezer M, Ozturk A, Ilvan A et al The hemostatic changes in active pulmonary tuberculosis.Turkish Journal of Haematology, 2001, 18:95-100.

[6] Boukhris I., Bouslama K., Abdallah M. et al Deep vein thrombosis revealing tuberculosis. Rheumatology review,, 2006, 73:1118-9. https://doi.org/10.1016/j.rhum.2006.10.249.

[7] Schitrit D., Preiss R., Bargil-Shitrit et al Incidence of venous thromboembolism in 474 patients with acute tuberculosis Am J Respir Crit Care Med, 2004, 169: 135-138.

[8] Toure N.O., Kane Y.D., Diatta A. et al Tuberculosis and thrombophlebitis of the lower limbs Journal of Respiratory Diseases 2007, 24: 126. https://doi.org/10.1016/S0761-8425(07)72789-4.

[9] Fall K.B, Camara P., Sane M. et al Tuberculosis and thromboembolic disease: a dangerous link not always apparent Trop Med, 2004, 64 : 271-274.

[10] Gogna A., Pradhan GR., Sinha RSH. et al Tuberculosis presenting as deep vein thrombosis Postgrad Med J, 1999, 75: 104-106. https://doi.org/10.1136/pgmj.75.880.104.

[11] Naithani R., Agrawa N., Choudhary VP et al Deep venous thrombosis associated with tuberculosis Blood Coagul Fibrinolysis, 2007, 18: 377-380. https://doi.org/10.1097/MBC.0b013e3280d942b4.

[12] Mark PL, Ashok PP, Deshpande RB et al A patient with hypercoagulable state due to tuberculosis. Indian J Chest Dis Allied Sci, 2009, 51(1):49-51. This article on PubMed.

[13] Nou M. Rodiere M. Schved J.F. et al Infections and venous thrombosis in pediatrics: analysis of a series of 24 cases Pediatric Archives, 2014, 21:697-704. https://doi.org/10.1016/j.arcped.2014.04.031.

[14] Turken O., Kunter E., Sezrz M., et al Hemostatic changes in active pulmonary tuberculosis. Int J Tuberc Lung Dis, 2002, 6(10):927-32. This article on PubMed

[15] Bourguignon L., Golfier L., Chatillon F. et al. Interaction between acenocoumarol and rifampicin: case report and pharmacokinetic mechanisms involved, Journal of Clinical Pharmacy 2006, 25(2): 105-109.

[16] Aissa I., Rachdi I., Ben Miled K. et al. Incidence of venous thromboembolic disease in men admitted to a pulmonology department for acute respiratory disease. Journal of Clinical Pneumology, 2011, 67: 129-135. https://doi.org/10.1016/j.pneumo.2010.04.003.

[17] Smeeth L, Cook C, Thomas S. et al Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet, 2006, 367:1075-9. https://doi.org/10.1016/S0140-6736(06)68474-2.