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Miliary pattern, a classic pulmonary finding of tuberculosis disease

Vanesa Alende-Castro[a], Cristina Macía-Rodríguez[b,*], Emilio Páez-Guillán[c], Alba García-Villafranca[d]

[a] Department of Internal Medicine, Hospital do Salnés, Rúa Hospital do Salnes, 30, 36619 Vilagarcía de Arousa, Pontevedra, Spain
[b] Department of Internal Medicine, POVISA Hospital, Rúa Salamanca 5, Vigo, Pontevedra, Spain
[c] Department of Internal Medicine, Complexo Hospitalario Universitario de Santiago de Compostela, Travesia da Choupana s/n, Santiago de Compostela, A Coruña, Spain
[d] Department of Internal Medicine, POVISA Hospital, Rúa Salamanca 5, Vigo, Pontevedra, Spain

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ABSTRACT

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 affectation. 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 Pyrazinamine, 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 a an important health concern [1,2] that affects more than 1.7 billion people worldwide [3]. Pulmonary affectation 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 [4]. 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 [4,5].

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

* Corresponding author.
E-mail address: cristina.macia.rodriguez@gmail.com (C. Macía-Rodríguez).

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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 immnunosuppresion (18.5%), followed by being treated with other immunosuppressants (14.8%), having malignant tumors (18.5%), diabetes (14.8%) and HIV infection (7.4%).

Concerning clinical manifestations, the most frequent manifestation was pulmonary affectation (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 *Mycobacteria* 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. Multiresistance 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 postmortem, 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 postmortem 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.

Table 1
Clinical, microbiological and epidemiological characteristics of the 27 included patients.

Characteristic (n = 27)	Total of patients Number (%)	Inmunosuppresed 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	13 (48.1)	**ALL**
Diabetes mellitus	4 (14.8)	
Corticosteroids	5 (18.5)	
Malignant tumors	5 (18.5)	
Human Immunodeficiency Virus	2 (7.4)	
Other immunosuppression	4 (14.8)	
Other epidemiological characteristics		
Social problems[1]	3 (11.1)	**2 (15.4)**
Tobacco	**6 (22.2)**	**2 (15.4)**
Species of mycobacterium		
M. Tuberculosis	24 (88.8)	**10 (76.9)**
M. Bovis	2 (7.4)	**2 (15.4)**
M. Avium	1 (3.7)	**1 (7.7)**
*Extrapulmonary **manifestation***	10 (37.0)	**5 (38.5)**
Limphadenopathy	4 (14.8)	**1 (7.7)**
Meningeal involvement	3 (11.1)	**1 (7.7)**
Bone marrow	1 (3.7)	**1 (7.7)**
Genitourinary involvement	1 (3.7)	**1 (7.7)**
Upper respiratory tract	1 (3.7)	**0 (0)**
Limphadenopathy and bone marrow involvement	1 (3.7)	**1 (7.7)**
Days of hospital stay (days, median, IQR)	25.0(15.0-35.0)	**27.0 (18.0-44.0)**
Number of days of treatment (days, median, IQR)	287.0(202-366)	**363.0 (198.0-365.0)**
Number of days of hospital stay before diagnosis (days, median, IQR)	**4.0 (1.0-9.0)**	**3.0 (0.0-8.5)**
Mortality		
Intrahospital mortality	2 (7.4)	**0 (0)**
During follow-up	1 (3.7)	**1 (7.7)**
Treatment		
Isoniazid	25 (92.6)	**13 (100.0)**
Rifampicin	25 (92.6)	**13 (100.0)**
Pyrazinamide	25 (92.6)	**13 (100.0)**
Ethambutol[2]	13 (48.1)	**5 (38,5)**
Quinolone	3 (11.1)	**1 (7.7)**
Other regimes	2 (7.4)	**1 (7.7)**
Corticosteroids[3]	**5 (18,5)**	**3 (23.0%)**

AFB: Acid-fast bacilli; IGRA: interferon-gamma release assay; IQR: intercuartile 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 thhe 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 isonizid resistance in our area. One patient received levofloxacin as well, due to an infection by *Haemophylus influenza.*
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 pancytopenia with coombs test positive.

Table 2
Diagnostic methods.

	Performed		Positive		Sensibility of test (%)	
	Total	IS	Total	IS	Total	IS
TST	27	13	4	1	14.8%	7.7%
IGRA	1	0	1	0	100%	0%
AFB smear						
Sputum	27	13	11	7	40.7%	53.8%
Broncoalveolar lavage (BAL)	17	9	9	6	52.9%	66.6%
Urine	24	11	0	0	0%	0%
Mycobacteria PCR						
Sputum/BAL	27	13	16	7	59.3%	53.8%
Cerebrospinal fluid	5	1	2	1	40.0%	100%
Urine	24	11	2	1	8.3%	9.1%
Lowenstein culture						
Sputum	27	13	22	11	81.5%	84.6%
Urine	24	11	3	1	12.5%	9.1%
Cerebrospinal fluid	6	1	2	0	33.3%	0%
Bone marrow	2	11	1	1	50.0%	100.0%
AFB in biopsy						
Limphadenopathy	7	4	3	3	42.8%	75.0%
Oral cavity	1	1	1	1	100.0%	100.0%100.0%

AFB: Acid-fast bacilli; IGRA: interferon-gamma release assay; IS: immunosuppressed patients; PCR: polymerase chain reaction; TST: tuberculin skin test.

4. Discussion

Our study describes the main characteristics of a cohort of patients diagnosed with miliary TB based on X-Ray findings. Miliary mottling on chest X-Ray is a key factor for the diagnosis of disseminated tuberculosis [5,7].

The incidence of TB has recently increased worldwide due to several factors including HIV infection, age and other forms of immunosuppression [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 *Lowenstein* 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 increase the results. The most frequently isolated species of mycobacterium 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 prevalence of multidrug resistant tuberculosis in our area, which is imported 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 multiresistent to first line antituberculosis drugs (rifampicin and isoniazid). In fact, the presence of multiresistent TB is a leading cause of morbidity and mortality worldwide [13] since the management of multiresistent TB can be difficult and the use of second-line drugs is needed [13]. In our cases of multiresistent TB, we used quinolones, amikacin and prothionamide with good response. As described in our study, treatment of drug-susceptible TB with standard four-drug treatment is often successful, 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 immunosuppresion. 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 regulations. Vulnerable populations did not participate in the study and neither was economic compensation given to patients for their participation. 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 influence the work reported in this paper.

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