Isolated hepatic tuberculosis in a middle aged diabetic lady: a rare case report
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ABSTRACT
Isolated hepatic tuberculosis is a rare clinical entity with non-specific clinical and imaging features that can result in a diagnostic challenge. A high index of suspicion is required and a definitive diagnosis can be very difficult. Here, we report a case of a 55-year-old Bangladeshi lady with type 2 diabetes mellitus and hypertension presenting with prolonged fever and tender hepatomegaly. After initial evaluation she was found to have raised alkaline phosphatase and \( \gamma \)-glutamyl transferase levels. A diagnosis of hepatic tuberculosis was confirmed from histopathology of liver tissue. Anti-tuberculosis therapy was started. Although rare, hepatic tuberculosis should be considered in any case of unexplained hepatomegaly or hepatosplenomegaly with prolonged fever. A liver biopsy should be performed, as this condition responds well to anti-tuberculosis therapy.

Key words: extra-pulmonary tuberculosis, isolated hepatic tuberculosis, liver biopsy.

BIRDEM Med J 2023; 13(3): 155-159
DOI: https://doi.org/10.3329/birdem.v13i3.68827

INTRODUCTION
Tuberculosis (TB) continues to be a global public health problem, particularly in the developing countries.\textsuperscript{1} TB and diabetes mellitus (DM) have synergetic relationship. People with DM are 2-3 times at higher risk of getting active TB disease.\textsuperscript{2} Extra-pulmonary TB (EPTB) constitutes about 15%-20% of all TB patients. Diabetes makes a substantial contribution to the incidence of EPTB.\textsuperscript{3} Virtually, every site of the body can be affected by TB.\textsuperscript{4} Hepatic involvement is a very rare clinical entity even in countries endemic for TB, representing less than 1% of all cases of TB. Hepatic TB usually occurs as a part of generalized military TB; isolated hepatic TB is extremely rare and poorly described in the literature\textsuperscript{5} and its diagnosis is challenging due to nonspecific signs and symptoms along with imaging features, sometimes mimicking hepatic tumors or metastases. Pyrexia of unknown origin (PUO) a common presenting feature.\textsuperscript{6-8} Liver biopsy is essential in cases where clinical and imaging features are equivocal and should not be delayed, even when there are other recognizable etiological factors of liver disease.\textsuperscript{9,10} Anti-TB treatment is effective and the prognosis is usually good in most cases with early diagnosis and treatment.\textsuperscript{11} Here, we report a case of isolated hepatic TB who presented with prolonged fever and tender hepatomegaly. In this case report we reinforce the importance of considering this diagnosis as well as considering liver biopsy in any case of unexplained hepatomegaly, hepatosplenomegaly or PUO.

CASE REPORT
A 55-year-old Bangladeshi woman with type 2 DM and hypertension presented with the complaints of low grade, intermittent fever with evening rise of temperature for 2 months without any focal symptoms. She also complained of severe anorexia and weight loss (approximately 10 kg during last 2 months). There was
no history of smoking, alcohol consumption or illicit drug use. She also denied recent history of travelling to endemic region for malaria and kala-azar. She was investigated and empirically received oral and intravenous antibiotics on multiple occasions including antimalarial drugs by local physicians but did not respond.

At our facility, the patient was found emaciated (weight: 46 kg, height: 158 cm, body mass index 18.40 kg/m²), febrile, tachycardic with mildly tender hepatomegaly (10 cm from right costal margin along the right mid-clavicular line) which was firm with rounded margin and smooth surface. Upper border of liver dullness was in the right 5th intercostal space with no hepatic bruit. Other systemic examinations revealed no abnormality. Clinically we diagnosed her as a case of chronic liver abscess with keeping in mind hepatic tuberculosis, lymphoma and occult malignancy with hepatic metastasis as differentials.

Complete blood count (CBC) and peripheral blood film revealed mild leukocytosis with non-specific morphology and an erythrocyte sedimentation rate of 82 mm/h. Biochemical tests showed normal alanine amino transferase (32 iU/L), aspartate amino transferase (24 iU/L) and total bilirubin (0.5 mg/dl) levels but markedly raised alkaline phosphatase (598 iU/L) and α-glutamyltransferase (702 iU/L) with altered albumin-globulin ratio and normal prothrombin time. No organisms were isolated from blood and urine cultures. Tests for malaria, kala-azar and triple antigens were negative. Tuberculin skin test response was 10 mm at 72 hr. Abdominal ultrasonogram (USG) revealed hepatomegaly with grade-1 fatty change in the liver (Figure 1). Computed tomography (CT) scan of the whole abdomen with contrast showed hepatomegaly with fatty change (Figure 2). The remaining studies such as chest radiograph (Figure 3), renal function, electrolytes, autoimmune serology, tumor markers, magnetic resonance cholangiopancreatography (MRCP) (Figure 4) were unremarkable. Finally, a liver biopsy was performed and found multiple granulomas with foci of caseating necrosis. Histopathological diagnosis was granulomatous hepatitis, consistent with TB. Although Ziehl-Neelsen stain of hepatic tissue for acid-fast bacilli was negative.

Standard anti-TB treatment with rifampicin, pyrazinamide, ethambutol and isoniazid (4FDC) along with pyridoxine supplementation was started. She was discharged with the advice to follow-up after 2 weeks. During 1st follow-up she had improved general wellbeing with no fever and hepatic tenderness. Her liver size was reduced to 7 cm from right costal margin. Hepatic enzyme levels were also improving. The patient received anti-TB treatment for 6 months as per standard regimen with periodic follow-up. At the end of 6th month she was found to have significant clinical response evident by weight gain and non-palpable liver along with normalization of hepatic enzyme levels. During the course of treatment, no complication related to the anti-TB drugs was reported.
DISCUSSION

Nearly one-third of the global population (i.e., two billion people) is infected with *Mycobacterium tuberculosis* (MTB) and is at risk of developing TB disease. According to the Global TB Report 2020, TB causes ill health among millions of people each year and is a leading cause of death from a single infectious agent. Globally, an estimated 10 million (range 8.9–11.0 million) population developed TB in 2019. DM is not only a risk factor for TB but also influences the disease presentation and treatment response. On the other hand, both TB and anti-TB medications might induce glucose intolerance or worsen glycemic control in people with DM. One of the most important factors for successful treatment in a diabetic patient is to achieve good glycemic control throughout the entire course of anti-TB treatment.

Extra-pulmonary involvement can occur in isolation or along with a pulmonary focus as in the case of patients with disseminated TB. Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) has resulted in changing epidemiology and has once again brought EPTB into focus. EPTB constitutes about 15 to 20 per cent of all cases of TB in immunocompetent patients and accounts for more than 50 per cent of the cases in HIV-positive individuals. Diabetes makes a substantial contribution to the incidence of EPTB as well. From a retrospective study, lymph nodes are the most common site of involvement (50%) followed by tubercular pleural effusion (15%) and virtually every site of the body can be affected by TB. Since the clinical presentation of EPTB is atypical, obtaining tissue samples for the confirmation of diagnosis can sometimes be difficult and conventional diagnostic methods have a poor yield, so the diagnosis is often delayed.

Hepatic TB is a rare form of TB with non-specific signs and symptoms which requires a high index of suspicion to reach a diagnosis. It may present in any age group but is most common among young adults. However, isolated hepatic TB is more common in the fourth to sixth decades of life. Hepatic TB has been described with a wide variety of terms and classifications. From literature review, varied nomenclature ranging from tuberculous liver abscess, tuberculous pseudo tumor, primary hepatic TB, tuberculous hepatitis, tuberculous cholangitis, TB of the bile duct were observed. Useful clinical classification: a. hepatic miliary TB i.e. part of generalized disease, b. localized or isolated hepatic TB which includes tuberculous hepatitis and hepatobiliary TB. Hepatobiliary TB further subdivided into with bile duct involvement i.e. tuberculous cholangitis, without bile duct involvement i.e. tuberculoma and tuberculous abscess. The most common form of hepatic involvement is miliary hepatic TB occurring in 50%–80% of cases due to haematogenous spread via hepatic artery. Hepatic TB is mostly secondary. Primary hepatic TB is rare because low oxygen tension in the liver, which is unfavorable for the growth of *Mycobacteria*, although the rich blood supply and the presence of the reticuloendothelial system facilitate granuloma formation once seeding of the TB bacillus occurs. The proposed mechanism for primary hepatic TB is that it begins as primary intestinal TB as a gateway to the TB bacilli entry into the portal vein and seed the liver parenchyma. The granulomas are usually located near the portal tract and there is only mild impairment of hepatic function, so most of these lesions are minimally symptomatic or asymptomatic.

The most frequently encountered clinical and laboratory findings described in literature are fever, weight loss, abdominal pain, hepatomegaly and elevated alkaline phosphatase level. In our case report, the patient presented with prolonged fever with hepatomegaly and elevated alkaline phosphatase and ß-glutamyltransferase. Non-specific laboratory alterations, such as anemia and leukocytosis can be found. Sometimes there is pancytopenia. The tuberculin skin test is of little value as a diagnostic method.

USG, CT scan and MRI are very sensitive for the detection of hepatosplenic nodules. However, hepatic TB has no characteristic imaging features. USG can demonstrate mostly hypoechoic lesions, while the typical CT finding is the heterogeneity of the lesions which may vary from hypodense to hyperdense. Nevertheless, the imaging manifestation can show a considerable overlap with other relatively more frequent primary or secondary lesions of the liver. Equivocal or normal USG and CT scan may arise further difficulty in determining the area from where to take liver biopsy. To this extent PET/CT showed diffuse increased metabolic activity in addition to focal areas of increased activity within liver, thus helping to identify a site to
biopsy that led to the correct diagnosis.11 In endemic countries and in appropriate clinical context an atypical imaging pattern of a hepatic lesion particularly presence of calcifications and the concurrent involvement of extrahepatic sites (spleen, lungs and nodes) should prompt the radiologist to consider hepatic TB as one of the differential diagnoses.12

Liver biopsy is the gold standard for the diagnosis and is often required, especially when malignancy needs to be excluded and should not be delayed. Histological findings may include a wide variety of hepatic lesions. In a clinical review of 96 cases of patients with a predominantly hepatic presentation of TB, the findings were: granulomas (95.8%), caseation (83.3%), fatty changes (42%), portal fibrosis (20%) and acid-fast bacilli in association with granulomas (9%); a mononuclear cell infiltrate was also common.5,8 Another study found that Ziehl-Neelsen stain is positive in only 40% of cases. The PCR for TB has a sensitivity of 82% and should be considered to confirm the diagnosis in such cases.9 In general, the finding of caseation in hepatic tuberculous granulomas, although variable, is not very frequent, on the other hand caseation may be seen in some other conditions like deep fungal infection, leprosy and berylliosis. However, the etiology of hepatic granulomas can seldom be established by histological appearance alone. Some authors suggest that, in appropriate clinical context, the finding of granulomas, especially with caseating necrosis, constitutes histopathological evidence of TB, unless proven otherwise. It is described in the literature that hepatic tuberculosis can present as ‘pseudo-cirrhosis’ as a result of scarring of multiple tubercles or small disseminated diffuse foci during the healing phase but no major hepatic dysfunction results from the cicatrisation process.12,13

Treatment for hepatic TB is standard anti-TB regimen consisting of a 2-month initial phase of isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of isoniazid and rifampicin along with pyridoxine. This regimen can cure tuberculosis in more than 90% of patients. However, the drugs and regimen need to be individualized according to the severity, response and liver function of the patient.1,2 Anti-TB treatment is effective and the prognosis is usually good in most of the cases with early diagnosis and treatment.9 Bacteriologic monitoring of patients with EPTB is more difficult and often not feasible. In these cases, the response to treatment must be assessed clinically, biochemically and radiologically.13 In this report, the patient completed the 6-month anti-TB regimen. At the end of therapy there was significant clinical response with normalization of both clinical and biochemical parameters without any reported complications related to the disease as well as anti-TB drugs, which were considered as a treatment success.

Authors’ contribution: MMH was involved in the diagnosis, patient management, manuscript writing and literature review. All authors were involved in evaluation and management of the case.

Consent: Informed written consent was taken from the patient for publication of the case report and any accompanying images.

Conflict of interest: Nothing to declare.

REFERENCES


