CLINICAL MANIFESTATIONS AND OUTCOME OF MILIARY TUBERCULOSIS

J. Ayatollahi*

Infectious and Tropical Research Center, Sadoughi Hospital, School of Medicine, Yazd University of Medical Sciences, Yazd, Iran

Abstract- Miliary tuberculosis (TB) is due to hematogenous spread of *Mycobacterium tuberculosis*. Clinical manifestations are nonspecific and protean, depending on the predominant site of involvement. We evaluated the clinical manifestations of 15 patients with miliary TB. The diagnosis of miliary tuberculosis was based on the identification of miliary nodules on chest radiography and one of the three following criteria: 1) positive acid-fast bacilli smear and/or culture (14/15), 2) histopathological identification of TB histopathological granuloma (4/15), or 3) radiological and clinical improvement after anti-tuberculosis treatment (14/15). The median age (±SD) of the patients was 52.6±19.1 years. Only one patient had underlying diseases, diabetes mellitus. Three patients developed acute respiratory distress syndrome (ARDS), one of whom died during intensive care. ARDS caused by miliary TB is associated with a high fatality rate, scope remains for improvement in its management.
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Key words: Miliary tuberculosis, ARDS, *Mycobacterium tuberculosis*

INTRODUCTION

The term miliary tuberculosis (TB), first used to describe the resemblance of the pathologic lesions to millet seeds, now describes any progressive disseminated hematogenous TB. In children, the illness is acute or subacute, with high intermittent fevers, night sweats, and occasional rigors. Pleural effusion, peritonitis or meningitis occurs in as many as two thirds of patients. The illness in young adults is usually more chronic and initially less severe. Miliary TB also is considered an unusual cause of acute respiratory distress syndrome (ARDS).

In the prechemotherapy era, miliary TB occurred either soon after primary infection in children or young adults or as a terminal event in untreated chronic organ TB. However, it is now more frequently observed in older individuals, often with underlying illnesses or conditions that may obscure diagnosis. Three large series in the chemotherapy era have emphasized the frequency of miliary TB in minority racial groups and the importance of underlying conditions such as alcoholism, cirrhosis, neoplasm, pregnancy, rheumatologic disease, and treatment with immunosuppressive agents (1-3). There is usually no prior history of tuberculosis, and the onset is often subtle.

The prognosis of miliary TB *per se* has clearly improved after the introduction of effective anti–tuberculosis drugs. However, the situation is quite different when ARDS develops after miliary TB. According to the limited number of articles reporting the outcome of ARDS caused by miliary TB, the fatality rate ranges from 33% to as high as 100% (4-7) which is far higher than for ARDS from other causes. Most articles about ARDS associated with miliary TB are case reports discussing the experience in a small number of cases (8, 9), and most of them are restricted to human immunodeficiency virus (HIV) seropositive patients (10, 11). In this study, we evaluate the clinical manifestations and outcome of miliary TB in HIV-seronegative patients.

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***Corresponding Author:**
J. Ayatollahi, Department of Infectious and Tropical Research Center, Sadoughi Hospital, School of Medicine, Yazd University of Medical Sciences, Yazd, Iran
Tel: +98 351 8224228, Fax: +98 351 8224001
E-mail: jamshidayatollahi@yahoo.com

MATERIALS AND METHODS

We diagnosed fifteen cases of miliary tuberculosis over a period of nearly 10 years. All available clinical informations, including demographic data, past medical history, laboratory findings, radiological presentations, data during ICU care and final outcome were evaluated.

The diagnosis of miliary TB required definite identification of miliary nodules on chest radiography or on high resolution computed tomography (HRCT) of the lung by a radiologist. Confirmation of TB as the cause of radiological abnormality of the lung required at least one of the following three criteria: 1) positive acid-fast bacilli (AFB) smear and/or culture for *Mycobacterium tuberculosis* from clinical specimens such as sputum, bronchial lavage fluid, pleural fluid and bone marrow aspirate, 2) histopathological identification of TB granuloma in biopsied tissues of lung, pleura and/or bone marrow, or 3) clinical and radiological improvement after anti-tuberculosis treatment.

ARDS was defined in accordance with the American-European consensus conference on ARDS (12). In cases where detailed figures for FIO_2 levels were not available, oxygenation impairment was diagnosed if arterial oxygen tension did not exceed 60 mmHg with supplemental oxygen of 6 L/min or more via nasal prong or face mask.

RESULTS

The mean age (±SD) of the 15 miliary TB patients (9 males and 6 females) was 52.6 (±19.1) years. One patient had underlying disease, diabetes mellitus.

Table 1 shows the clinical manifestations. The duration of symptoms (mean ±SD) was 6.7±8.2 weeks. Presenting signs included fever (15/15,100%), rales (5/15, 33.3%), altered mental status (4/15, 26.6%), lymphadenopathy (1/15, 6.6%) and signs of pleural effusion (1/15, 6.6%).

In all patients, the miliary nodules were confirmed by a radiologist on chest radiography (Fig.1) and/or lung HRCT. In addition to miliary nodules, pneumonic infiltration (in 3 patients) and cavitation (in 1 patient), pleural thickening (in 1 patient) and pleural effusion (in 1 patient) were accompanying radiological findings. Three patients showed diffuse bilateral infiltration compatible with the radiological diagnostic criteria for ARDS (Fig. 2).

M. tuberculosis as the causative organism of the abnormal chest radiology was confirmed in all patients. Of these, 8 tested positive for AFB smear of sputum and 7 were reported to be positive for *M. tuberculosis* culture at a later follow-up stage. Bronchial wash for AFB smear was positive in 2 and transbronchial biopsy showed caseating granuloma and positive culture of biopsy specimen in 1. Lymph node biopsy was done in 1 patient in whom smear and culture were negative and showed caseating granuloma. Anti-HIV antibodies were negative in all patients.

ARDS developed in three of the 15 patients with miliary TB (20%). One was detected at the time of admission and the other two developed ARDS during hospitalization. All of the three patients were positive for AFB smear. All three patients with ARDS required ICU transfer and mechanical ventilation; the durations of ICU stay of two survivors were 7 and 5 days and both required mechanical ventilation for all of this period. The duration of ICU stay of non survivor, from ICU admission to death, was 1.5 days.

Anti-tuberculosis drugs were prescribed and all of the patients were treated with isoniazid, rifampin, pyrazinamide and ethambutol. Systemic corticosteroids were prescribed for all ARDS patients. One of the patients died of the disease, suggesting an overall fatality and 6.6% in all patients and a 33.3% in ARDS patients.

Table 1. Clinical characteristics of miliary tuberculosis in 15 patients

Symptoms	Number	Percent
Fever	15	100
Night sweats	15	100
Anorexia	15	100
Weight loss	13	86.6
Cough	13	86.6
Sputum	11	73.3
Dyspnea	4	26.6
Altered mental status	4	26.6
Vomiting	3	20

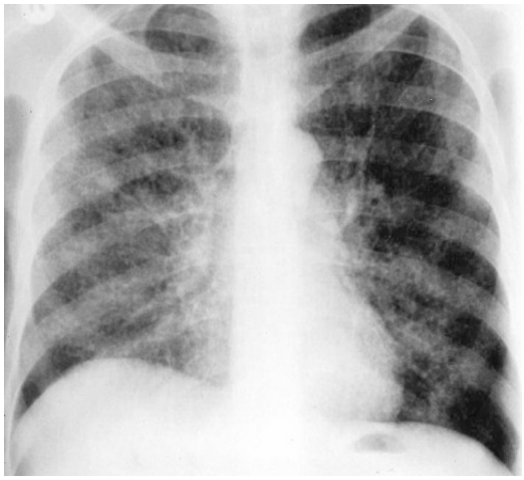

Fig. 1. Miliary tuberculosis. Fine nodules scattered throughout both lung fields.

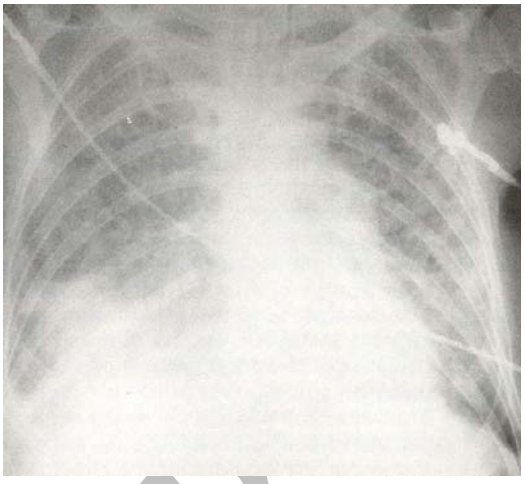

Fig. 2. Adult respiratory distress syndrome. Diffuse ill-defined patchy shadowing of non-specific appearance

DISCUSSION

Miliary TB is due to hematogenous spread of tubercle bacilli. The successful dissemination of TB depends on the balance between mycobacterial virulence and host immune defence.

Although in children it is often the consequence of a recent primary infection, in adults it may be due to either recent infection or reactivation of old disseminated foci. Miliary TB may occur in young children, especially those under one year of age (13-15). While infants are highly susceptible to progressing to miliary TB, presumably due to their relatively immature systems, most cases occur in elderly adults due to the relative waning of their cellular immunity (16). This tendency corresponds well with this study, which showed the mean age of the patients to be 52.6±19.1 years. This finding should be considered seriously, because it suggests that miliary tuberculosis is no longer a disease of extreme ages, at least in Yazd. Interestingly, there was no patient with a prior TB history in our study (corresponds with Kim *et al.* study), indicating that progressive primary disease might play an important role in the pathogenesis of miliary TB in this group (4-6). Miliary TB was proved by bacteriology and/or pathology in all cases, and supported by clinical and radiological improvement. Clinical conditions associated with impaired cellular immunity are important risk factors for the development of miliary TB.

The percentage of miliary TB patients with some identifiable medical condition has been reported to be in the range of 38% to 70% (17-19). In the present study, there was only one case with underlying disease, diabetes mellitus. Noticeably, there were no demonstrable risk factors in other patients in our study. Therefore, miliary TB should not be excluded by the absence of underlying medical illnesses.

Miliary TB is a rare cause of acute respiratory failure and ARDS (7, 20). In one series from South Africa, it was estimated that 2% of ARDS cases were associated with disseminated TB (9). In this regard, the diagnosis of miliary TB as the cause of ARDS seems to be delayed or even missed. In our study, however, the time lag from admission to prescription of anti-tuberculosis drugs in ARDS patients was a few hours, which is far shorter than that reported by Kim *et al.* (2.5±4.2 days) (4) and Heffner *et al.* (7.2±1.7 days) (21). This can be explained by the awareness among our physicians of the possibility of TB due to the high prevalence and morbidity of TB in Iran.

The fatality rate (33.3%) of ARDS caused by miliary TB in the present study was lower than previous reports (70% to 100%) (6). Till now, no specific method has been developed for the treatment of ARDS caused by miliary TB. Although Sun *et al.* reported promising results regarding the efficacy of steroids as a treatment modality for ARDS caused by miliary TB (22), their experience is too limited for general application and there have been no follow-up

studies to support their results. Therefore, the best policy for management of ARDS associated with miliary TB would be early suspicion and a prompt diagnostic work-up by attending clinicians. Unfortunately, the early diagnosis of miliary TB is often hampered for several reasons: 1) insufficient clinical suspicion on the part of the attending physician, 2) non-specific clinical symptoms and signs in most patients, and 3) delay in the examination of accessible body fluids by smear and culture (20). What is promising in our data is that, contrary to prior thinking (1, 23), AFB smear for clinical specimens was positive in half of cases (8/15). Based on this finding, early suspicion alone can lead to correct diagnosis in approximately half of the patients with miliary TB. For the remaining half, multimodality diagnostic work ups would be helpful, including recently developed rapid diagnostic methods for TB (4, 24, 25).

Despite the limitations associated with a retrospective study by a single center, we nevertheless consider that this investigation contributes to a greater understanding of this rare and fatal disease. Although the prognosis of ARDS has improved in recent decades, there remains scope for further improvement of ARDS associated with miliary TB.

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