**Title:** Miliary Tuberculosis in an Immune-Competent Bangladeshi Male- case report

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**BACKGROUND**

Miliary tuberculosis (MTB) is a rare and fatal infectious disease that occurs due to the lympho-hematogenous spread of *Mycobacterium tuberculosis* bacilli.1 It involves commonly the lung but may also affect other systems in the body. In all forms of tuberculosis cases MTB occurs in 1-2% and extrapulmonary tuberculosis, it is approximately 8%.2 Clinical features of MTB are non-specific, such as prolonged pyrexia, night sweats, weight loss, lassitude, anorexia, hepatomegaly, and abdominal pain. When the lungs are, an affected patient presents with cough, dyspnea, and chest pain. Occasionally Patients with miliary tuberculosis can present with “pyrexia of unknown origin” (PUO).

Atypical clinical manifestation often delays the diagnosis and may cause a fatal outcome. Therefore, a high index of clinical suspicion is needed to diagnosing of MTB. Chest radiography plays a vital role in the initial detection and final diagnosis of MTB. But miliary mottling is seen in only 50% of cases of miliary tuberculosis.3 Only one-third of MTB patients are sputum smear-positive. Histological demonstration of granulomatous inflammation in biopsy tissue (e.g. in liver lung and bone marrow) is usually required to make a prompt diagnosis.4 The molecular diagnosis of mycobacterium tuberculosis DNA by polymerase chain reaction is helpful and it is rapid, sensitive, and specific.5 MTB is more likely to see in an immune-compromised patient due to suppression of their cellular immunity and is rarely affected in an immune-competent patient.

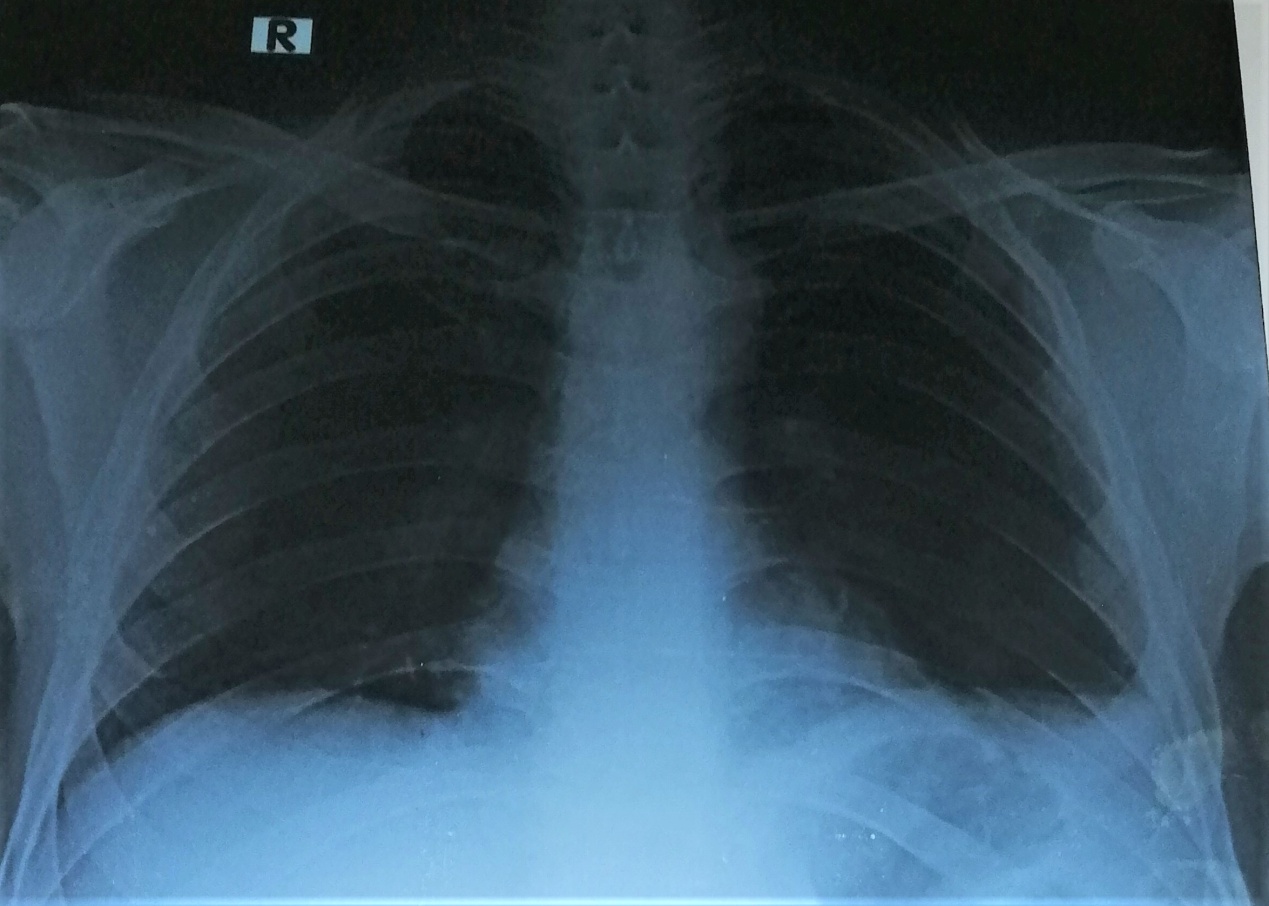
In this report, we present a case of miliary tuberculosis in an immune-competent male presenting with pyrexia of unknown origin and hyponatremia.

**CLINICAL PRESENTATION**

A 40-year-old nonsmoker from a middle-class family with a rural background presented with periumbilical pain with weight loss for 3 months and high-grade fever with cough for 21 days. He worked in Malaysia from 2006 as a manual worker in a furniture factory. His disease started in Malaysia and continued here. He had insidious progressive dull aching intermittent pain at the periumbilical region without any radiation. The pain was usually aggravated after the meal and relieved by taking a proton pump inhibitor for two hours then recurred the pain. He had about 12 kilograms of weight loss during this illness. He denied any vomiting, diarrhea, alternation of bowel habits, joint pain, rash, or headache. With the above complaint, he consulted with a physician in Malaysia and was treated with some medication but did not improve. So, he returned to Bangladesh and was admitted to our department with a high-grade fever for 21 days. Fever was intermittent mostly coming in the evening and night associated with chills and rigors, and subsided after taking the tablet paracetamol 500mg with profuse sweating. The highest recorded temperature was 103F. Along with fever patient developed a cough that was dry and occasionally becomes productive which was whitish, not foul-smelling, or had any hemoptysis. He had no chest pain, shortness of breath, joint pain, rash, photosensitivity, and burning sensation during micturition. His bowel and bladder habits were normal. He had no previous history of pulmonary tuberculosis or contact with a smear-positive pulmonary tuberculosis patient. On general examination, the patient was toxic and emaciated, the temperature was 1020F, and vitals were normal with Spo2 98% at room temperature. Systemic examination revealed no abnormality.

On investigation, CBC showed mild anemia (Hemoglobin 10.9g/dl) with leukocytosis (total WBC count 11,200/ cumm). The ESR (80mm/1st hour) and CRP (75.87mg/L) were elevated. Complete urine analysis, liver and renal function, RBS, serum amylase, lipase, and lipid profile were normal. Serum electrolytes showed hyponatremia (Sodium 125mmol/l) but normal serum Cortisol level. ICT for Kala-azar, Malaria, Dengue, and *Mycobacterium tuberculosis* was negative. Blood and urine culture was sterile. RT-PCR for Covid-19 was negative. Upper GI endoscopy, colonoscopy, ultrasonography, and CT scan abdomen found no abnormality. Chest X-ray showed pleural reaction (Figure1) and a High-resolution CT scan chest showed miliary infiltrates (Figure2). Mantoux (Tuberculin) test, Sputum for AFB, and Gene X-pert MTB/RIF were negative. Immediately after diagnosis of miliary tuberculosis oral Anti-tuberculous treatment with isoniazid (INH), rifampicin, ethambutol, pyrazinamide, and pyridoxine with steroids (30mg/day) was started. After three days of starting anti-tuberculous drugs, the patient becomes afebrile and the cough improved. No immediate drug side effects were observed. So patient was discharged with anti-tuberculous drugs with steroids and advised to follow up after one month.

At follow-up, the patient was asymptomatic, and liver and renal function tests and chest x-ray were normal. After six months of antitubercular treatment, the patient improved significantly without any side effects.



**Figure 1. Chest X-ray showing the presence of left-sided pleural reaction.**

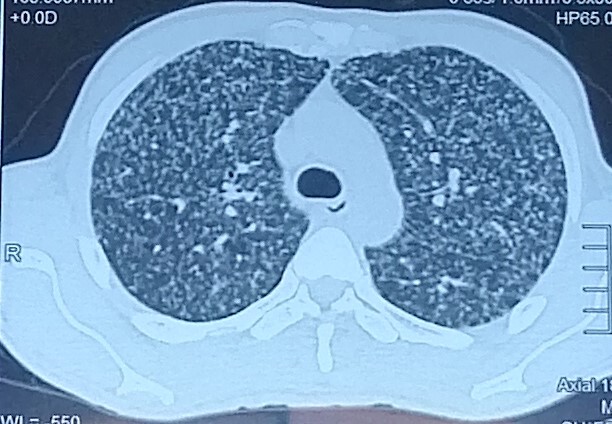


Figure 2. HRCT of the chest(non-contrast) shows the presence of innumerable miliary nodules scattered throughout both lungs.

**Discussion:**

Miliary tuberculosis is a rare but lethal infectious disease caused by the lympho-hematogenous spread of *Mycobacterium tuberculosis* bacilli. MTB most commonly occurs in an immune-compromising condition such as advanced age, uncontrolled diabetes mellitus, cancer, malnutrition, immunosuppressive and cytotoxic drugs, corticosteroids, end-stage renal failure, and most importantly HIV/AIDS.6 Among the immune-competent individuals, miliary tuberculosis occurs in less than 2% but in the case of HIV/AIDS, MTB accounts for more than 10% of all tuberculosis cases.7 Although miliary tuberculosis is rare in immune-competent patients, certain genetic defects such as abnormalities in the production or metabolism of interferon-gamma and interleukin-12 may responsible for the immune-competent individuals developing disseminated tuberculosis.8 In the miliary tuberculosis mortality is about 25-30% either delay in diagnosis or no diagnosis.

The clinical manifestation of miliary tuberculosis can be acute, subacute, and chronic. Acute presentation is rare and seen in advanced HIV/AIDS patients or immune-compromised conditions. Subacute or chronic presentation is more common in miliary tuberculosis than acute presentation and Patients can present with pyrexia of unknown origin, night sweats, failure to thrive, or dysfunction of one or more organ systems. Therefore, a high index of suspicion is required for the diagnosis of MTB attributable to unusual symptoms, and non-specific clinical signs, and it can mimic several other disorders.9

Our patient presented with periumbilical pain with weight loss for 3 months, high-grade fever, and cough for 21 days but no response to different medications. He was no lymphadenopathy or organomegaly except at high temperatures (1020F). There were no systemic examination findings even in the respiratory system. Before admission to our department, he visited several physicians and did several investigations including CBC, ESR, CRP, urine routine microscopic examination, sputum for Gram stain and culture sensitivity, ultrasonography of the abdomen even upper GI endoscopy and colonoscopy but there was no conclusive diagnosis.

We diagnosed him with pyrexia of unknown origin before doing further investigation. A study by Mart *et al.* found that 50% of patients with miliary tuberculosis presented as pyrexia of unknown origin.10 There are so many causes of pyrexia of unknown origin but infections, inflammations, malignancy, and miscellaneous are the main categories ultimately responsible for the majority of the cases of PUO. Extrapulmonary tuberculosis or miliary tuberculosis is the single most common infection, amongst the infectious cause in most PUO series.11

However, for the diagnosis of tuberculosis in our patient, the initial negative point was the patient complaint of periumbilical pain and weight loss later developed a high-grade fever but he had no history of contact with a smear-positive pulmonary tuberculosis patient, presence of BCG mark, no history of chest pain, lymphadenopathy and organomegaly. Chest X-ray showed an absence of lung findings for tuberculosis. In miliary tuberculosis, hepatomegaly is present in 20% of cases, and splenomegaly in 19% of cases among 269 adults diagnosed cases.12 Study by Sayantan *et al.* described that lymphadenopathy and organomegaly are more common in children compared to adults.13 However, BCG vaccination protects miliary tuberculosis but it is controversial. A study conducted by Hussey *et al.* stated that the incidence of military tuberculosis was approximately 88% among BCG-vaccinated patients.14

In miliary tuberculosis, several hematological and biochemical abnormalities have happened among them anemia, leukopenia, thrombocytopenia, lymphopenia, elevated ESR and CRP, sterile pyuria, and changes in plasma electrolyte levels like hyponatremia, hypercalcemia. In pulmonary tuberculosis, hyponatremia may occur in up to 50% of patients. It occurs as a result of either dysregulation in ADH (Antidiuretic hormone) release or involvement of the adrenal gland.15 In our patient anemia, elevated ESR and CRP, sterile pyuria, and hyponatremia was observed. Hyponatremia was due to dysregulation in ADH releases because of normal serum cortisol levels, and liver, renal, and thyroid function, ultrasonography and CT scan of the abdomen exclude Addison’s disease.

The classical radiological presentation consists of miliary pattern shadow in chest imaging. However, in the primary stage, the chest x-ray may be found normal or with other various radiological patterns like reticulonodular/interstitial, cavities, mediastinal or hilar lymphadenopathy, or even pleural effusion may be present. For that reason, diagnosis of miliary tuberculosis by a chest x-ray is challenging. The miliary pattern of infiltrates is found in about 84% of cases.16 High-resolution CT scan of the chest is more sensitive to assess miliary tuberculosis. The most common HRCT chest features of military tuberculosis that have been defined by a radiologist are miliary mottling17, reticular opacity, and ground-glass attenuation. It is also different in images between patients with or without HIV/AIDS.18 Our patient chest x-ray showed only pleural reaction (Figure 1) but the CT scan chest showed numerous tiny nodules evenly distributed in all segments of both lungs (Figure 2) suggestive of miliary tuberculosis.

In suspected MTB, to confirm the histopathological and/or microbiological diagnosis appropriate samples should be collected according to organ involvement. Microscopic examination and culture of sputum, body fluids, and tissue confirm the diagnosis if Acid Fast bacilli or caseating granulomas are seen. Among the biological specimens microscopically AFB was found in sputum (41.4%), bronchoscopic aspirates (46.8%), urine (32.7%), cerebrospinal fluid (21.2%), lymph node biopsy (91%), liver biopsy (89%) and bone marrow biopsy (67%).6 Fiber-optic bronchoscopy is usually indicated if acid-fast bacilli are not detected in sputum or body fluid and chest radiography shows miliary shadow infiltrates.19 In our patient Sputum for AFB and Gene X-pert MTB/RIF was negative. The sensitivity of sputum smear for acid-fast bacilli is only 35% to 70%, requiring 5000 to 10,000 bacteria/ml of sputum. The nucleic acid amplification (NAA) method is quick with high specificity and low sensitivity for M. tuberculosis. The sensitivity of the NAA test in a smear-negative patient is only 60% to 70%.20

Transbronchial lung biopsy (TBLB) may have a potential role in the diagnosis of miliary tuberculosis. In TBLB, granulomatous inflammatory lesions can be demonstrated in up to 60% of cases.21 For a patient with miliary tuberculosis, a tuberculin skin test (PPD) can be a supportive diagnostic tool if positive, but anergy is observed frequently in up to 68% of cases. Unfortunately, many patients with miliary tuberculosis remained undiagnosed before their death and were confirmed during autopsy.22

Mantoux test was negative in our patient and a Transbronchial lung biopsy was not available.

**Conclusion:**

Though miliary tuberculosis mostly presents in immune-compromised patients but can also affect immune-competent adults. In a highly prevalent, country where the patient presents with pyrexia of unknown origin, tuberculosis should be kept in mind as a differential diagnosis and an extensive search should be performed to confirm or refuse tuberculosis even for an immune-competent individual.

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