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A rare unusual case report of Hepatic Tuberculosis in a Yemeni Child, presented with Pyrexia of Unknown Origin

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Abstract: Hepatic Tuberculosis (HTB) is a rare form of tuberculosis. The disease presentation and characteristics have been described in a number of adult cases from low resource settings, however, little is known about the disease in children. We report a case of 9-year-old boy who had a prolonged history of fever. His clinical data were nonspecific. Laboratory and imaging data were not helpful. We did laparoscope biopsy of liver and histopathological study was done, which showed chronic granulomatous inflammation. He diagnosed as Hepatic Tuberculosis and received anti tuberculosis therapy; his condition got better. The age of our case indicates that the disease can infrequently occur in children in contrast to what is written in literature.
Keywords: Hepatic Tuberculosis, Tuberculosis, Extrapulmonary Tuberculosis, Tuberculosis of Liver, Pyrexia of Unknown Origin, Children, Yemen.

INTRODUCTION

Hepatic Tuberculosis (HTB) also known as 'localized hepatic tuberculosis; Idiopathic Tuberculosis; and Granulomatous Hepatitis', is a rare clinical presentation of abdominal tuberculosis [1]. The disease can start at any age and has been identified in primary and secondary tuberculosis. In the primary form, HTB can occurred via access of tubercular bacilli from primary infected source in bowel into the portal vein, while in the secondary form, it can occur as a disseminated diffuse hepatic tuberculosis, comes along with pulmonary or miliary tuberculosis [2,3]. Clinically, the disease may present with prolonged fever, poor gaining weight, abdominal discomfort and even serious manifestations of hepatic failure [4]. Diagnosis of HTB in children is very challenging, need high index of suspicion, eliminating all other differentials, and require histopathological examination of liver biopsy specimens.

We share our experience in managing a case of HTB in a 9 year Yemeni child, which to our knowledge is the first case to be reported in the region.

CASE REPORT

A 9-year-old boy, from Al-Daleh Governorate, Yemen, was presented with complains of low grade fever (intermittent, not associated with chills or sweating), loss of appetite and malaise for the past two months. His father has reported that, there was some weight loss along with fatigue and general weakness. Initially, his mother brought him to Primary Health Unit where physician noticed that, he had congestion of his tonsils, diagnosed with Upper Respiratory Tract Infection (URTI), and treated for one week with antibiotics (Augmentin Tablet) but not improved. Parents have reported that their child was non-immunized at all and findings from his past medical history and family history were unrelated.

On admission, the child looked alert, thin, and febrile. There were no signs of respiratory distress and no jaundice was observed by examination of palbebral or bulbar conjunctiva. His vital signs were; Temperature, 38.3°C; respiratory rate (RR), 22/min; and pulse rate, 125 beats/min. his growth parameters showed weight, 23 kg (< 10^{th} percentile); and length, 135 cm (< 75^{th} percentile). There was found no clubbing of fingers and no enlargement of lymph nodes. Chest was clear with vesicular breathing, and heart was normal on auscultation. Palpation of abdomen revealed no any abnormalities in liver, gallbladder or spleen.

Laboratory data showed hemoglobin, 9.6 g/dl; white blood cell count, $6.6*10^9$/L; platelet cell count, $171*10^9$/L; erythrocyte sedimentation rate, 70 mm/hr; bilirubin, 0.8 mg/dl; total protein, 8 g/dl; albumin, 4 g/dl; Alanine aminotransferase (ALT), 238 U/L; Asparatate aminotransferase (AST), 284 U/L; Alkaline phosphatase, 889 U/L; HBsAG, HCV, HIV all non-reactive; renal function tests and urine analysis were within normal ranges, urine culture yield no microorganism growth; blood film for malaria yield no parasite; serology for leishmaniasis, brucellosis,

shistosomiasis were negative. A tuberculin skin test was negative. A trial of antibiotics and antimalarial drugs were prescribed for a week, fever is still continued and no clear improvement had seen. Bone marrow examination was done and yields myelopoiesis – normoblastic with shift to left and eosinophilia, erythropoiesis–hyperplastic with megaloblastic changes, megakaryocyte normal and productive, no malaria, no lieshamania donufani bodies and no AFB seen. Chest x ray was normal. Abdominal ultrasonography has demonstrated an increase size of liver and spleen. Echo cardiac study was normal. We diagnosed him as a case of acute malnutrition with complications as his nutritional assessment has demonstrated a weight for height profile below -2 Z score. He supported with essential package of nutrition, and regular monitoring of temperature chart. His temperature is still high at 38.5°C. Computerized scan of abdomen were studied after ingestion of oral contrast and administration of iodinated contrast showed hepato-splenomegaly, abdominal enlarged lymph nodes; CT-Scan signs of lymphoma. On the basis of bone marrow result, lab investigations and clinical history, a differential diagnosis of lymphoma was suspected and thus, we planned for abdominal lymph node and liver biopsies. After detailed discussion, parents agreed to abdominal laparoscope for abdominal lymph node and liver biopsy, the specimens underwent histopathological examination, reveals; liver parenchyma with wide spread chronic inflammation predominantly lympho-plasmacytic centered mainly at the portal area with scattered epitheloid granuloma, some shows central caseaous necrosis and scattered multinucleated giant, a picture consistent with chronic granulomatous inflammation (Table 1 and 2). Tuberculosis hepatitis had been diagnosed and anti TB therapy was prescribed. Initially, good response had been achieved and fever had subsided, however, four weeks later, he complained of gastro-intestinal upset and other side effects of anti TB drugs which treated accordingly. Standard TB therapy continued, fever subsided and his general condition was markedly improved. Figure 1.

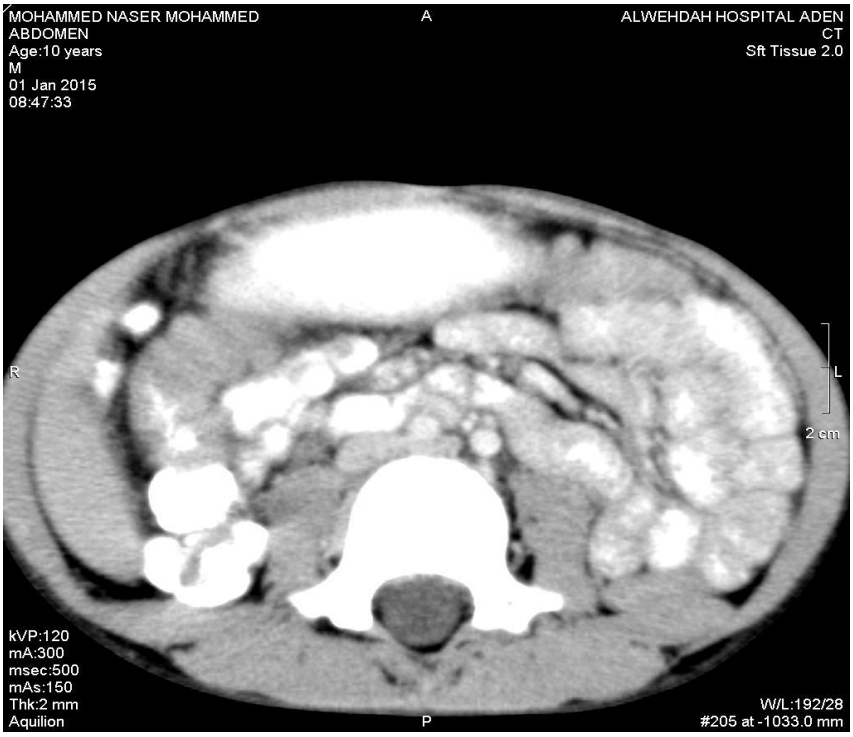

Fig 1: computerized scan of abdomen showed hepato-splenomegaly, and abdominal enlarged lymph nodes

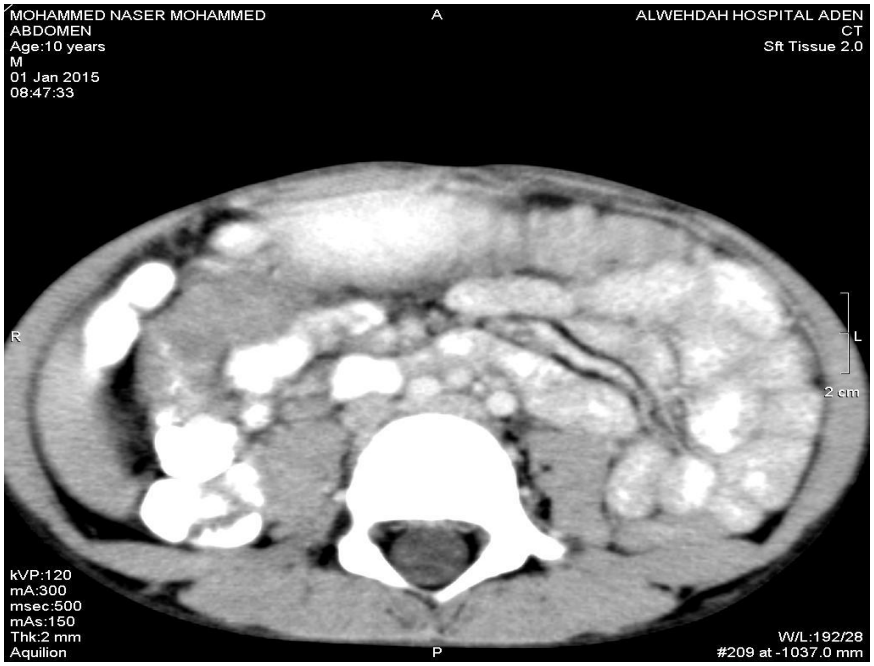

Fig 2: computerized scan of abdomen showed hepato-splenomegaly, and abdominal enlarged lymph nodes

Table 1: Histological findings of the patient's Liver Biopsy

Characteristic Details	**Biopsy Data**
Macro	Received one labeled containers, 1st (Liver), contains multiple fragments of tissue biopsies, measure in aggregate 1x1 cm irregular, firm pale gray to dark brownish.
Micro	Microscopic examination reveals of liver parenchyma shows lobular disarray with wide spread chronic inflammation predominantly lympho-plasmacytic centered mainly at the portal area with few scattered epitheliod granuloma, some shows central caseous necrosis and scattered multinucleated giant.

Table 2: Histological findings of the patient's Para-aortic and Mesenteric Lymph Nodes

Characteristics Details	**Biopsy Data**
Macro	Received two labeled containers, 1st (Para-aortic Lymph Node), contains one fragment of tissue biopsy, measure 0.5x0.5 cm, irregular, firm pale gray. The second container was for Mesenteric Lymph Node, contains one fragment of tissue biopsy, measure 0.5x0.5 cm irregular, firm pale gray.
Micro	Microscopic examination of both samples reveals that the lymph nodes shows distortion of the lymphoid architecture with multiple reactive follicles with prominent germinal centers surrounded by mantle zone of mature lymphocytes, the para-follicular area formed by mixed proportion of lymphoid cells with prominent post-capillary venules with plump endothelial cells and the medullary region shows prominent dilation of medullary sinus filled by proteinous material (Lymph) and histocytes.

DISCUSSION

Tuberculosis, both pulmonary and extra-pulmonary is a public health problem in Yemen. Our case had been presented with prolonged fever, abdominal discomfort and weight loss. Histopathological examination of liver specimen has showed HTB. To our knowledge, this would be a first case report of the disease among children in the country and its findings are essential in addressing this clinical problem.

HTB also known as atypical tuberculosis of liver, hepatobiliary tuberculosis, localized hepatic tuberculosis, and isolated tuberculosis, is a rare and poorly defined disease of abdominal tuberculosis [2-4]. According to Leavine, Tubercli bacilli can reach liver by spread through hepatic artery, portal system or lymphatic tissue, categorized the disease into; miliary tuberculosis, pulmonary tuberculosis with hepatic involvement, primary hepatic tuberculosis, focal tuberculoma/abscess or tuberculous cholangitis [5]. In our case, we refer HTB to local tuberculosis of liver without involvement of other organs. In some rarer

cases, HTB may coalesce forming tuberculoma, the caseation and necrosis of tuberculoma will end in a tubercular abscess [1]. Despite HTB is rare and relatively well described in middle aged adults as the report of Sneh and colleagues from India for a case of 24 year old female who died of primary hepatic tuberculosis [6], and a report by Shatri and colleagues for a 20 year old women who presented with a sub-acute a febrile hepatic failure and found to have granulomatous hepatitis [7], the finding of local tuberculosis of liver in our case is consistent with a case report of 17 year old male from Brazil presented with daily fever bouts, anorexia and weight loss over a six months period, diagnosed finally as a case of localized hepatic tuberculosis [1], indicating the possibility of occurrence of HTB in children. In such cases, it is more likely that, the tubercular bacilli has reached the liver by portal vein spreads from a primary, subsequently healed focus in the bowel or from adjacent healed involved tissues, brought a dilemma in the diagnosis and even proves to be fatal.

Clinical presentations of HTB are non-specific and cases often prone to be missed [4], but it may also, seriously end in hepatic failure and death. In our case, the clinical presentation was consistent with the case from Brazil [1], and also the case reported by Sneh and Colleagues of a 24 year old female who complaint from fever and weight loss for two months, went into hepatic encephalopathy and died from primary hepatic tuberculosis, indicating a need for a careful history, examination and high index of suspicion. Interestingly, HTB is often misdiagnosed and mimicked with other etiologies of granulomatous hepatitis, lymphoma and other liver diseases. In endemic areas and many parts of developing countries, HTB is the commonest cause of granulomatous hepatitis. Other etiologies have been attributed to; sarcoidosis which considered as the prominent cause, hodgkin's disease, non-hodgkin's lymphoma, primary biliary cirrhosis, cryptococcosis, brucellosis, and some drugs. Careful evaluation of the case, geographical assessment, risk factors, race and trial of treatment are all play an important role in approaching HTB. Pyrexia of unknown origin can mimic diagnosis of HTB with many systemic diseases. One interesting case has been reported by Holla and colleagues of a 12 year old male child from India, is a good example of such a challenge. He firstly presented at the age of five years with high grade fever and hepatosplenomegaly, continued for 7 years, through which the liver biopsy showed presence of non-caseating granlomas with epitheliod cells, and he received anti-tuberculous therapy and other empiric therapies with no improvement. He then, diagnosed as a case of Idiopathic Granulomatous Hepatitis (IGH), treated successfully with immunosuppressive drugs at 12 years of age [7]. According to Loja and his colleagues [8], the criteria for diagnosis of HTB should include recent evidence of tubercular infection, presence of non-caseating necrotizing granulomatosis in liver, and leaving no old tuberculous lesions elsewhere in the body. In this context, we proposed that, the evidence of tuberculosis endemics, positive family history together with prolonged fever, weight loss and abdominal discomfort are good indicators for liver biopsy confirmation of necrotizing gramulomatous and culture for acid fast bacilli [9].

In corresponding to the laboratory data, our case showed anaemia, elevated erythrocyte sedimentation rate, elevated alkaline phosphatase, moderately elevated aminotransaminases and normal bilirubin; all are consistent but nonspecific with HTB [9]. These findings are in agreement with an important review carried out by Harsch [10], had studied 200 cases of tuberculosis of the liver and identified a moderate or marked elevation of alkaline phosphatase, normal or moderately elevated aminotransferase, low serum albumin and hyperglobulinaemia. Another clinical review carried out by Essop et al. on 96 cases of tubrrculous hepatitis has found anaemia and increased sedimentation rates [11].

As the size of granuloma is small and less the 2mm, the role of imaging techniques is limited and only to tuberculoma or tubercular abscess [1]. Tuberculin test is not useful as yields false positive reaction and false negative results of cases with tuberculosis [2]. Laparoscopic liver biopsy was done and the specimen underwent for macroscopic and microscopic histopathological examinations, yield hepatic granuloma with central caseating necrosis. The findings in our case are characteristic and should be considered diagnostic of tuberculosis until proven otherwise [9]. The clinical review by Essop et al. had studied 96 cases of HTB; showed a percentage of 95.8% were with granulomas, 83.3% caseation, 42% fatty changes, 20% portal fibrosis and only 9% growing acid-fast bacilli in association with granulomas [11]. Confirmation of AFB in the cultured specimen is diagnostic but however, cultivating of tubercle bacilli from specimen is low ranged from 0 – 10%, mostly from granuloma of caseating necrosis [10]. PCR is an alternative technique for diagnosis of tuberculosis but this technique would be limited in low resource settings. Based on the elicited evidences, we proposed that, the case has HTB, starting treating him with Anti TB therapy which composed of intensive phase lasting for two months with 4 drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) and the continuation phase lasting for 4 months with two drugs (isoniazid, rifampicin), both summarized as a 2 (RHZE) / 4 (RH) regimen. As the case was malnourished, Pyridoxine (5 mg once daily) was added throughout the course therapy. The overall treatment duration of this case was six months, and is in agreement with other reports from the world [8, 9]. However, some experts recommend an extension of 9-12 months treatment plan for HTB [4,13], and we argued that, the prolonged approach is more suitable for adults, in contrast to children, where treatment

outcomes are generally good and they tolerate the anti-TB drugs better than adults. Moreover, the World Health Organization guidance recommended that both pulmonary and extra-pulmonary disease should be treated with the same regimens lasting 6 months, and at least 9-12 months treatment plan for TB meningitis, TB of bones or joints [14]. The case has been followed from the first day of treatment with close monitoring of liver function tests and/or any complications. Though minimal side effects were observed, he in general responded well to the course therapy with fever had subsided and his well-being status improved dramatically.

COCLUSION

TB of liver should be suspected in cases presented with pyrexia of unknown origin and weight loss within these communities. The age of the case indicates that HTB can infrequently occur in children. Histopathological study of liver biopsy is the preferred technique for diagnosis of HTB, and the presence of granuloma with caseation and necrosis is characteristic and diagnostic of the disease, worth anti-tuberculosis therapy.

ABBREVIATIONS

AFB: Acid Fast Bacilli; ALT: Alanine Aminotransferase; ASP: Asparatate Aminotransferase; HBsAG: Hepatitis B Surface Antigen; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; HTB: Hepatic Tuberculosis; IGH: Idiopathic Granulomatous Hepatitis; RR: Respiratory Rate; TB: Tuberculosis; URTI; Upper Respiratory Tract Infection.

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