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RESEARCH ARTICLE

THROMBOEMBOLIC DISEASE DURING TUBERCULOSIS: A SERIES OF 47 CASES

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Abstract

Tuberculosis (TB) is considered a risk factor for thromboembolic venous disease (VTE). The prevalence of this association ranges from 0.6% to 10%. This work aims to analyze the epidemiological and clinical aspects and the therapeutic management of VTE during tuberculosis and discuss the diagnostic and especially therapeutic particularities of this association.

Introduction:-

Tuberculosis remains a significant public health problem in Morocco and around the world. Globally, WHO estimates that 10.0 million (range 8.9-11.0 million) people became ill with TB in 2019 [1], TB caused 1.2 million (range 1.1-1.5 million) deaths worldwide among HIV-negative people in the same year (a reduction from 1.7 million in 2000), and 208,000 additional deaths (range 177,000-242,000) among HIV-positive people (up from 678,000 in 2000) [1]. In Morocco, in 2019, 30,762 cases, or 86/100,000 inhabitants, were reported for all Tuberculosis forms [2].

Tuberculosis can cause hypercoagulability and thromboembolic complications with a prevalence of 0.6% to 10% [3].

This work analyzes the epidemiological aspects and discusses the different diagnostic and therapeutic aspects of this association.

Materials And Methods:-

This paper presents a retrospective study of the association between VTE and tuberculosis collected in the pneumo-phtisiology department of the Moulay Youssef hospital in Rabat from January 2015 to September 2020. Includeall cases of confirmed pulmonary and extra-pulmonary tuberculosis associated with documented pulmonary embolism (PE) or deep venous thrombosis (DVT); during this period, the department hospitalized 2550 patients, of whom 47 patients (1.8%) had this association.

Results:-

There are 29 men and 18 women. The average age is 42 years, with extremes of 15 and 84 years. Twelve of our patients had a history of treated pulmonary tuberculosis. Twenty cases were of smoking patients. Pulmonary damage was found in 37 cases against 10 cases of extra-pulmonary form with 6 cases of pleural tuberculosis, 2 cases of peritoneal tuberculosis, 1 case of lymph node tuberculosis, and 1 case of tuberculous meningitis. VTE occurred

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before 15 days in 26 cases, between 15 and 30 days in 13 cases, and between 30 and 60 days in 8 cases. The diagnosis of pulmonary tuberculosis was based on the presence of acid-fast bacilli in the sputum on direct examination in 27 patients and by GeneXpert in 10 cases. For the extra-pulmonary form, the diagnosis was based either on the presence of acid-fast bacilli in the biological fluid (cerebrospinal fluid, ascites) or compatible histology (pleura, peritoneum). All patients received a quadritherapy combining isoniazid, rifampicin, pyrazinamide, and ethambutol during the attack phase. This combination was followed by rifampicin with isoniazid during the maintenance phase.

VTE was evoked either by clinical signs, mainly unilateral edema of the lower limbs or hemoptysis and thoracic pain or by biological signs, particularly elevated plasma D-dimer levels. VTE was confirmed by venous echo-doppler or thoracic angioscanner, which led to 29 cases of pulmonary embolism (PE) and 18 cases of DVT; the latter concerned the upper limb in 4 cases and the lower limb in 14 cases. The treatment was based on effective anticoagulation combining low molecular weight heparin (LMWH) at a curative dose of 100 IU/Kg twice a day with a vitamin K antagonist relay. The latter administered orally, preferably in the evening. After the International Normalized Ratio(INR)results, we could either adjust the dosage or change for a new oral anticoagulant (NOACs). The initial treatment was 15 mg of rivaroxaban 'Xarelto' twice daily for three weeks, then changed to 20 mg once daily for continuous treatment. This anticoagulation was achieved in our study only after 38 days on average.

Table:- Statistical Analysis Of The Different Variables.

Variables			**Nbr of cases**	**Percentage**
Sex		Female	18	38%
		Male	29	62%
TB		Pulmonary	37	79%
		Extra Pulmonary	10	21%
History		TB treatment	12	26%
		Smoking	20	43%
ClinicalSigns	General	Alteration of general condition	29	62%
		Fever	29	62%
		weightloss	11	23%
		Asthenia	12	26%
	PE	Dyspnea	22	47%
		Chest pain	5	11%
		Hemoptysis	5	11%
		Chest pain + Dyspnea	6	13%
	DVT	Oedema of an extremity	15	32%
		Homans sign	9	19%
		Limb pain	6	13%
Seat PE		Lobar	15	32%
		Segmental	8	17%
		Sub-Segmental	6	13%
Location DVT		Before 15 days	26	55%
		Between 15 and 30 days	13	28%
		Between 30 and 60 days	8	17%
Treatment		LMWH	47	100%
		VKA	47	100%
		NOAC	10	21%

Discussion:-

Tuberculosis (TB) is a contagious and potentially fatal infectious disease caused by Mycobacterium tuberculosis [4,5]. An estimated 1.2 million people died of tuberculosis in 2019, with an additional 208,000 deaths among people infected with the human immunodeficiency virus (HIV) [1]. This high mortality is partly due to the emergence of drug resistance and the presence of co-morbidities such as venous thromboembolism (VTE) [6, 7].

Indeed, many studies suggest a plausible epidemiological and pathophysiological association between tuberculosis and VTE [8,9]. Most studies report VTE prevalence in tuberculosis patients between 0.6% and 3.9% [2].
However, some authors have estimated that the true prevalence of VTE may be more than 10%, but it remains unknown in two-thirds of cases [10]. Célestin D et al. found that the global prevalence was 4-8 times higher than that estimated in the general population (1.2%-2.7%) [11,12]. This suggests that patients with active tuberculosis are at higher risk of developing VTE than the general population. In Morocco, exact data are not available, but reported cases support a relatively high frequency [13].

The increased risk of VTE can be due to tuberculosis itself or can be induced by the rifampicin used to treat tuberculosis [14]. Indeed, three elements represent the cornerstone of the pathophysiology of VTE: stasis, endothelial lesions, and hypercoagulability [15,16].

Active tuberculosis induces hypertrophy of the lymph nodes, which can lead to venous compression and stasis [17]. Gogna reported two patients aged 21 and 60 years with retroperitoneal, para-aortic, and iliac lymphadenopathies of tubercular origin with iliofemoral thrombophlebitis and inferior vena cava [18].

Immobility and prolonged bed rest due to the morbidity caused by TB disease are some of the risk factors for thrombosis. They cause circulatory slowdown and venous stasis, which increases the risk of hypercoagulability [19].

For hypercoagulability, tuberculosis induces chronic inflammation and increases plasma levels of factor VIII, fibrinogen, and plasminogen activator inhibitor 1, while reducing plasma levels of protein C and antithrombin III [8,9]. This was reported in a Nigerian study that measured blood fibrinogen levels in 100 tuberculosis patients and a control population. According to this study, the fibrinogen concentration was significantly higher in TB patients compared to the control group (6.3 ± 2.5 g/L versus 3.17 ± 0.55 g/L) [20]. Koster et al. showed that the risk of DVT increases when fibrinogen levels exceed 5 g/L [21].

Also, chronic inflammation associated with Mycobacterium tuberculosis and the use of rifampicin as an antituberculosis drug are thought to cause endothelial damage [22]. In a study of a sample of 7,542 patients, White et al. found that the risk of DVT in patients treated with rifampicin was five times higher than in untreated patients [14]. 14] This risk exists primarily during the first month of treatment [9].

Our study shows a slight male predominance (59%), while Borjas-Howard [23], Shaarawy [24], Marjani [24] found 70%, 81%, 81% respectively. Smoking is a well-established risk factor for atherosclerotic disease, but its role as an independent risk factor for venous thromboembolism (VTE) remains controversial; according to a meta-analysis including 32 observational studies over ten years [25], smoking could also be a factor in the occurrence of venous thromboembolic events, the relative risk is 1.23 with a 95% confidence index of 1.14 to 1.33 for active smokers. The time of onset of VTE was variable. Indeed, it may precede the manifestations of TB, appear concomitantly, or in some cases occur during tuberculosis treatment [9,10,26]. This delay is early in most cases, at a stage when the patient is still bedridden and blood levels of proinflammatory cytokines are still elevated [27,28]. In the study by Kouismi et al. [13], the onset of DVT was found to occur after an average of 7 days, whereas, in the series by Ben Amar et al. [3], the meantime to onset of the thromboembolic event compared to the time to initiation of tuberculosis treatment was 9.73 days. In our result, the onset of DVT occurred on average eight days, after 15 days in 21 cases, while it occurred concomitantly with TB treatment in 26 cases.

In the case of association with TB, the clinical picture of both DVT and PE was unremarkable.

For several authors, the severity of TBT was related to the fragility of the terrain (associated co-morbidities) and, for others, to the extent of radiological lesions in tuberculosis [8,29]. Several studies have found a correlation between the risk of developing VTE and the severity of TB disease [26,30,31]. In our result, more than half of our patients had lesions extended to more than one-third of a lung field or bilateral lesions, underscoring the severity of the disease.

The D-dimer assay is primarily used to exclude VTE diagnosis in patients with a low or intermediate clinical probability score.

Confirmation of the diagnosis is made by thoracic angioscan and Doppler ultrasound. In our study and the literature, we found a higher prevalence of PE than DVT. This is due to the tendency of clinicians to request chest scans in any patient with persistent pulmonary symptoms, especially in patients with tuberculosis (worsening of dyspnea, oxygen desaturation...), which generally leads to an over-diagnosis of pulmonary embolism. On the other hand, Doppler ultrasound of the lower limbs has much more limited indications.

Pulmonary involvement was by far the most common site of tuberculosis reported in the literature [32,33]. However, thromboembolic complications have been reported with different locations, pulmonary or extra-pulmonary [18,31,34-36]. In our series, the location of tuberculosis was pulmonary in (78%) of cases.

DVT is often in the lower limb, with damage to the femoral and popliteal veins in particular [36,18,30,29]. However, other locations have been reported, including hemorrhoidal[37], cerebral [27], superior vena cava [34], intestinal [35], renal [31], retinal [38] and cutaneous [39].

Interactions between rifampicin and VKA are described, represented essentially by an acceleration of the catabolism of VKA and thus a decrease in their efficacy [40].

The pharmacokinetic interaction appears to be significant, with rifampin inducing several cytochrome P450 isoenzymes (CYP2C9, 2C19, 1A2, and 3A4). The CYP2C9 isoenzyme is significantly involved in the metabolism of warfarin and acenocoumarol. Therefore, the induction of these enzymes leads to increased degradation of administered oral anticoagulants and a significant decrease in their activity [40,41].

The other mechanism involved is the induction of P-glycoprotein by rifampicin, leading to a decrease in the concentrations of associated drugs [42].

Low molecular weight heparins may be a good alternative, but their high cost and the parenteral route cause poor compliance. Early lifting and elastic restraint have always been recommended in our patients.

The use of direct oral anticoagulants (DOAs) for the treatment of venous thromboembolic disease (VTE) is already widely implemented [42,43]. Indeed, their non-inferiority compared to anti-vitamin K anticoagulants(VKA) for the recurrence of venous thromboembolic events has been widely demonstrated, as has their favorable safety profile in - terms of hemorrhagic risk. Their ease of use and administration, a wide therapeutic range, and the absence of the need for monitoring also contribute to their inclusion as the treatment of first choice in international recommendations.

Conclusion:-

Tuberculosis is an indisputable risk factor for venous thromboembolic disease. Its prevalence is not negligible, hence the need to systematically look for clinical signs of venous thromboembolic disease at the time of diagnosis of tuberculosis and during follow-up, particularly during the first month of treatment.

Management poses the problem of interaction between rifampicin and VKA's, responsible for the delay of effective anticoagulation.

Data availability

Patient data (age, gender, disease history, diagnosis, treatment, a follow-up...) used to support the results and conclusions of this study are available upon request from the corresponding author.

Conflicts of Interest:

None.

Funding Statement:

None.

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