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Immunosuppressive Treatment of Connective Tissue Disease and Occurrence of Tuberculosis

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Abstract

Introduction: The occurrence of tuberculosis (TB) during the follow-up of Connective tissue diseases (CTD) is a particular situation often posing real diagnostic problems. This is an association described in the literature. **Patients and methods**: We conducted a retrospective and descriptive study at the internal medicine department of Aristide Le Dantec Hospital. **The purpose of this study was to determine the treatment that patients followed for CTD and suffering from TB took before the occurrence of this one. Results:** During a study period of 11 years and 6 months, 21 cases of TB were diagnosed in 602 cases of CTD (0.03%). The predominance was female with a sex ratio (H/F) of 0.6. The median age was 42 years old. The majority of cases originated from the Dakar region (13 patients or 61.9%) and 85.7% had previous follow-up exclusively in modern medicine and 21 cases (95%) received the CTD's treatment. This consisted of prednisone (90.5%) combined with methotrexate (52.4%), azathioprine (23.8%) or cyclophosphamide (19.4%). The respective medians doses of these drugs were **12.5 mg** per day for prednisone, 13.5 mg per week for methotrexate and 100 mg per day for azathioprine. The median duration of patient follow-up was 36 months. The cumulative dose of prednisone during this period was 23.6 g and that of methotrexate 2.25 g. CTD were dominated by rheumatoid arthritis (RA) (57.1%), and systemic lupus (19%). Isolated cases of systemic scleroderma, primary Sjögren, SHARP syndrom, mixed connective tissue disease, and multiple autoimmune syndrom were noted. TB was localized in 95% of cases, readily bilateral and poorly disseminated. The respective medians diagnostic delays for systemic disease and TB were 21 months and 5 months. Tuberculin intradermal reaction was performed in 16 cases and was positive in 9 cases, sputum bacilli was performed in 19 cases and was positive in 15 cases. **Conclusion:** The association of TB and CTD was characterized by its rarity, its poorly disseminated character and its frequency on RA field.

Keywords

Tuberculosis, Connective Tissue Disease, Corticosteroid, Immunosuppressive Therapy

1. Introduction

Tuberculosis (TB) is a contagious infectious disease with human-to-human transmission due to the pathogenic effects of *Mycobacterium tuberculosis bacteria* (*MT*) on the body [1]. It is a major public health problem and affects about 1/3 of the world's population. In 2016, the World Health Organization (WHO) recorded nearly 10.4 million people, including 6.4 million new and 1.3 million deaths in the non-HIV-negative population [2]. It is the ninth leading cause of death worldwide and the leading cause of death due to a single infectious agent in front of HIV/AIDS [2]. In Senegal, the National Tuberculosis Program (NTP) estimated the annual incidence at 136 cases per 100,000 habitants [3].

Connective Tissue Diseases (CTD) are a very heterogeneous group of affections related to mechanisms considered most often as dysimmun [4].

They are a field of immunodepression. Their therapeutic management has evolved a lot, because of a better knowledge of their pathophysiological mechanisms. The treatment is mainly based on corticosteroids, immunosuppressants and the use of biomedicines. Although these treatments are effective, they pose a high risk of opportunistic infections, particularly tuberculosis [1].

In Senegal, most of the studies on TB in the field are devoted to its association with HIV. The only study devoted to tuberculosis during systemic diseases was conducted by Diallo *et al.* [5]. In this context, we conducted a retrospective, descriptive and analytical study at the Internal Medicine Department of Aristide Le Dantec Hospital. **The purpose of this study was to determine the treatment that patients followed for CTD and suffering from TB took before the occurrence of this one.**

2. Methodology

This was a retrospective, descriptive and cross-sectional study from January 1st, 2005 to July 1st, 2016 over a period of 11 years and 6 months conducted at the Internal Medicine department of Aristide Le Dantec Hospital. All patients hospitalized during this period or followed by outpatients with a combination of tuberculosis and systemic disease was included. The diagnosis of systemic diseases was based on international criteria and the diagnosis of tuberculosis on the basis of a bundle of epidemiological, clinical and paraclinical arguments: evidence of MT or tuberculous granuloma in sputum and other tissue or fluid samples. All incomplete files were not included.

Data collection was done using a standard form. The sphinx version V software was used for data entry and analysis. There was no ethical problem or con-

flict of interest.

3. Results

During a study period of 11 years and 6 months, 21 cases of TB were diagnosed in 602 cases of systemic diseases (0.03%). The predominance was female 13 women out of 08 men is a sex ratio (H/F) of 0.6. The average age was 41 years old with extremes ranging from 21 to 78 years old. The age group of 40 - 50 years was the most represented with 1/3 of patients. The majority of cases originated in the Dakar region (13 patients or 61.9%). The Wolof ethnicity was more represented in the study population with 8 patients. Thirteen (13) out of 21 patients were unprofessional.

TB was pulmonary localized in most cases, bilateral and poorly disseminated. In fact, 20 patients had a pulmonary localization, 17 had isolated pulmonary tuberculosis, 03 had multifocal tuberculosis, including two ganglionic and coxal locations and one peritoneal localization, only one (01) patient had isolated extra-pulmonary tuberculosis. Pulmonary tuberculosis was often bilateral, had alveolar syndrom in most cases found on radiography. Three (03) cases of miliary tuberculosis and 02 cases of parenchymatous cavern were noted. The respective median timeframes for systemic disease and TB were 21 months and 5 months. Tuberculin intradermal reaction was performed in 16 cases and was positive in 9 cases, sputum smear was performed in 19 cases and was positive in 15 cases. Ten patients had a CRP greater than 40 mg with a median value of 154 mg/L.

CTDs were dominated by rheumatoid arthritis (RA) (57.1%), and systemic lupus (19%). There were isolated cases of systemic scleroderma, primary Sjögren's syndrome, SHARP syndrome, mixed connective tissue disease, and multiple autoimmune syndrome (**Figure 1**). Pulmonary fibrosis was the most common complication in 06 patients.

Regarding previous follow-up, the majority **(19 cases or 95%)** received a specific treatment for **CTD** and 85.7% were followed exclusively in modern medicine. The rest of the patients benefited from both modern and traditional medicine follow-up. In the majority of cases, prednisone treatment (90.5%) was associated with methotrexate (52.4%), azathioprine (23.8%) or cyclophosphamide (19.4%). The respective median doses of these drugs were 12.5 mg per day for prednisone, 13.5 mg per week for methotrexate and 100 mg per day for azathioprine. The median duration of patient follow-up was 36 months. The cumulative dose **(CD)** of prednisone during this period was 23.6 g and that of methotrexate 2.25 g. Seven cases of death (33%) were found, three of which probably related to tuberculosis and four others probably related to systemic diseases.

4. Discussion

Of 602 cases of systemic diseases recruited, tuberculosis occurred in 21 cases (0.03%). This low prevalence rate contrasts with the relative endemicity of tuberculosis in our regions. Worldwide, the overall epidemiological data available

were systemic Lupus. It is noted that the prevalence of tuberculosis in this condition is estimated to be between 0.66% and 13.8% in South-East Asian countries, corresponding to an average prevalence of tuberculosis of 7 to 10.6 cases. 1000 patient-years, while the incidence of tuberculosis in the general population ranges from 105 to 300 cases per 100,000 population [6]-[12].

Systemic diseases were represented by rheumatoid arthritis (12 cases), systemic lupus (04 cases), isolated cases of SHARP, mixed connective tissue disease (PR and PM), systemic scleroderma, multiple autoimmune syndrome (PR, Biermer and Diabetes) type 2, primitive Sjögren (**Figure 2**).

Most patients have a hospital follow-up specialized center, this high rate of patients followed in modern medicine is surely related to the dispersion mostly urban our study population. This predominantly hospital-based follow-up rate could account for the delayed diagnosis of tuberculosis and was associated with a greater requirement for CTD treatment. This is associated with an increased risk

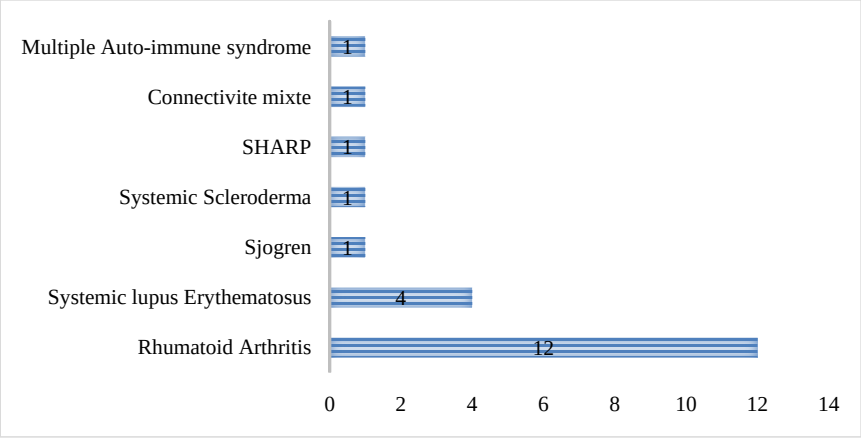

Figure 1. Connectivite Tissue Disease of the patients.

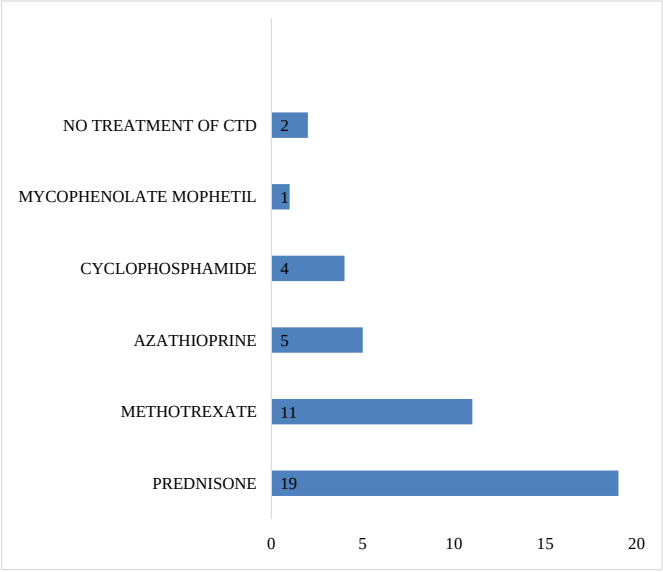

Figure 2. Distribution of treatment of CTD in 21 patients.

of occurrence of infectious complications [6] [7] [8] [9] [13] [14] [15] [16] [17]. Two patients had never taken any CTD treatment before admission, they were followed in non-specialized levels 1 and 2. On the other hand, 19 patients (90.5%) were on prednisone during their follow-up, 11 on methotrexate (52.4%) in combination with prednisone. The other two immunosuppressants used in these patients and in combination with prednisone are azathiopirine (5 cases) and cyclophosphamide (4 cases).

The most commonly prescribed doses of prednisone were 10 to 15 mg (7 patients or 33%), 5 to 10 mg (6 patients or 28.6%), and more than 15 mg (6 patients or 28.6%). The median dose of prednisone was 12.5 mg. It can thus be said that out of 21 patients on prednisone, 15 were in doses of less than 15 mg per day. It should be noted that the prescription of this infraphysiological dose was justified by the research of the anti-inflammatory benefit on the one hand, in fact most of these patients suffered from rheumatoid arthritis and at the time of the diagnosis of the TB did not have high doses; on the other hand the cortisonic sparing effect has been implicated with the progressive introduction of the other immunosuppressants mentioned above.

The use of prednisone with an average dosage of 15.79 mg and a median of 12.5 mg was therefore found in our study. In studies in the medium-TB incidence zone all patients with systemic disease are treated with glucocorticoids at the time of diagnosis of tuberculosis at 5 to 60 mg/d of prednisone equivalent [13] [14] [15] [16] [17]. The American Thoracic Society and the Centers for Disease Control and Prevention established in 2000 that a dose >15 mg/day of prednisone equivalent administered for one month or more was a risk factor for tuberculosis because it suppressed tuberculin reactivity. The UK case-control study from 1990 to 2001 by Jick *et al.*, comparing 497 new TB cases to 1966 controls, showed an adjusted OR of 4.9 for GC use versus non-use and OR adjusted for use of <15 mg and ≥15 mg/day prednisone equivalent of 2.8 and 7.7, respectively [18].

Beyond the daily dosage of glucocorticoids, the duration of administration also seemed to play a role in the occurrence of tuberculosis [18]. This duration was often confused in our study with the duration of follow-up of the systemic disease until the occurrence of tuberculosis. It averaged 53.47 months. The glucocorticoid/immunosuppressive association was found in 18 of the 19 patients treated, *i.e.* 85% of patients in our series.

The main immunosuppressive agent for prednisone was methotrexate, with 11 patients in the series (52.3%) taking this drug at an average dose of 11.25 mg weekly with a median dose of 13.5 mg per week. During RA, the rate of MTX-reported infections ranged from 0% to 16% in the retrospective series, while a randomized, double-blind, controlled trial of the efficacy of MTX showed an increased risk of infection (mainly urinary and pulmonary infections) with an incidence of pneumonia of 33 events/patient-years. There does not appear to be an increased risk of tuberculosis with MTX alone, but rather with the combination of different IS (prednisone, leflunomide), which is often the case

during RA. In our series there is no statistically significant association between the use of methotrexate and the pulmonary location of tuberculosis.

Azathiopirine was prescribed in 5 patients (23%) with an average dose of 100 mg per day.

In our study, with an average treatment duration of 53.47 months and average doses of prednisone (15.79 mg/day) and methotrexate (11.25 mg/week), the average cumulative doses of prednisone and methotrexate were estimated at 23.6 mg and 2.25 g. In France, a retrospective study conducted by Darra-Joly C., Wechsler B. *et al.* [18] between 1976 and 1993 had collected 16 cases of tuberculosis associated with systemic HIV-negative diseases. In this series, the cumulative dose of prednisone was 7 g. The cumulative dose is an independent risk factor for tuberculosis (each gram increasing this risk by 23%) [13] [14] [15] [16] [17].

The main limit of our study was its retrospective character that may be responsible of some misses datas.

5. Conclusion

The occurrence of tuberculosis during the follow-up of systemic diseases seems to be rare and of clinical presentation not much different from that occurring on immunocompetent ground. Its prevention is essentially based on the treatment of latent TB cases and a well-conducted background treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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