Case Report

Microbiology & Infectious Diseases

Miliary Tuberculosis in Bahrain: Case Reports and Epidemiology Review

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ABSTRACT

Miliary Tuberculosis (TB) is a severe, acute form of tuberculosis due to lymphohaematogenous dissemination of tubercle bacilli from a focal lesion. Here we are reporting 2 cases of miliary TB among HIV infected patients over the past 6 months, both patients have presented with non-specific symptoms which raise the importance of lowering the threshold of diagnosing miliary TB, particularly among high risk patients. Alongside we are presenting in this paper epidemiological review of Miliary TB in the kingdom of Bahrain over the past 10 years.

Keywords

HIV-Infection, Mycobacterium tuberculosis, Disseminated TB, Miliary, Immune reconstitution.

Introduction

Miliary tuberculosis (TB) is defined as the hematogenous dissemination of Mycobacterium tuberculosis from an established focus, producing numerous lesions of approximately the same age and size, which usually progress to necrosis and caseation in multiple organs [1-2]. In the pre-chemotherapy era, the disease was usually fatal [3] and was most often an early complication of primary TB in children particularly among Infants and young children who are highly susceptible to miliary TB [4-9]. Nowadays, the epidemiology of miliary TB has changed [10-12], numerous reports have indicated an increasing number of elderly patients afflicted by the disease due to relative waning of cellular immunity, with relative concomitant increase among young adults who are coinfected with HIV [13,14].

The epidemiology of miliary tuberculosis (TB) has been also altered in the last few years by the widespread use of biologic agents such as tumor necrosis factor (TNF)-alpha inhibitors which has been associated with a disproportionate increase in extrapulmonary and miliary tuberculosis among individuals treated with these agents [15-16].

Other Risk factors for development of miliary TB include presence of underlying medical conditions, the percentage of patients with miliary TB and some identifiable underlying medical condition in various studies ranged from 38 to 70 percent. However, a significant percentage of cases described in the literature have no demonstrable high-risk condition for dissemination [17-23].

The presentation of miliary TB can mimic other infections, which is a reason behind the expected delay in its diagnosis in a significant number of cases, or even missing the diagnosis. In some case series, up to 50% of cases are not diagnosed until postmortem [24]. The most common site for miliary TB are bones, liver, adrenal glands, central nervous system and the lymphatic system, which all have subtle & nonspecific manifestation [25].

Here we are reporting 2 recent cases of miliary TB over the last 6 months, both cases were managed in Salmaneya medical center which is the main governmental hospital that treat TB cases in Bahrain.

Authors also took the initiative to review the epidemiology of miliary TB in Bahrain over the past 10 years in reference to

national TB surveillance data in the national TB program.

Case Reports

Case 1

34 year old Thai male with no previous medical illness,presented to Salmaniya Medical Complex (Manama, Bahrain) with complain of generalized body weakness, loss of appetite, intermittent fever and weight loss of two months duration. The patient was admitted for investigation and evaluation. He had on admission fever of 38.2°C, blood pressure 125/82mmHg, pulse 105/min and O_2 saturation of 97%. The initial chest x-ray (CXR) has hazy reticulonodular shadows with minimal bilateral pleural effusion [Figure 1]. He was alert, oriented but looked wasted and pale on general examination with mild generalized abdominal discomfort. He was managed as community acquired pneumonia and started on Ceftriaxone and azithromycin after full septic work up. The initial blood investigations done showed an ESR of 90mm/hour, normal WBC, Hb 8.3g/dl with hypochromic microcytic parameters and elevated liver enzymes of cholestatic picture with elevation of total bilirubin mainly of direct component.

Blood culture and urine microscopy and culture were sterile, but the patient continued to have abdominal discomfort not responding to analgesia. Ultrasound abdomen was requested and it showed a small amount of free fluid with no other significant findings.

The viral serology came back as being positive for HIV, and the patient continued to spike temperature between 38°C to 39.5°C, accordingly, the antibiotic was changed to broad spectrum regimen with empiric coverage for PCP, so he was shifted to Cefipime, Vancomycin, and Cotrimoxazole, and deep tracheal aspirate was requested for microbiology & pneumocystis immunoflouresence and for AFB stain, PCR and MTB culture.

CT abdomen was arranged urgently in view of progressive increase in abdominal girth with development of rigidity on examination. The CT showed a circumferential wall thickening involving the ascending colon extending to the hepatic flexure, the terminal ileum and adjacent distal ileal loops are all thickened with free fluid in the right flank, the iliac fossae and pelvis. The spleen showed multiple small hypodensities of various sizes suggesting multiple abscesses, while on bony window the images showed lytic lesions involving the acetabulum possibly tuberculous in origin. The chest showed moderate right side pleural effusion, mild pericardial effusion and the lung parenchyma had nodular shadows suggestive of miliary Tuberculosis [Figure 2-5]. Quadruple Antituberculous medications were commenced (rifampicin 450mg, isoniazide 300mg, pyrazinamide 1000mg, ethambutol 800mg and vitamin b6 one tablet per day) based on clinical diagnosis & radiological finding.

CXR was repeated in view of progressive hypoxia and showed a significant right side pleural effusion that mandate insertion of pig tail for drainage of pleural fluid.

The deep tracheal aspiration result came as being positive for AFB smear & by RT-PCR for MTB with no genetic detection of Rifampicin resistance. The drained pleural fluid was showing an exudative pattern but with negative AFB stain & PCR.

The patient started to defervesce gradually after commencing antituberculous therapy with gradual decrease in abdominal girth.

After 3 weeks stay in the hospital on antituberculous therapy, the patient had significant clinical improvement and DTA was repeated and reported as negative for AFB smear, then he travelled to his home country to complete his therapy for miliary tuberculosis and HIV.

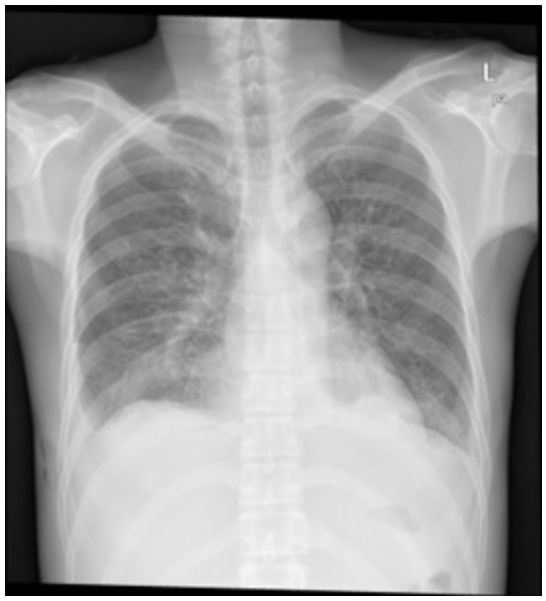
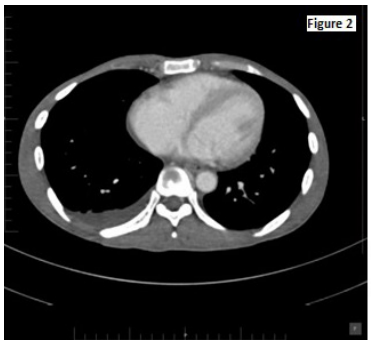


Figure 1: CXR with retculonodular pattern & bilateral minimal pleural effusion.



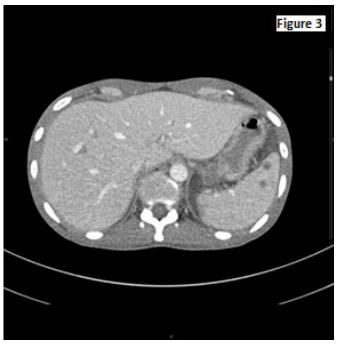
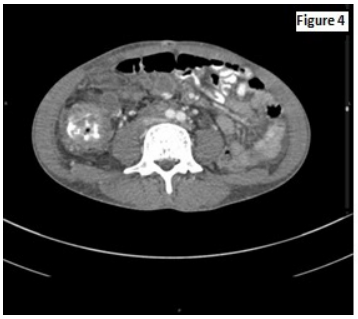


Figure 2: Initial CT chest showed pleural & pericardial effusion.
Figure 3: CT abdomen showed Splenic abscesses.



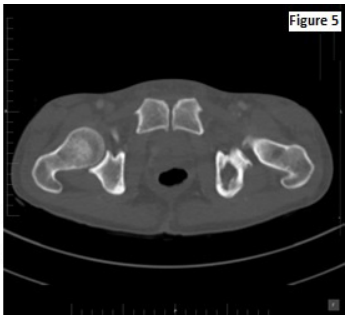


Figure 4: CT abdomen showed circumferential bowel thickening and ascites.

Figure 5: CT pelvis, Bony window showed Lytic acetabular lesion.

Case 2

43 year old Bahraini male known case of HIV, hepatitis C and schizophrenia who recently released from jail. The patient was not compliant to antiretroviral therapy, he presented to accident and emergency department with history of decrease oral intake and self-isolation since release from jail 3 weeks prior to his presentation. No history of other symptoms. He was admitted and evaluated by neurologist, psychiatrist and infectious diseases physician. He was clinically oriented with no abnormal behavior, vitally stable and no significant abnormalities on physical examination apart from cachexia.

His initial chest x ray on admission showed diffuse nodular opacities over both lungs (Figure 6). CT brain & CSF analysis were done in view of abnormal behavior and showed normal finding on CT and CSF parameters all septic workup was collected & came to be all negative.

In view of positive history of HIV and given that the patient is not on antiretroviral regimen, he was started empirically on antibiotics therapy for PCP & community acquired pneumonia (Cotrimoxazole with Ceftriaxone & azithromycin) and further investigation with three morning specimen of sputum samples for AFB stain & PCR and they were all negative. The patient strongly refused obtaining deep respiratory specimen like deep tracheal aspiration or bronchioalveolar lavage. CXR was discussed with two consultant radiologist and the impression was highly suggestive of military TB (Figure 6).

Therefore, the patient was commenced empirically on quadruple Antituberculous medications (rifampicin 600 mg, isoniazide 300 mg, pyrazinamide 1500 mg, ethambutol 1200 mg and vitamin B6 one tablet per day) based on clinical & radiological finding, his CD4 count result came to be 38, so a decision to delay starting the antiretroviral therapy for a minimum period of 2 weeks after commencing antituberculous medications was taken.

The patient during hospital stay; few days after starting antituberculous therapy developed severe ataxia and difficulty in maintaining posture, so MRI brain was done and it showed multiple cortical and subcortical lesions with post contrast enhancement, finding highly suggestive of miliary tuberculosis (Figures 7-10).

Patient clinically started to improve by the second week of antituberculous therapy with gradual diminution in the intensity of his neurological symptoms.

After 4 weeks, the result of sputum reported as being positive for MTB culture with fully sensitive isolates, the patient continued on initial phase of antituberculous therapy, other antimicrobial that include cotrimoxazole & azithromycin was converted to prophylactic dose for PCP and MAC respectively and the patient was started on antiretroviral therapy by the that time.

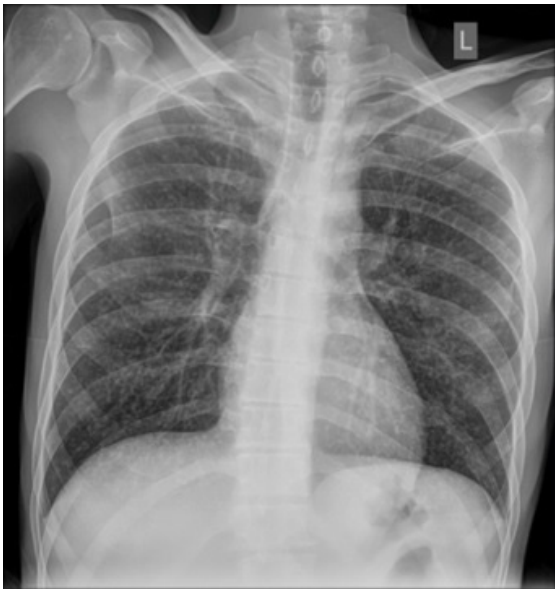
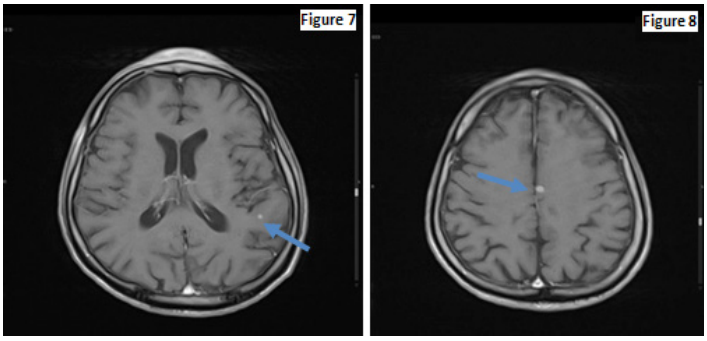


Figure 6: CXR with diffuse miliary pattern.



Figures 7 and 8: MRI brain (Axial T1 post contrast) showed multiple cortical and subcortical lesions in the left parasagittal, left occipital and right high parietal areas. These lesions are isotense to gray matter in T1 these lesions are high T2 and and show post contrast enhancement, however, these lesions do not demonstrate any restricted diffusion on DWI/ADC. No evidence of leptomeningeal enhancement seen.

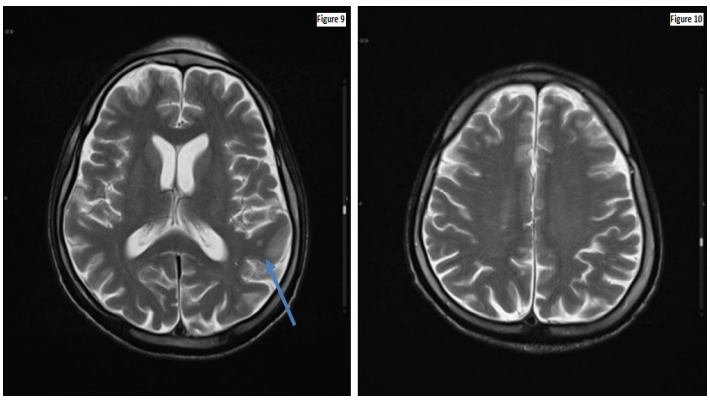


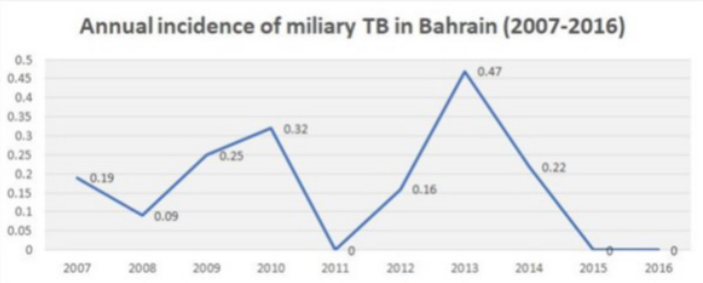
Figure 9-10: MRI brain (T2 weighted images) showed these lesions with high T2 and post contrast enhancement, but with no any restricted diffusion on DWI/ADC and No evidence of leptomeningeal enhancement seen.

Miliary TB in the kingdom of Bahrain

Reviewing available data over the past 10 years (2007-2016) from national TB program in Bahrain revealed that miliary TB constitute around 1% of TB cases in Bahrain with no single reported case of miliary among Bahrainis over the review period, the disease been reported only among expatriate during this past 10 years and more predominant among young expatriate in the age group of 25-34 years with no reported cases among pediatric <15 years or elderly >65 years (demographic details in the below table).

Variable	Number of patients (%)
Age groups	
0-4	0 (0%)
5-14	0 (0%)
15-24	3 (14%)
25-34	8 (38%)
35-44	5(24%)
45-54	5(24%)
55-64	0 (0%)
> 65	
Nationality	
Bahraini	0 (0%)
Non Bahrainis	21 (100%)

Table 1: Demographic data of miliary TB in Bahrain (2007-2016).



Graph 1: Annual Incidence of miliary TB in Bahrain (2007-2016).

The annual incidence of miliary TB in Bahrain was on average of 0.16 /100,000 population during the review period, the trend (As shown in the above graph) revealed minimal fluctuation with no reported cases of miliary TB over the last 2 years (2015-2016), but we reported 2 cases consecutively over the past 6 months (October 2017- March 2018).

Discussion

We are reporting 2 cases of miliary TB, the first case presented with full blown disseminated TB that involve the lung, pleura, pericardium, peritoneal, gastrointestinal tract, bone, liver and spleen as evidenced by radiological and laboratory finding; the diagnosis was confirmed microbiologically by positive AFB smear & MTB PCR from deep tracheal aspirate, this protean manifestation was the first presentation of his HIV infection, he was already in advanced immunosuppressed stage with CD4 count of 49 at the time of this presentation and he had good clinical response after starting antituberculous therapy.

The second case was known case of HIV, but not on antiretroviral therapy and came with advanced immunosuppression with CD4 of 39, he had disseminated TB that mainly involve the lung with the absence of any respiratory symptoms, but having the typical miliary pattern on radiological appearance of plain chest x ray with early brain involvement suggested by his neurological symptoms in the absence of any abnormal finding on brain CT scan & CSF parameters but the diagnosis was established with early changes on brain MRI. Microbiologically, his initial AFB smears & MTB PCR was repeatedly negative from sputum (3 specimens) and from CSF, but ultimately came positive on sputum culture. The patient had initial worsening of his neurological symptoms just upon commencing antituberculous therapy, which is expected as part of immune reconstitution considering his advanced immunosuppression stage, but then had good clinical response and improvement of his neurological symptoms by the second week with the continuation of antituberculous therapy and starting antiretroviral therapy was delayed till the 4th week of commencing antituberculous therapy, after that it was started with no any clinical worsening of his symptoms

Miliary TB in the kingdom of Bahrain

In the kingdom of Bahrain; reviewing previous studies (26-30) have shown that the kingdom is considered as an area of low endemicty for TB (incidence of 11/ 100,000 population in 2016) with discernable predominance of TB among expatriate (around 80 % of TB cases).

Our review of national TB data in Bahrain revealed that miliary TB in Bahrain was predominantly a disease of expatriate over the past 10 years, as we didn't report any single case among Bahrainis during our review period, till we reported this case (in this paper) among this Bahraini HIV infected patient.

It was also clear from our reviewed data, which miliary TB is more predominant (87% of all cases) among young expatriate in the working age group (25-54 years) which reemphasize the importance of pre-employemnt screening program for expatriate coming from TB endemic areas.

Similar demographic data of miliary TB with predominance among young Non-Nationals was published in a recent study in Qatar which shared with us similar demographic characteristics of large expatriate population and reported that 90% of miliary TB cases are among expatriates and among the young adult age group [31,32].

Different epidemiological pattern of miliary TB was obtained from other GCC countries like Saudi Arabia where majority of cases are among elderly (68%) which is expected as nationals (Saudi) constitute more than half of the cases [33,34].

Lesson learned

Possible reappearance of miliary TB among Bahrainis should make us very vigilant in following our statistics during the coming years for any further cases as such reemergence might warrant other

vigorous preventive strategy for combating TB in the kingdom.

Other important message is to expand early diagnosis of miliary TB among HIV patients through ensuring integration of TB screening diagnostic in the initial management of all HIV patients & keeping high level of suspicion with lowered threshold for clinical diagnosis, sending proper investigation complemented by early empirical antituberculous therapy for possible but not yet microbiologically confirmed miliary TB,as such early initiation of treatment would have a great impact in improving the survival of HIV infected patients and prevent transmission of the disease in the community [35].

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