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Thromboembolic Disease during Tuberculosis

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Abstract

Tuberculosis remains a significant public health issue, an infectious disease that can cause hypercoagulability responsible for thromboembolic complications. We report a retrospective descriptive study involving 39 patients with active TB combination and confirmed venous thromboembolic disease with pulmonary embolism or deep venous thrombosis. It is about 24 men and 15 women. The mean age for both sexes was 42. Ten patients had a history of pulmonary tuberculosis. Thromboembolic disease was discovered during tuberculosis in 30 cases while it was indicative of tuberculosis in 9 patients. There are 31 cases of pulmonary tuberculosis and 8 cases of extrapulmonary tuberculosis including 4 cases of pleural tuberculosis, 2 cases of peritoneal tuberculosis, 1 case of lymph node tuberculosis and 1 case of tuberculosis meningitis. Pulmonary tuberculosis was confirmed by direct examination of sputum in 22 cases and GeneXpert in 9 cases. Extrapulmonary tuberculosis cases were confirmed by direct examination in 6 cases, GeneXpert in 2 cases and histology in 2 others. All patients received antibacillary treatment. Venous thromboembolism occurs on average 17 days after the onset of tuberculosis. It is revealed by clinical signs and elevated plasma D-dimers. Venous thromboembolism is confirmed by echo-Doppler or thoracic angioscanner. There are 20 cases of pulmonary embolism, 16 cases of deep venous thrombosis and 3 cases of phlebitis and pulmonary embolism. Cases of deep vein thrombosis include 13 locations in the lower limbs and 4 in the upper limb. During hospitalization, all patients were in the attack phase of anti-bacillary treatment and one patient was in the maintenance phase. The treatment was exclusively medical, based on: antivitamin K combined with low molecular weight heparin in 33 cases and in 6 cases new oral anticoagulants are prescribed.

Keywords: Tuberculosis; Thromboembolic disease; Pulmonary embolism; Deep vein thrombosis

Introduction

Tuberculosis remains a significant public health issue, an infectious disease that can cause hypercoagulability responsible for thromboembolic complications with prevalence between 0.6% and 3.9% [1]. Pulmonary Embolism (PE) and Deep Vein Thrombosis (DVT) are two clinical presentations of Venous Thromboembolic Disease (VTE) and share the same predisposing factors. PE is most often (70%) secondary to PST. We report a descriptive study involving 39 patients with active tuberculosis and VTE combination.

Materials and Methods

This is a retrospective descriptive study conducted at the Department of Pneumophtisiology of the Moulay Youssef Hospital of Rabat between January 2015 and August 2019 including 39 patients with a combination of active tuberculosis, and thromboembolic disease confirmed type of pulmonary embolism or deep vein thrombosis.

Results

It is about 24 men and 15 women. The mean age for both sexes was 42 years. The smoking patients in our series accounted for 41%. Ten patients had a history of pulmonary tuberculosis. Thromboembolic disease was discovered during tuberculosis in 30 cases while it was indicative of tuberculosis in 9 patients. There are 31 cases of pulmonary tuberculosis and 8 cases of extrapulmonary tuberculosis including 4 cases of pleural tuberculosis, 2 cases of peritoneal tuberculosis, 1 case of lymph node tuberculosis and 1 case of tuberculosis meningitis (Table 1). Pulmonary tuberculosis was confirmed by direct examination of sputum in 22 cases and GeneXpert in 9 cases. Pulmonary tuberculosis was confirmed by direct examination of sputum in 18 cases, and by GeneXpert in 4 cases. Extrapulmonary tuberculosis cases were confirmed by direct examination in 6 cases, GeneXpert in 2 cases and histology in 2 others.

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Table 1: Number of extra pulmonary tuberculosis cases associated with VTE.

Type	Pulmonary tuberculosis	Pleural tuberculosis	Ganglionic tuberculosis	Tuberculosis meningitis	Peritoneal tuberculosis
Number of cases	31	4	1	1	2

Table 2: Characteristics of VTE during tuberculosis disease.

	kuissmi et al. [5] n=30	Ben Amar net al. [1] n=15	Our study
The median delay of the diagnosis	7 days	9.73 days	17 days
Pulmonary Tuberculosis (PT)/Extrapulmonary Tuberculosis (Extra-PT)	PT=30	PT=6 *vs.* Extra-PT=3	PT =69% *vs.* Extra-Pt=31%
Type VTE	DVT=30n	PE=6n	EP =20n
		DVT=9n	DVT =16n
			PE+DVT=3n

All patients received anti-bacillary treatment. Venous thromboembolism occurs on average 17 days after the onset of tuberculosis. In our study, besides the general signs dominated by alteration of the general state and fever followed by weight loss, the clinical signs of venous thromboembolism are typical, dominated by dyspnea in 75% of cases associated with chest pain for PE cases and limb edema (61%), limb pain or Homans sign for DVT. This clinical context was a plasmatic-dimer elevation in all cases of our series. VTE is confirmed by echo-Doppler for all DVT cases and chest angioscanner for pulmonary embolism. There are 20 cases of pulmonary embolism, 16 cases of deep vein thrombosis and 3 cases of phlebitis and pulmonary embolism (Figure 1). Cases of deep vein thrombosis include 13 locations in the lower limb and 4 in the upper limb. During the hospitalization period, patients were most often (97%) in the phase of initial treatment with quadruple therapy (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol) and one patient (3%) in the maintenance phase (Rifampicin and Isoniazid). The anticoagulant treatment was exclusively medical, based on: Anti-Vitamin K (AVK) combined with Low Molecular Weight Heparin (LMWH): 33 cases. An effective anti-coagulation is achieved in 38 days on average with extremes between 14 and 51 days except for a case that left the service against medical advice and a patient who died before balancing oral treatment. The new oral anticoagulants (Xarelto at the dose of 20 mg/d, Pradaxa at the dose of 300 mg/d) was proposed for an average duration of 3 months in 6 patients of our series. The trend was favorable for 31% of the cases, especially in which, in addition to the measures adopted, a specialist consultation check was carried out (INR check, echo-Doppler). In 16% of cases, a complication occurred; two cases of IMD phlebitis, one case of IBV thrombus, a recurrence of deep vein thrombosis and one case of persistence of DVT. Fifty three percent of patients are referred in consultation to the CDTMR (Center for Diagnosis and Treatment of Tuberculosis and Respiratory Diseases) for the follow-up of venous thromboembolic disease.

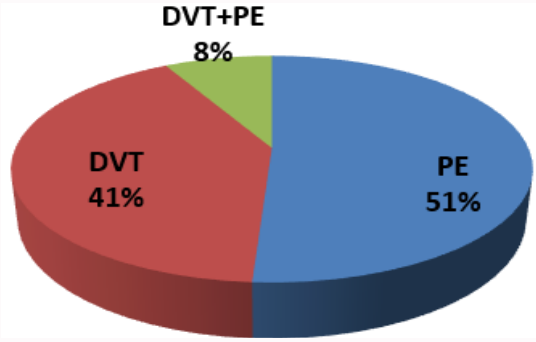

Figure 1: VTE in tuberculosis.

Discussion

Tuberculosis is considered to be a risk factor for thromboembolic venous disease, with a prevalence of VTE between 0.6% and 3.9%. It is associated with a state of hypercoagulability responsible for potentially fatal thromboembolic accidents [1]. In our study 1.6% of hospitalized TB patients have thromboembolic venous disease.

Data from the literature remain controversial regarding the role of rifampin in the genesis of EVTE. Studies have demonstrated possible association between DVT and use of Rifampicin with a relative risk of 4.74 in patients treated with rifampicin containing regimens [2]. Raschilas et al. [3] conducted a study of hemostasis in 10 patients hospitalized with TBC, before and one month after starting TB treatment including rifampin. It concluded that no abnormalities were found to explain the increase in the incidence of DVT reported with the use of rifampin, including no acquired resistance to protein C as described with oral contraceptives.

Our study population shows a slight male predominance (57%) and 52% of TB patients with thromboembolic venous disease are between the ages of 25 years and 34 years for both sexes. This distribution is close to that of tuberculosis in the General population (64% of cases of tuberculosis reported in Morocco during 2017 belong to the age group between 15 years and 34 years with a male predominance and a sex ratio of 1.5 [4]). In the literature it is found that Ben et al. [1] stated that the population studied in their series was predominantly male (62%) with a higher frequency in the age group between 20 years and 40 years (62%). Also, Kouismi et al. [5] found a large male predominance in the study sample (70%) and the average age was 45 years.

According to another study by Tachfouti et al. [6] in 2011, exposure to tobacco smoke increases susceptibility to respiratory tract infections, including TB. Smoking increases susceptibility to bacillary TB in a dose-dependent manner. Smoking negatively affects the clinical manifestations of tuberculosis and the disease progresses more rapidly among smokers than among non-smokers. Smoking is also associated with increased relapse and accounts for 12% of all TB deaths [6]. The smoking patients in our study accounted for 41% of the sample studied, which leads us to conclude that smoking would be a major risk factor in the development of thromboembolic disease in tuberculosis. Thromboembolic disease appears on average 17 days after the diagnosis of tuberculosis and the start of anti-bacillary

treatment. In the study conducted by Kouismi et al. [5] the onset of DVT occurs in an average of 7 days, whereas in the series of Ben et al. [1] it is found that the occurrence of the thromboembolic accident compared to the initiation of anti-tuberculosis treatment was within an average time of 9,73 days (Table 2).

Lung damage is by far the most common location of reported tuberculosis in the world. But in Morocco, pulmonary tuberculosis accounts for only 52% of all forms of tuberculosis [7]. Thromboembolic complications have been reported with different locations, pulmonary or extra-pulmonary. In our work, the location of tuberculosis was pulmonary in 69% of cases. This rate is slightly higher than that of pulmonary tuberculosis (52%) in Morocco.

The clinical signs of DVT are typically characterized by edema of the peripheral limbs, which can be falsely attributed to hypoproteinemia in patients with tuberculosis or a side effect of isoniazid. Pain and increased limb temperature are important signs that help in the diagnosis of DVT [8]. While PE is suspected in dyspnea, chest pain, syncope, inconstamely associated. In our study, besides the general signs dominated by alteration of the general state and fever followed by weight loss, the clinical signs of VTE are typical, dominated by dyspnea in 75% of cases associated with chest pain for PE cases and limb edema (61%), limb pain or Homans sign for DVT. The D-dimers assay is used primarily to exclude the diagnosis of VTE in patients with a low or intermediate clinical probability score [9], if it finds a DVT with suggestive signs of pulmonary embolism, the diagnosis of PE is made. In our series, no cases of pulmonary embolism have been confirmed by Doppler ultrasound. The Thoracic Angioscanner is the most commonly used exam for PE with excellent sensitivity and specificity up to segmental or sub-segmental arteries. A negative pulmonary angioscan excludes PE in patients with a low or intermediate probability score [9]. The detection of sub-segmental thrombus in a patient without DVT calls into question the diagnosis and the need for anticoagulant treatment. In our series, after the D-dimers were found to be positive, 23 angioscanners were performed and all came back positive to make the diagnosis of pulmonary embolism.

The evolution of knowledge and treatment in the field of VTE, particularly in recent years, has led to increasingly complex decisions in some cases, to which official recommendations do not always provide answers. Most studies conducted in the past are retrospective in nature and do not mention treatment or duration. In a study of 30 cases conducted by Kouismi et al. [5], treatment with LMWH and Warfarin was administered for 3 months in 25 cases and in 3 cases; treatment was extended by 3 months. In nine patients, only Enoxaparine was administered due to the difficulty of reaching the target prothrombin time. In our study we used the Enoxaparine followed by the Acenocoumarol, and in one case we only used the Enoxaparine because of the difficulty of reaching the target INR.

The treatment, in our study was mainly made of Enoxaparin (LMWH) in curative dose (0.6 mL/12 h) relayed on the 1st day by the AVK (Acenocoumarol). This classic attitude is consistent with the recommendations of the literature. An effective anti-coagulation is achieved in 38 days on average with extremes between 14 days and 51 days except for a case that left the service against medical advice and a patient who died before balancing oral treatment. In 5 cases or 17% of our sample, effective anticoagulation cannot be reached according to the classic therapeutic regimen, a treatment based on new oral anticoagulants (Xarelto at the dose of 20 mg/d, Pradaxa at the dose of 300 mg/d) has been proposed for an average duration of 3 months. Literature [10] demonstrated a possible association between DVT and the use of rifampin with a relative risk of 4.74 in patients treated with rifampin-containing regimens. The use of anticoagulants in these patients is of concern due to the interaction of anti-tuberculosis therapy, in particular rifampin and Warfarin analogues, whose efficacy may be reduced by enzymatic induction.

Data from the literature remain controversial regarding the role of rifampin in the genesis of EVTE. Studies have demonstrated possible association between DVT and use of Rifampicin with a relative risk of 4.74 in patients treated with rifampicin containing regimens [2]. Raschilas et al. [3] conducted a study of hemostasis in 10 patients hospitalized with TBC, before and one month after starting TB treatment including rifampin. It concluded that no abnormalities were found to explain the increase in the incidence of DVT reported with the use of rifampin, including no acquired resistance to protein C as described with oral contraceptives.

The new Xa inhibitors offer several advantages over traditional parenteral anticoagulant therapy, such as a faster onset of action, Lack of initial heparin phase and less bleeding compared to standard treatment. The concomitant use of rifampin results in a 50% to 54% decrease in the plasma concentration of these drugs [11]. A higher dose of Warfarin is often required to reach INR therapeutic levels, due to the effects of Rifampin on cytochrome P450 [10]. In the study by Ben et al. [1], 15 patients (9 cases of DVT and 6 cases of isolated PE) had a favorable development. In patients with DVT, the progression under anticoagulant treatment was unfavorable in 7 patients either by the extension of DVT to the contralateral limb (1 case), or by the occurrence of an embolic pulmonary accident in 6 patients of which 3 died. In patients with isolated PE (10 cases), the outcome was fatal following massive PE in 3 patients and hemoptysis of high abundance in 1 case. A study conducted in Algeria by Hadjer et al. [13], shows that in a series of 12 cases, with the exception of two deaths, the evolution was good in the majority of cases.

In our study we note the occurrence of death, and in 16% of cases of complications; we note two cases of phlebitis of the lower limb, one case of thrombus of the inferior vena cava, a recurrence of deep venous thrombosis and a case of persistence of DVT.

Conclusion

Thromboembolic disease is a common complication in tuberculosis patients with a thromboembolic risk factor, hence the need to systematically look for clinical signs of thromboembolism, in order to establish an early diagnosis.

However, preventive measures against the occurrence of thromboembolic complications must be taken in the case of tuberculosis, such as the active mobilization of limbs with possibly preventive treatment by anticoagulants in certain specific situations (malnutrition, bed rest and general impairment).

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