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Miliary tuberculosis: A new look at an old foe

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ABSTRACT

Miliary tuberculosis (TB), is a fatal form of disseminated TB characterized by tiny tubercles evident on gross pathology similar to innumerable millet seeds in size and appearance. Global HIV/AIDS pandemic and increasing use of immunosuppressive drugs have altered the epidemiology of miliary TB. Keeping in mind its protean manifestations, clinicians should have a low threshold for suspecting miliary TB. Careful physical examination should focus on identifying organ system involvement early, particularly TB meningitis, as this has therapeutic significance. Fundus examination for detecting choroid tubercles can help in early diagnosis as their presence is pathognomonic of miliary TB. Imaging modalities help in recognizing the miliary pattern, define the extent of organ system involvement and facilitate image guided fine-needle aspiration cytology or biopsy from various organ sites. Sputum or BAL fluid examination, pleural, pericardial, peritoneal fluid and cerebrospinal fluid studies, fine needle aspiration cytology or biopsy of the lymph nodes, needle biopsy of the liver, bone marrow aspiration and biopsy, testing of body fluids must be carried out. GeneXpert MTB/RIF, line probe assay, mycobacterial culture and drug-susceptibility testing must be carried out as appropriate and feasible. Treatment of miliary TB should be started at the earliest as this can be life saving. Response to first-line anti-TB drugs is good. Screening and monitoring for complications like acute respiratory distress syndrome (ARDS), adverse drug reactions like drug-induced liver injury, drug-drug interactions, especially in patients co-infected with HIV/AIDS, are warranted. Sparse data are available from randomized controlled trials regarding optimum regimen and duration of anti-TB treatment.

1. Introduction

Tuberculosis (TB) is still a global public health problem in spite of worldwide control efforts (Table 1). As per the year 2014 estimates published in the Global Tuberculosis Report in 2015 [1], an estimated 9.6 million people developed TB and 1.5 million died from the disease globally. Miliary TB is a fatal form of disseminated TB that results from a massive lymphohematogeneous dissemination from a *Mycobacterium tuberculosis*-laden focus [2–6]. Radiologically, the miliary pattern has been defined as "a collection of tiny discrete pulmonary opacities that are generally uniform in size and widespread in distribution, each of which measures 2 mm or less in diameter" (Fig. 1) [7].

Manget, is credited to have coined the term "miliary TB" in 1700 [8]. He likened the tiny tubercles evident on gross pathological examination to that of innumerable millet seeds in size and appearance [*miliarius* (Latin), translation: related to millet seed]. Miliary TB is uniformly fatal if untreated. Due to varied clinical manifestations, atypical radiographic findings and difficulties in establishing TB as the aetiological diagnosis, even today, miliary TB remains a formidable diagnostic and therapeutic challenge [2,9]. In this review, we have attempted to provide an overview regarding the changing clinical picture of miliary TB and issues related to diagnosis and management.

2. Epidemiology

2.1. Methodological issues

Reliable community-based epidemiological data are not available on the prevalence of miliary TB. Some of the methodological issues include different denominators used, lack of a "gold standard" for diagnosis, variations in the choice and nature of invasive diagnostic methods used for securing tissue to confirm the diagnosis among others. These issues should be kept in mind while

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Table 1
Epidemiology of tuberculosis 2014.

Variable	Estimate
Incidence*	133 (126–141)
Prevalence*	174 (158–190)
Prevalence of HIV in incident TB cases*	12 (11–13)
Mortality*	16 (13–18)
HIV-positive TB mortality*	5.3 (4.8–5.9)
% of new cases with MDR-TB†	3.3 (2.2–4.4)
% of retreatment cases with MDR-TB†	20 (14–27)
Prevalence of XDR-TB among MDR-TB cases†	9.7 (7.4–12)

Source: Ref. [1].
HIV = human immunodeficiency virus; TB = tuberculosis; MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant tuberculosis.
* Expressed as estimate (lower and upper bounds of 95% uncertainty levels)/100,000 population.
† Numbers in parentheses indicate 95% confidence intervals.

comparing and interpreting published epidemiological data on miliary TB.

2.2. Clinical and autopsy studies

In various clinical studies among immunocompetent adults, miliary TB accounts for less than 2% of all cases of TB and up to 20% of all extra-pulmonary TB (EPTB) cases [10–15]. In late HIV infection, EPTB accounts for more than 50% of all cases of TB and miliary TB is more frequently encountered [2–5]. In autopsy studies in adults, miliary TB was documented in a higher proportion of patients, accounting for 0.3%–13.3% of all autopsies and 11.9%–40.5% of all cases of TB [16–22].

2.3. Demographic trends

Before the advent of anti-TB treatment, miliary TB was predominantly seen as a disease of infants and children [23,24]. However, since the 1980s a changing epidemiological trend has been observed and miliary TB is increasingly being recognized in adults also. Two peaks are evident, one involving adolescents, young adults and another later in life among elderly individuals [2–5,14,25–50]. This epidemiological change has been thought to be due to global pandemic of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), increasing occurrence of organ transplantation, use of immunosuppressive drugs including anti-TNF-α, chronic hemodialysis program, among others.

In pediatric as well as adult series [2–5,14,25–50], male gender seems to be more frequently affected by miliary TB. In some adult series on miliary TB [14,22,34,39] a female preponderance has been documented. A higher occurrence of miliary TB among African Americans has been observed in some of the earlier publications from the USA, though such a trend is not evident in later studies [2–5,29,40].

3. Predisposing, associated conditions

In patients with miliary TB, several predisposing or associated conditions have been documented. Some of these conditions include childhood infections, malnutrition, HIV/AIDS, alcoholism, chronic kidney disease, dialysis, post-gastrectomy status, organ transplantation, immunosuppressive drug use, connective tissue disorders, pregnancy, postpartum, presence of an underlying malignancy, and silicosis [2–5]. Recent evidence has brought into focus diabetes mellitus and tobacco smoking as newer emerging risk factors in the causation of TB [9].

In addition to glucocorticoids, immunosuppressive, cytotoxic drugs that are known to predispose to the development of miliary TB, use of immunomodulatory biologicals has been reported to cause fatal TB including miliary TB [51–54]. In a prospective study among patients who received anti-tumor necrosis factor (anti-TNF) therapy [51], disseminated and miliary TB accounted for 27.5% of all TB cases and 44% of EPTB. In this study [51], it was also observed that the rate of development of TB was higher for adalimumab (136 events/100,000 person-years) and infliximab (144 events/100,000 person-years) than for etanercept (39 events/100,000 person-years). In a prospective population-based national cohort study (2002–2011) from Sweden [53] the rate of incident TB in the general population and in a cohort of biological-naïve and biological-exposed patients diagnosed with RA was estimated. In comparison to the general population, patients with RA who were not exposed to biologicals had a four-fold increased risk of TB (hazard ratio [HR] 4.2; 95% confidence intervals [CI] 2.7–6.7), which did not decline over calendar time. Further, compared to etanercept, the HRs for most recent exposure to adalimumab and infliximab were 3.1 (95% CI 0.8–12.5) and 2.7 (95% CI 0.7–10.9), respectively; and the HR for etanercept compared with biological-naïve RA was 1.7 (95% CI 0.6–4.6). In another recent study [54] that investigated incidence of TB following anti-TNF therapy from Korea, a significantly lower incidence of TB was observed in patients treated with etanercept (reference), compared with those treated with infliximab (incidence rate ratio [IRR] 6.8, 95% CI 3.74–12.37) and adalimumab (IRR 3.45, 95% CI 1.82–6.55). A systematic

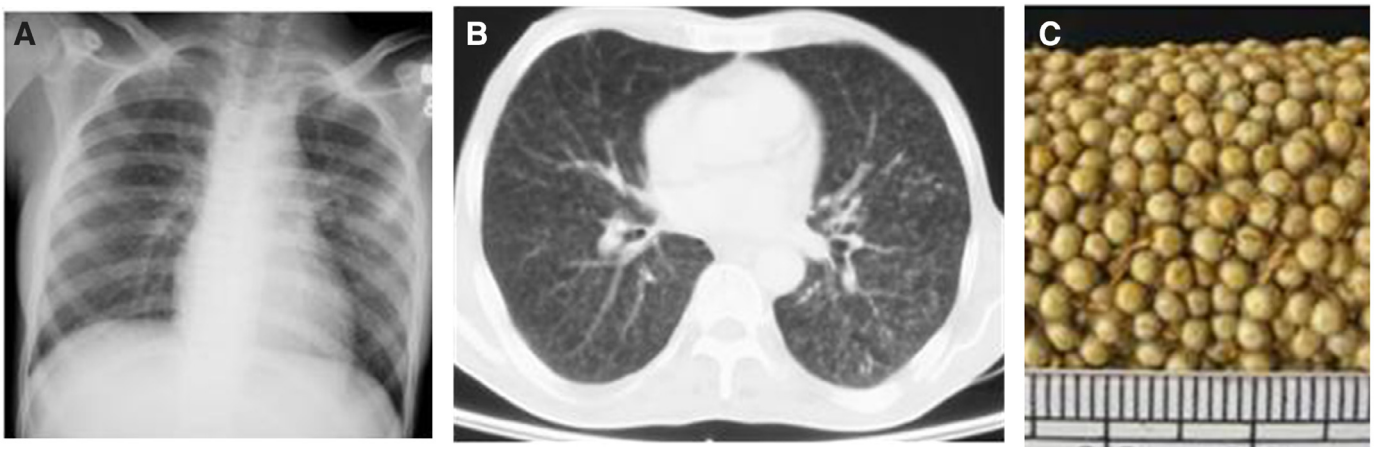

Fig. 1. Chest radiograph (postero-anterior view) (**A**) and chest CT (lung window) (**B**) showing classical miliary pattern. The nodules (<2 mm) evident in miliary tuberculosis resemble the grains of pearl millet (*Pennisetum typhoides*, bajra) (C).