



Miliary tuberculosis and acute respiratory distress syndrome

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ABSTRACT

Background: Miliary tuberculosis is a serious and uncommon form of tuberculosis due to hematogenous dissemination of *Mycobacterium tuberculosis*.

Objective: This study aimed to describe the epidemiological and clinical features of miliary tuberculosis.

Patients and Methods: Data were collected from clinical files between August 2016 and July 2018.

Results: In 2 years, 24 cases were recorded, representing a proportional morbidity of 13%. Among them, 71% were smokers and 38% had diabetes. The presence of a BCG vaccination scar was observed in 2 patients (8%). Human immunodeficiency virus (HIV) serology was positive in 4 cases (17%). The symptomatology was dominated by: fever (100%), cough (83%), and chest pain (79%). Radiological images with micronodular opacities were the most common (54%), followed by macronodular densities (33%), and reticulonodular densities (13%). The evolution was favorable in 77%, with no patient lost to follow-up, but 7/24 (29%) died, either before the initiation of therapy ($n = 2$) or during therapy ($n = 5$).

Conclusion: Miliary tuberculosis is an acute and severe form of life-threatening tuberculosis. It requires a prompt and accurate diagnosis and treatment. An improved accessibility to early diagnosis and treatment and prevention of TB infection should reduce its prevalence.

1. Introduction

Tuberculosis (TB) remains one of the most important causes of death from infectious diseases and poses a serious challenge to global health. Miliary TB is a potentially fatal form of TB that results from massive lymphohematogenous dissemination of *Mycobacterium tuberculosis* [1–3]. The incidence of miliary TB in relation to all forms of TB is between 0.15% and 10%, depending on the studies conducted by different authors [1,4,5]. Its mortality rate has been reported to lie between 13% and 25%, and even up to 65% in patients requiring mechanical ventilation [3,6]. Miliary TB still faces diagnostic difficulties even in developed countries, sometimes leading to delays in initiating appropriate treatment, thus compromising the vital prognosis [4,6,7]. No studies on the description of clinical aspects of miliary TB have been conducted in Mauritania. This work aimed to evaluate the epidemiological, clinical and evolutionary aspects of miliary TB in patients hospitalized in our hospital in Mauritania.

2. Patients and methods

This is a retrospective study of patients with miliary TB hospitalized between August 2016 and July 2018 in the Department of Internal

Medicine and Infectious Diseases of the Kiffa Regional Hospital Center. TB diagnosis was established based on the presence of clinical and radiological signs suggestive of miliary TB. Pulmonary nodules were classified as follows: micronodular (1 to 3 mm in diameter), macronodular (> 3 mm in diameter), and reticulonodular densities characterized by nonspecific interstitial patterns. For each patient, epidemiological data (age, sex, geographical origin, bacille Calmette Guerin (BCG) vaccination status, history of TB), clinical and laboratory examinations (chest x-ray, search for acid-alcohol-fast bacilli), and information on disease evolution were collected.

The anti-TB treatment administered to all patients consisted of quadruple combination regimen administered in two phases: rifampicin (10 mg/kg/day), isoniazid (5 mg/kg/day), ethambutol (20 mg/kg/day), and pyrazinamide (30 mg/kg/day), during two months of intensive treatment phase, followed by bithérapie with rifampicin and isoniazid at the same doses for four months of maintenance phase.

2.1. Statistical analysis

Data entry and analysis were performed using EPI INFO software version 6.4. For the comparison of qualitative variables, a chi-square test was used. A value of $p \leq 0.05$ was set as the threshold of

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significance. Incomplete medical files with missing data were excluded from the study.

3. Results

During the period of our study, 24 cases of miliary TB were diagnosed. The presenting signs and symptoms included fever (24/24; 100%), chronic cough (20/24; 83%), chest pain (19/24; 79%), and impairment of general condition (11/24; 46%). These 24 cases represented 13% (24/185 admissions) of patients hospitalized for acute respiratory distress syndrome (ARDS). The male:female sex-ratio was 5:1. The mean (\pm standard deviation) age of the patients was 45.2 ± 15.0 years old (range, 21 to 76 years old). The most affected age groups were 21–40 years old (12/24; 50%) and 41–70 years old (10/24; 42%). The other two patients (2/24; 8%) were aged > 70 years. The majority of the patients (15/24; 63%) came from rural areas while the remaining 9 patients (37%) resided in urban areas. Of 24 patients, 17 (71%) were regular smokers, 10 (42%) had at least one of the family members with active TB, 9 (38%) had insulin-dependent (1/9) or non-insulin-dependent (8/9) diabetes, 1 (4%) had herpes zoster, and 1 (4%) was in postpartum period. The presence of a BCG vaccination scar was observed in two cases (8%). HIV serology was performed in all patients and was positive in 4/24 (17%) cases.

The follow-up period varied between 63 and 541 days, with a mean (\pm standard deviation) of 143.5 ± 131.0 days (median, 191.8 days). Clinical examination identified a wide range of non-respiratory physical signs that are summarized in Table 1. Pulmonary X-rays showed micronodules in 13/24 (54%) cases (Fig. 1), macronodular opacities in 8 cases (33%), and reticulonodular densities in 3 cases (13%). The other associated radiological anomalies included pulmonary cavitations in 4 cases (17%) and mediastinohilar adenopathy in 7 cases (29%).

Furthermore, hepatomegaly, splenomegaly, and ascites were found in 7 (29%), 5 (21%), and 2 (8%) patients, respectively. Thrombocytopenia was found in 18 (75%) patients, leukopenia in 7 (29%) patients, and anemia in 18 (75%) patients. Of 24 cases of miliary TB, 22 (92%) received anti-TB treatment. Two (8%) patients died before starting a specific treatment. Corticosteroid therapy was administered in 10 (42%) patients suffering from ARDS. Among 22 patients treated with anti-TB drugs, 17 (71%) completed the treatment regimen and were cured, while 5 (21%) died during treatment.

4. Discussion

Patients with miliary TB represented 13% of patients with pulmonary TB diagnosed over 2 years in the Department of Internal Medicine and Infectious Diseases of the Kiffa Regional Hospital Center. The proportion of miliary TB in our study is lower than that observed in other studies carried out in Africa, notably in other countries in the region, including Tunisia [7], Morocco [6], Mali [4], and Senegal [5]. The male:female sex ratio was higher in our study than that observed in other African countries [5,6,8]. In our study, the most affected age

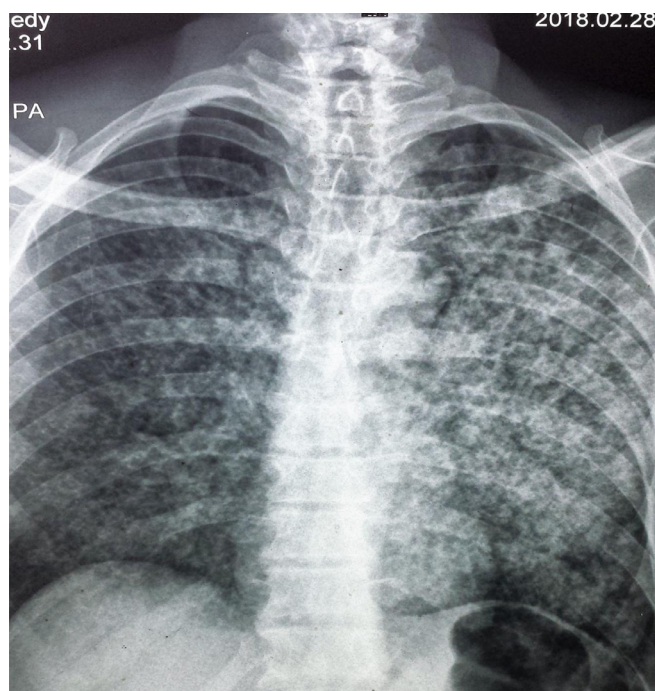


Fig. 1. Frontal chest radiograph showing well-defined and diffuse micronodular opacities in both lung fields.

group was 21–40 years old. These results are consistent with those observed earlier by other authors who found that in developing countries TB is most likely to affect young male adults in full socio-economic activity, which may lead to increased poverty in affected persons or families [2,5,9]. Smoking is likely to play a role in the emergence of miliary TB by local alteration of defense mechanisms [6,10]. Previous studies have shown that 33.5% of patients with miliary TB were smokers, compared to 22.4% and 46.7% in the studies performed by Touré et al. [5] and Zaghba et al. [6], respectively. In our study, regular smokers accounted for 17/24 (71%) of patients with miliary TB. In addition, many of our patients (10/24; 42%) were most likely exposed to active cases of TB in his or her immediate entourage. Other studies have reported that between 15% and 35% of patients with miliary TB have been exposed to other patients with active pulmonary TB [6,11,12].

As TB prevalence has declined considerably in the developed countries before the advent and spread of acquired immunodeficiency syndrome (AIDS), the tendency of elderly people to develop miliary TB could be explained by age-related decline in immune defenses and frequent contact with TB bacilli during their younger years. TB is most often the result of endogenous reactivation. Favorable predisposing factors that we noted in our patient population include co-morbidities, such as diabetes in 38% of cases. This percentage is higher than that reported by many authors [5,6,11]. In our series, BCG vaccination scar was found in only two cases (8%). This observation tends to support the data in the literature that BCG efficacy is well established in the prevention of serious forms of TB, such as miliary TB and TB meningitis [4,13]. However, confirmation of BCG efficacy is difficult to demonstrate in a context where vaccination coverage is still insufficient in many countries where TB is highly prevalent.

The seroprevalence of HIV infection in our study was 17%. HIV-TB co-infection is a well-established fact, documented and reported by several authors [2,4–6,9], especially for pulmonary TB.

Diagnostic delay of miliary TB beyond two months was reported by several authors [4,7,8]. This corroborates the results of our study and could be related to the progressive installation of the disease, as well as to its insidious character during the early phase of its development.

Table 1

Clinical presentation of 24 cases of miliary tuberculosis in our study.

Clinical signs	N (%)
Fever	24 (100)
Chronic cough	20 (83)
Chest pain	19 (79)
Impairment of general condition	11 (46)
Dyspnea	10 (42)
Polyadenopathy	8 (33)
Hepatomegaly	7 (29)
Splenomegaly	5 (21)
Ascitis	2 (8)
Abdominal pain	1 (4)

Only respiratory symptoms usually attract attention and lead to chest X-rays [4,6,14], which explains the long diagnostic delay that we observed.

Clinically, we noted the usual signs of TB, with chronic cough as the most common symptom indicating routine chest X-ray. The functional signs found in the patients were varied and not specific to miliary TB as many other respiratory pathologies also present these signs and symptoms [2,4–7,10].

Radiological image of miliary TB often shows punctuated micronodular opacities whose diameter hardly exceeds 3 mm in diameter and which are disseminated uniformly in both lung fields. Atypical aspects may exist, including the presence of macronodules, defined as nodules greater than 3 mm in diameter. In one study, macronodules were present in 10% of cases [2]. In our series, chest x-rays of all patients showed typical radiological images of micronodules or, to a lesser extent, macronodular or reticulonodular densities. Our study demonstrates that the role of pulmonary x-ray is vital for diagnosis in TB endemic area [4] to avoid delay in the therapeutic management of miliary TB which may compromise the patient's vital prognosis. Indeed, in a country with a high TB prevalence, the presence of a clinical and radiological evidence suggestive of TB may be sufficient to establish the diagnosis and initiate treatment without delay. This point of view is shared by many authors [2,4,5,9,15].

In our study, lymphopenia, leukopenia with or without anemia, and/or thrombocytopenia were the main hematological findings. These results are in agreement with those observed earlier by other authors [2,15]. Other complementary examinations were performed depending on functional and clinical signs of each patient. However, despite limited health resources in many endemic countries, including Mauritania, clinical and radiological assessment should be completed as soon as possible to establish a diagnosis and specific anti-TB treatment should be initiated to minimize mortality. Corticosteroid therapy was indicated in 42% of our patient population. This rate was higher than that reported by Sharma et al. [2] but is lower than in other studies [5,6]. Corticosteroids have anti-inflammatory and analgesic activities which may be beneficial when combined with specific anti-TB treatment in some patients (16/24). The case fatality rate in our hospital was 21%, which is higher than that reported from Senegal and Morocco [5,6] but lower than that reported from Mali [4]. This high mortality rate could be explained by the delay in consultation, poor health resources, and impact of HIV infection [16]. Similar findings were reported from Burkina Faso [17].

5. Conclusion

Although relatively infrequent, miliary TB is an acute, severe, life-threatening form of TB which constitutes a therapeutic emergency. Its diagnosis is based on the standard chest X-ray. Mortality was high in our setting but could be improved by early diagnosis and prompt management.

Transparency declaration

The authors have no conflicts of interest to declare.

CRediT authorship contribution statement

Boushab Mohamed Boushab: Writing - original draft, Conceptualization, Data curation. **Leonardo Kishi Basco:** Supervision.

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Ethical statement

We did not obtain any ethical approval for this retrospective clinical study because we followed the national guidelines to treat cases of miliary tuberculosis and acute respiratory distress syndrome. In all cases that were included in this study, we were confronted with an emergency situation that did not allow any possibility or time for discussion or explanation to adult patients to obtain their written informed consent prior to and during the first few days of treatment. We consider that, in these circumstances requiring a rapid, emergency treatment, informed consent is not applicable.

Conflict of interest

The authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jctube.2019.100113.

References

- [1] Ray S, Talukdar A, Kundu S, Khanra D, Sonthalia N. Diagnosis and management of miliary tuberculosis: current state and future perspectives. *Ther Clin Risk Manag* 2013;9:9–26.
- [2] Sharma SK, Mohan A, Sharma A, Mitra DK. Miliary tuberculosis: new insights into an old disease. *Lancet Infect Dis* 2005;5(7):415–30.
- [3] Han Y, Kim SJ, Lee SH, Sim YS, Ryu YJ, Chang JH, et al. High blood neutrophil-lymphocyte ratio associated with poor outcomes in miliary tuberculosis. *J Thorac Dis* 2018;10(1):339–46.
- [4] Toloba Y, Diallo S, Maïga Y, Sissoko BF, Keïta B. Miliare tuberculeuse au Mali pendant la décennie 2000–2009. *Rev Pneumol Clin* 2012;68(1):17–22.
- [5] Touré NO, Cissé MF, Dia Kane Y, Diatta A, Bouker Bakioui B, Ndiaye EHM, et al. Miliare tuberculeuse: à propos de 49 cas. *Rev Mal Respir* 2011;28(3):312–6.
- [6] Zaghba N, El Hachimi K, Benjelloun H, Yassine N. La miliare tuberculeuse, une série rétrospective marocaine. *Rev Pneumol Clin* 2018;74(1):28–34.
- [7] Cherif J, Mjid M, Ladhari A, Toujani S, Mokadem S, Louzir B, et al. Délai diagnostique de la tuberculose pulmonaire et pleurale. *Rev Pneumol Clin* 2014;70(4):189–94.
- [8] Msaad S, Fouzi S, Ketata W, Marwen I, Yangui M, Ayoub A. La miliare tuberculeuse: à propos de 29 cas. *Rev Tunis infectiol* 2010;4:46–52.
- [9] Haloui I, El Biase M, Rochaidi Z, Bakhatar A, Yassine N, El Meziane A, et al. La miliare tuberculeuse: à propos de 10 cas. *Rev Mal Respir* 2006;23:27.
- [10] Rizzi EB, Cristofaro M, Goletti D, Palmieri F, Bevilacqua N, Lauria FN, et al. Detection of pulmonary tuberculosis: comparing MR imaging with HRCT. *BMC Infect Dis* 2011;11(1):243.
- [11] Kim DK, Kim HJ, Kwon SY, Yoon HI, Lee CT, Kim YW, et al. Nutritional deficit as a negative prognostic factor in patients with miliary tuberculosis. *Eur Respir J* 2008;32(4):1031–6.
- [12] Ballouhey Q, Lau S, Accadbled F, Wahn U, Kaiser D, Rothe K, et al. Miliary tuberculosis complicated by pulmonary cavitations and pneumothorax in a 14-month old boy. *Ann Thorac Cardiovasc Surg* 2012;18(4):355–8.
- [13] Brosch R, Che D, Decludt B, Durieux P, Gaudelus J, Gicquel B, et al. Tuberculose: place de la vaccination dans la maîtrise de la maladie. Institut national de la santé et de la recherche médicale (INSERM) Paris: Les Editions INSERM; 2004.
- [14] Hussain SF, Irfan M, Abbasi M, Anwer SS, Davidson S, Haqee R, et al. Clinical characteristics of 110 miliary tuberculosis patients from a low HIV prevalence country. *Int J Tuberc Lung Dis* 2004;8(4):493–9.
- [15] Escobedo-Jaimes L, Cicero-Sabido R, Criales-Cortez JL, Ramirez E, Romero M, Rivero V, et al. Evaluation of the polymerase chain reaction in the diagnosis of miliary tuberculosis in bone marrow smear. *Int J Tuberc Lung Dis* 2003;7(6):580–6.
- [16] Swaminathan S, Padmapriyadarsini C, Ponnuraja C, Sumathi CH, Rajasekaran S, Amerandran VA, et al. Miliary tuberculosis in human immunodeficiency virus infected patients not on antiretroviral therapy: clinical profile and response to shortcourse chemotherapy. *J Postgrad Med* 2007;53(4):228–31.
- [17] Ouedraogo M, Ouedraogo G, Ohedraogo SM, Zoubga ZA, Bambara M, Ky C, Badoum G, Zigani A, Some L, Drabo YJ. Aspects épidémiologiques et cliniques des miliars tuberculeuses au Burkina Faso: a propos de 93 cas. *Méd Afr Noire* 2000;47(4):180–3.