

Miliary Tuberculosis: Moroccan Series of 101 Cases

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Abstract

Original Research Article

Introduction: Miliary tuberculosis is an increasingly rare form (2% to 8%), defined by the hematogenous or lymphatic dissemination of the tubercle bacillus from a pulmonary or extra-pulmonary focus but which remains serious and can lead to acute respiratory failure due to lesional pulmonary edema. **Patients and Methods:** This is a retrospective study of 101 cases of miliary tuberculosis hospitalized between January 1989 and July 2019 in the pneumology department of "20 Aout" in Casablanca. **Results:** The average age is 43 years with a predominance of men (64%), the history of tuberculosis is found in 8 cases and tuberculosis contagion in 10 cases. The common symptom in all cases (100%) is an alteration of the general condition, fever is present in 76% of cases, dry cough is found in 75.5% of cases and dyspnea is found in 38.3% of cases. Among the causes of immunosuppression, we noted: 3 cases of neoplasia, 5 cases of diabetes, 5 cases of pregnancy and 4 cases of system diseases. The chest X-ray (frontal view) found an aspect of pulmonary miliary in all cases associated with pleurisy in 18 cases, an excavated opacity in 3 cases and pneumothorax in 1 case. Tuberculin intradermal reaction (tIDR) was positive in 35 cases. Antibacillary treatment was started urgently in all cases. The outcome was good in the majority of cases with 10 deaths. Further work-up allowed confirmation of the diagnosis either by direct isolation of the koch bacillus or by biopsy in 47.52% of cases.

Keywords: Miliary tuberculosis, Tuberculin intradermal reaction (tIDR), pneumology, lesional pulmonary edema.

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INTRODUCTION

Miliary tuberculosis is a severe, acute form of tuberculosis caused by lymphohematogenous spread of tuberculosis bacilli from a focal lesion ruptured in the blood or lymphatic flow. Its definition is radiological: it is a seedling of small punctiform opacities the size of a "millet grain" (1 to 2 mm) rounded and well limited, not very dense, equal to each other and usually disseminated with regularity in the whole two lung fields. It is a relatively uncommon condition, accounting for less than 2% of tuberculosis according to some authors and around 8% of extrapulmonary tuberculosis [1, 2]. The Possible extrapulmonary localizations during miliary tuberculosis are: meningeal, hepatic, ganglionic, peritoneal and osseous. BCG, an integral part of Morocco's expanded vaccination program, plays a protective role in the onset of severe forms of tuberculosis, including miliary the HIV-AIDS pandemic [3].

We carried out this work in order to assess the epidemiological, clinical, biological, radiological and evolutionary profile of the disease.

PATIENTS AND METHODS

This is a retrospective study carried out at the pneumology service "20 Aout" of the Ibn Rochd's University Health Centre of Casablanca, between January 1989 and July 2020. All cases of radiological miliary whose tuberculous nature was strongly suspected on a set of epidemiological arguments, clinical, paraclinical and progressive were retained.

We completed an operating sheet for each patient which enabled us to collect the socio-demographic characteristics, the antecedents (history of tuberculosis, recent tuberculosis contagion, contributing factors and associated pathologies (diabetes, HIV, system disease, etc), clinical signs, radiological images, treatment and evolution. Data was entered and analyzed using EXCEL software.

RESULTS

One hundred and one cases were collected during the study period. The sex ratio (male / female) was 1.7. The ages ranged from 20 to 67 with an average age of 43. All patients were vaccinated with BCG. Tuberculosis contagion was found in 10 patients (9.9%), tuberculosis treated in 8 patients (7.9%). Active smoking was noted in 26 patients (25.74%) of which 19 were male. The contributing factors and associated pathologies were: immediate postpartum in 4 cases (3.9%), diabetes in 3 cases (2.9%), Lupus in one case and HIV infection in 8 patients (7.9%). The diagnostic delay was more than one month in 80% of cases. All the patients had a deterioration in their general condition, with weight loss, asthenia and / or anorexia. Fever was present in 76.7% of cases, dry cough in 75.5% of cases, dyspnea in 38.3% of cases and hemoptysis in 7.9% of cases.

Pleuropulmonary examination revealed fluid effusion syndrome in 16.1% of cases, crackling rales in 42% of cases and substantially normal in 15% of cases.

The complete blood count (CBC) revealed lymphopenia in 27% of cases, leukopenia in 20% of cases, thrombocytopenia in 30% of cases and anemia in 94% of cases (the anemia was inflammatory in 20% and due to malnutrition in 80%).

The chest x-ray, carried out in all patients, showed an image of miliaria (Fig. 1), associated with pleural involvement in 15 cases (14.8%), mediastinal opacities in 7 cases (6.9%), and pericardial in 3 cases (2.9%).



Fig 1: Miliary tuberculosis

Thoracic CT was performed in only 15% of patients, in addition to chest X-ray which was indicated to explore mediastinal opacities that were related to mediastinal lymphadenopathy.

Abdominopelvic ultrasound, performed in 70 patients, showed 15 cases of hepatomegaly, isolated in

8 cases and associated with splenomegaly in 7 cases, 4 cases of ascites and 3 other cases of coeliomaenteric lymphadenopathy.

The tuberculin skin test (tIDR), performed in all patients, was positive in 35 cases (34.6%). The bascilloscopies were positive in 16 cases (15.8%), as well as the culture in 10 cases (9.9%).

Patients who presented with pleurisy underwent pleural biopsy biopsies which supported tuberculosis in 10 cases, and chronic nonspecific fibroinflammatory rearrangement in 5 cases. The associated extra-pulmonary involvement was represented by retinal involvement in the form of Bouchut tubercles in 5 cases (4.9%), bone marrow involvement confirmed by bone marrow biopsy in 5 cases (4.9%), pericardial involvement in 3 cases (2.9%) urinary tract involvement in 7 cases (6.9%), cerebrospinal involvement in 6 cases (5.9%), mediastinal and peripheral lymph node involvement were found in 7 cases each (6.9%).

The HIV serology carried out systematically in all the patients was positive in 8 cases (7.9%). Antibacillary treatment was started urgently before confirmation in all cases, according to the 2002 national tuberculosis control program, revised in 2011. The therapeutic regimen was 2RHZE / 7RH (either rifampicin, isoniazid, pyrazinamide, ethambutol (ERIP k4)) for two months, followed by four months of rifampicin, isoniazid). Ten patients (10.7%) received adjunct corticosteroid therapy at a dose of 1 mg / kg / day, decreasing over 40 days on average for cerebral-meningeal involvement and significant dyspnea.

Twenty patients experienced side effects, 8 cases complicated by pyopneumothorax, 3 cases of isolated pneumothorax, 3 cases of drug-induced hepatitis, 2 cases of Dress syndrome, and 1 case of polyneuropathy secondary to isoniazid.

The outcome was favorable in 90 cases of the treated patients, while 11 patients died from multiorgan involvement in HIV in 2 cases, acute respiratory distress in 8 cases, and meningitis in one case.

DISCUSSION

Miliary tuberculosis is a severe form that is life-threatening, making it a diagnostic and therapeutic emergency. Its frequency is variable according to the authors, it varies between 1% and 5% of all forms of tuberculosis and represents 25% of mortality [4].

The predominance of miliary tuberculosis in young subjects is noted in the majority of series from countries with high tuberculosis endemia, particularly in Africa [3, 6, 10] and India [3]. Thus, the average age was 35 years for Sharma [3], 36 years for Oué-draogo [5], 37 years for Touré [12], 39 years for Haloui [11],

and 41 years for Toloba [8]. This is also the case in our study with an average age of 43 years

In the literature, the male predominance in miliary tuberculosis is classic [5, 9], as in our study; however, a slight female predominance is described by some authors [6, 14]. The notion of tuberculosis contagion should be systematically researched in the patient's entourage; it varies according to the authors from 15% to 35% [10, 14, 15]. In our work, it was found in 13.5% of cases.

Several studies have confirmed that active smoking probably plays an important role in the occurrence of miliary tuberculosis through local alteration of the defense mechanisms [5,7], in our series smoking was 25.7%.

Tuberculosis-HIV co-infection is a well-established fact reported by several authors [3, 11, 8, 20], particularly for pulmonary localization. Toloba *et al.*, [8] reported 23.4% [8] Touré *et al.*, [12] 32% of cases of miliary tuberculosis HIV co-infection, and, while in our series 7.9% of patients were infected by HIV.

Other factors of immunosuppression can promote the onset of miliary tuberculosis such as diabetes, the immediate postpartum, neoplasms, systemic diseases, malnutrition [5, 16, 12]. In our series, diabetes was found only in 3 cases, lupus in 1 case, behcet in 2 cases and neoplasia in 3 cases.

A diagnostic delay of more than two months is found in various series [5, 10, 14], which agrees with the results of our study (60 days) and could be explained by the progressive onset of the disease, as well as its insidious and not very suggestive character at the beginning.

Clinically, fever is present in the majority of cases [6] justifying the systematic practice of a chest X-ray. Cough remains the most reported functional sign in all series [5, 6, 9], in our study it is present in 75.5% of cases, crackling rales were reported in 42% of cases in our study against 34% in Ouédraogo. The association of pleurisy was reported in 22.5% by Ouédraogo [5] vs. 16.1% in our series.

Among the extrathoracic locations, neuromeningeal involvement is variously assessed in the literature, varying between 10% to 30% [3], it is 3% according to Ouédraogo *et al.*, [5], and 6.4% in our series.

Hepatic involvement is very common in miliary tuberculosis, is often clinically silent and occurs only rarely [3, 17]. However, Ouédraogo *et al.*, [5] found one case of hepatomegaly, and 15 cases were found in our series

Laboratory abnormalities are most often summed up in lymphopenia, leukopenia whether or not associated with anemia and / or thrombocytopenia [2-4], which is consistent with the results of our study.

Radiologically, miliary tuberculosis is classically manifested by micronodular opacities in millet grain, punctiform, the diameter of which does not exceed 3mm and which are disseminated uniformly in the two pulmonary fields. Nodules or macronodules with a diameter greater than 3mm can also be seen and are present in 10% of cases according to Sharma [2]. In our series, the chest x-ray shows typical images of miliary in all cases

Chest CT, which is more efficient than chest x-ray, allows the detection of small parenchymal abnormalities that would go unnoticed on a standard chest x-ray [17, 18]. It is also useful for demonstrating associated involvement, in particular mediastinal lymph node [2, 3].

Tuberculin anergy is common in miliary tuberculosis. It is a testament to the immunosuppression in this severe form of tuberculosis. However, IDRT is not useful for diagnosis [2, 4], in our series 66 cases had negative IDRT.

In the presence of tuberculous miliaria, a dissemination assessment should be systematically carried out to search for other locations, including: search for BK in the urine, fundus of the eye, lumbar puncture, bone marrow biopsy, abdominopelvic ultrasound, other examinations are requested according to the warning signs (lymph node biopsy, pleural puncture biopsy, cerebral CT scan, cardiac ultrasound, medullary MRI, etc.) [13, 23]. The clinical picture of meningitis is not very specific, making lumbar puncture systematic in front of any tuberculous miliary [13]. In our series, the lumbar puncture performed in all of our patients demonstrated cerebrospinal fluid involvement in 6 cases (5.9%). The fundus revealed retinal involvement in the form of Bouchut tubercles in five cases (4.9%). Seven patients presented with urinary tract involvement (6.9%). Three patients (2.9%) presented with pericardial involvement and mediastinal and peripheral lymph node involvement was found in seven cases each.

According to the literature, the percentage of confirmed tuberculous miliaria is variable. Thus, it is 82% for Kim *et al.*, [16], 36% for Ouédraogo *et al.*, [5] and 24% for Toloba *et al.*, [8].

In our series, tuberculosis was confirmed in 48 cases (47.52%), by the isolation of Koch bacilli (BK) on direct examination and sputum culture in 26 cases, in 5 cases by bone marrow biopsy, in 7 cases by lymph node biopsy, and in 10 cases by pleural biopsy puncture. The positivity of the bacilloscopies would be

attributable either to a confluence of the nodular lesions followed by bronchial drainage, or to pre-existing micro-excavations or to a gangliobronchial fistula [5]. However, it can be estimated that in a country with a high tuberculosis endemicity, the presence of a radioclinical picture suggestive of tuberculosis may be sufficient to retain the diagnosis and start treatment. This view is shared by other authors [2-12].

The advent of anti-tuberculosis drugs and the improvement of resuscitation facilities have changed the course and prognosis of this condition and have helped to reduce its mortality.

According to our national tuberculosis control program, four major anti-tuberculosis drugs are used: rifampicin (RMP), isoniazid (INH), pyrazinamide (PZA) and ethambutol (ETB). In the absence of anti-tuberculosis treatment, miliaria was spontaneously fatal after one year [2, 3]. Mortality varies between 25 to 30% according to Sharma *et al.*, [3], 52% according to Ouédraogo *et al.*, [5], 12% according to Touré *et al.*, [12] and 44.3% according to Toloba *et al.*, [8]. The cause of death was mainly linked to acute respiratory failure and multiple organ disease from tuberculosis, including association with meningitis. We recorded in our series 11 cases of death dominated by acute respiratory failure in 8 cases (7.9%), multiorgan involvement in HIV in 2 cases and meningitis in only 1 case.

The indications validated by corticosteroid therapy by controlled studies are classified by the American Society of Infectious Diseases into 3 categories [25]: tuberculous pericarditis [26], tuberculous meningitis [27, 28] and tuberculous pleurisy [25]. Other forms [29] such as dyspnea miliaria should be discussed on a case-by-case basis. The initial daily dose is between 0.5 and 1 mg / kg of prednisone equivalent and should be rapidly reduced to try to achieve withdrawal in 3 months [13].

Corticosteroid therapy was indicated in 20% in the series by Sharma *et al.*, [3] and 44.8% in the series by Touré *et al.*, [12]. In our series, 10 patients (56.7%) received adjunct corticosteroid therapy at a dose of 1 mg / kg / day, decreasing over 40 days on average, the indication of which was significant dyspnea and cerebromeningeal damage. This corticosteroid therapy is believed to have anti-inflammatory and analgesic activity linked to the effects of corticosteroids on cytokines [18, 30].

Several complications can be seen, some are due to miliary tuberculosis itself such as the occurrence of acute respiratory distress syndrome [31], pneumothorax [32, 33], purulent pleurisy [34], hematological complications such as disseminated intravascular coagulation (DIC) [31], macrophage activation syndrome [35] and Schwartz Bartter

syndrome [36]. The other complications are due to the associated localizations [19, 37, 38], the decompensation of a defect, the adverse effects of anti-tuberculosis treatment and the sequelae that miliary tuberculosis can leave. In our study, 20 patients presented complications including 8 cases (9.8%) of pyopneumothorax, 3 cases of isolated pneumothorax, 3 cases of drug-induced hepatitis, 2 cases of Dress syndrome and one case of polyneuropathy secondary to isoniazid.

CONCLUSION

Miliary tuberculosis is a severe acute form that is life-threatening. Its diagnosis is most often radioclinical because of the rarity of the positivity of the bacilloscopy. Its prognosis depends on the early diagnosis and treatment, hence the importance of rapid management.

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