Miliary pattern, a classic pulmonary finding of tuberculosis disease

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A R T I C L E   I N F O

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A B S T R A C T

Introduction: The increase in age of the population and in the use of immunosuppressive treatment makes tuberculosis (TB) with hematogenous or lymphatic dissemination a current problem.

Methods: We collected all the patients diagnosed with tuberculosis with miliary pulmonary pattern at the Santiago de Compostela University Teaching Hospital (NW Spain) from 1 January 2006 to 31 December 2015.

Results: A total of 27 patients were included, 70.4% women, with a median age of 69.0 years old. A cause of immunosuppression was observed only in 51.9% of patients. The majority of the cases (65.0%) presented pulmonary affection. The most frequently isolated species was Mycobacterium tuberculosis (88.9%). Multiresistance to first-line antituberculosis drugs was observed only in 3.7%. 92.6% of the patients received treatment with Isoniazid, Rifampicin and Pyrazinamide, associated in 48.1% of them with Ethambutol. Two patients died during admission and there were no recurrences in the 2-years follow-up.

Conclusions: Miliary tuberculosis remains a current pathology. Most patients do not have a known cause of immunosuppression. The response to the typical treatment is usually good.

1. Introduction

Tuberculosis (TB) is an important health concern that affects more than 1.7 billion people worldwide. Pulmonary affection is presented in most cases of M. tuberculosis primary infection and tuberculosis disease. TB is caused by the aerobic acid-fast rod-shaped bacterium M. tuberculosis. Worldwide poverty, Human Immunodeficiency Virus (HIV), or drug resistance are the main causes for the resurging global TB epidemic. However, in our area (Galicia, North-West Spain), the increase in the age of the population, which is associated with an increase in the use of immunosuppressive treatments, makes tuberculosis with hematogenous or lymphatic dissemination a current problem. In order to have a correct diagnosis of military TB it is usually necessary to have a clinical suspicion and a radiological diffuse miliary infiltrate. A miliary infiltrate is defined as multiple small (1–3 mm), round opacities located in the bilateral pulmonary interstitium.

The aim of this study was to analyze epidemiological and clinical characteristics, method of diagnosis, treatment received and mortality of patients with miliary tuberculosis in our area.

2. Material and methods

2.1. Study population

We conducted a retrospective analysis which covered all of the patients diagnosed with tuberculosis with miliary pulmonary pattern at the Santiago de Compostela University Teaching Hospital (NW Spain) from January 1st 2006 to December 31st 2015. This search included all of the patients identified with tuberculosis disease and miliary pattern in chest X-Ray or Computed Tomography (CT). Through a review of the patients’ medical histories, we first excluded all the patients who did not meet inclusion criteria.

We considered as immunosuppressed patients those patients who had received treatment with corticosteroids or other immunosuppressant treatments, as well as those who had malignant tumors, diabetes mellitus or Human Immunodeficiency Virus infection. All these criteria are previously considered risk factors to develop

Abbreviations: AFB, acid-fast bacilli; BAL, broncoalveolar lavage; CT, computed tomography; HIV, human immunodeficiency virus; IGRA, interferon-gamma release assay; PCR, polymerase chain reaction; TB, tuberculosis; TST, tuberculin skin

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military TB [4].

2.2. Statistical analysis

A descriptive analysis was performed, by calculating the qualitative variable rates and the median and interquartile range of the quantitative variables. All of these analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

2.3. Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki [6] and in full conformity with prevailing regulations. Vulnerable populations did not participate in the study and neither was economic compensation given to patients for their participation. All analyzed data were anonymized.

3. Results

During the study, there were 27 patients with miliary pulmonary pattern, 70.4% women, with a median age of 69.0 years old. All clinical characteristics are shown in Table 1.

Regarding the presence of immunosuppression, more than half of the patients (51.9%) did not have a known cause of immunosuppression. Treatment with glucocorticosteroids was the principal cause of the patients (51.9%), did not have a known cause of immunosuppression (14.8%), having malignant tumors (18.5%), diabetes (14.8%) and HIV infection (7.4%).

Concerning clinical manifestations, the most frequent manifestation was pulmonary affection (65.0%). The most frequent extrapulmonary manifestation was lymph nodes (4 cases). Regarding complementary tests, the most frequent was thoracic CT (70.4%), followed by bronchoscopy (63.0%).

With regard to the microbiological characteristics, the tuberculin skin test (TST) was positive only in 4 patients; in one case, this test was repeated in order to find a booster effect, which was negative. The interferon-gamma release assay (IGRA) was performed and found positive only in one patient. The diagnosis was obtained in the majority of cases (81.5%) with *Lowestein* culture of sputum. Acid-fast bacilli (AFB) smear in sputum was positive in 40.7% of the patients, while the same AFB smear applied to broncoalveolar lavage (BAL) was positive in 52.9% of the 17 patients with bronchoscopy. The *Mycobacterium* polymerase chain reaction (PCR), was positive in a greater number of patients: 59.3% of PCR tests on respiratory samples were positive. Four patients were diagnosed after the observation of AFB in biopsy of lymphadenopathy (3 patients) or oral ulcers (1 patient). All diagnostic methods used are shown in Table 2.

The most frequently isolated species of mycobacterium was *M. tuberculosis* (88.9%).

The most commonly used treatment was isoniazid, rifampicin and piracinamide in 92.6%. Ethambutol was associated in 48.1% of patients and was more likely to be associated with more recent cases. Multi-resistance to first-line antituberculosis drugs was used only in 3.7% (2) of the patients; these were treated with a combination of quinolones, amikacin and prothionamide. In just one case no treatment was performed because diagnosis was made post-mortem, and in another one we could not find the treatment on the records. Only in four cases the treatment was started before microbiological confirmation of TB. The median duration of treatment was 287 days (IQR: 202–366 days) and the median time from admission to confirmation of diagnosis, and therefore start of the treatment, was 4.0 days (IQR: 1.0–9.0).

The median length of hospital stay was 25 days (IQR: 15–35 days). Two patients died during admission. In one case the diagnosis was reached post-mortem and the patient had not received treatment. In the other case empirical treatment was started with isoniazid, rifampicin and piracinamide, but the patient died at the fifth day of treatment and the diagnosis was confirmed with *Lowestein* culture of sputum. We did not find factors associated with mortality. There were no recurrences during the 2-year follow-up.

| Characteristic (n = 27) | Total of patients | Immunosuppressed patients n = 13; (%) |
|------------------------|-------------------|--------------------------------------|
| Gender                 |                   |                                      |
| Male                   | 8 (29.6)          | 3 (23.1)                             |
| Female                 | 19 (70.4)         | 10 (76.9)                            |
| Age (year, median, IQR) | 69.0 (43.0–76.0)  | 73.0 (43.75–78.0)                    |
| Immunosuppression       |                   |                                      |
| Diabetes mellitus       | 4 (14.8)          | ALL                                  |
| Corticosteroids         | 5 (18.5)          |                                      |
| Malignant tumors        | 5 (18.5)          |                                      |
| Human Immunodeficiency Virus | 2 (7.4)      |                                      |
| Other immunosuppression | 4 (14.8)          |                                      |
| Other epidemiological characteristics | | |
| Social problems1 | 3 (11.1) | 2 (15.4) |
| Tobacco                | 6 (22.2)          | 2 (15.4)                             |

Table 1

Clinical, microbiological and epidemiological characteristics of the 27 included patients.

AFB: Acid-fast bacilli; IGRA: interferon-gamma release assay; IQR: interquartile range; PCR: polymerase chain reaction; TST: tuberculin skin test.

Notes in Table 1:
1. Social problems: refers to those patients with little or no family support, who live in poor hygienic conditions or are homeless.
2. Of the patients who did not receive ethambutol one did not receive treatment because the diagnosis of tuberculosis was reached post-mortem. The rest of the cases received only a three-drug treatment due to the low incidence of isoniazid resistance in our area. One patient received levofloxacin as well, due to an infection by *Haemophylus influenzae*.
3. Corticosteroids were used in 5 patients. Two individuals received them previously to admission because of previous pathologies. In one case, steroids were added in the days before admission due to the presence of ulcerous injuries in the amygdale and the epiglottis. In another case, the patient had persistent fever and steroids were prescribed before the diagnosis of tuberculosis. Finally, another patient received steroids because of pancycopenia with coombs test positive.
such as amikacin in our empirical treatments. In fact, we did the use of triple therapy alone can be acceptable. Due to the low pre-
crease the results. The most frequently isolated species of myco-
in the majority of the patients and booster e
enstein culture [4]. In fact, in our study, the sensibility of 
what other studies have found[4], the AFR smear can diagnose almost 
this culture, other methods have been used. In our series, similarly to 
smear urine simple. As other studies found[4,9], the TST was negative 
almost 60% of our patients. We did not found usefulness in PCR or AFR 
help in the diagnosis, with PCR being positive in respiratory samples in 
half of the patients. Moreover, nucleic acid tests such as PCR assay can 
HIV status among other conditions of immunosuppression including 
and old people. The incidence of TB has recently increased worldwide due to several factors including HIV infection, age and other forms of im-
unosuppression [8]. It should be noted that more than half of the 
cases in our series were elderly patients without another known cause of immunosuppression. Previous studies found two peaks of miliary TB: one in adolescents and young adults and the other one in old people. However, less than 2% of the cases were immunocompetent adults [4].

Clinical suspicion and radiological findings are very important for an early diagnosis and a correct treatment. It is important to evaluate HIV status among other conditions of immunosuppression including age, uncontrolled diabetes, chemotherapy, organ transplant, and corticosteroid therapy [2,10–12]. To confirm the diagnosis a microbiological isolation is necessary. The gold standard remains the Lowen-stein culture [4]. In fact, in our study, the sensibility of Lowenstein 
culture was more than 80%. However, because of the time needed by this 
culture, other methods have been used. In our series, similarly to 
what other studies have found [4], the AFR smear can diagnose almost half of the patients. Moreover, nucleic acid tests such as PCR assay can help in the diagnosis, with PCR being positive in respiratory samples in almost 60% of our patients. We did not found usefulness in PCR or AFR smear urine simple. As other studies found [4,9], the TST was negative in the majority of the patients and booster effect was not useful to in-
crease the results. The most frequently isolated species of myco-
bacterium was M. tuberculosis (88.9%). The most commonly used treatment was isoniazid, rifampicin and piracinamide, associated with ethambutol in more recent cases. In our region, the prevalence of isoniazid resistant is low. As a consequence, the use of triple therapy alone can be acceptable. Due to the low pre-
valence of multidrug resistant tuberculosis in our area, which is im-
ported in the majority of cases, we did not include active antibiotics 
such as amikacin in our empirical treatments. In fact, we did find not 
any recurrence during the 2-year follow-up.

We observed, unlike other published studies [1,4,7], a good 
response to treatment and low mortality; only two patients died during admission. This can be explained because of the fast diagnosis and treatment of the patients and the low presence of TB multiresistant to first line antituberculosis drugs (rifampicin and isoniazid). In fact, the presence of multiresistant TB is a leading cause of morbidity and mortality worldwide [13] since the management of multiresistant TB can be difficult and the use of second-line drugs is needed [13]. In our cases of multiresistant TB, we used quinolones, amikacin and proth-
ionamide with good response. As described in our study, treatment of drug-susceptible TB with standard four-drug treatment is often suc-
cessful, with a low rate of relapse [14,15].

One of the keys in the treatment of TB is the long duration of treatment; six months is the standard duration of therapy [4,7]. In our series, we found a longer duration of treatment with a median of 287 days (IQR 202–366 days).

The main limitation of this study lies in the retrospective nature of the analysis, which could compromise the accuracy of some of the clinical data. Besides, the absence of an established protocol for TB management at our hospital implies that the treatment of patients is not systematic.

5. Conclusions

Miliary tuberculosis remains a relevant pathology in our area, even in patients with no known cause of immunosuppression. Although miliary tuberculosis is a potentially lethal disease, we see in our study that with the optimal treatment, the rate of recurrence and mortality is low.

Ethical statement

The study was conducted in accordance with the principles of the Declaration of Helsinki (4) and in full conformity with prevailing reg-
ulations. Vulnerable populations did not participate in the study and neither was economic compensation given to patients for their parti-
cipation. The study protocol was reviewed and approved by the Galician Clinical Research Ethics Committee. All data analyzed were anonymized. The investigators are free to publish the results of this study, regardless of the results obtained.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influ-
ence the work reported in this paper.

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