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Isolated hepatic Tuberculosis Presenting as an Uncommon Cause of Pyrexia of Unknown Origin.

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Abstract

***Introduction**: We here by present a case of isolated hepatic tuberculosis (TB) in the absence of pulmonary involvement, presenting as pyrexia of unknown origin (PUO).*

***Case Presentation**: A 48-year-old man of Indian origin, has presented with PUO of 6 weeks duration. Initial routine etiological work up for PUO was negative. Ultrasonography (USG) abdomen was normal except for abdominal lymphadenopathy. Computed tomography (CT) abdomen revealed suspected liver granulomas with stricture at distal end of CBD (Common bile duct) with oedema of duodenal papilla, mesenteric and peripancreatic lymphadenopathy. A diagnosis of hepatic TB was confirmed by liver biopsy and histological examination of liver tissues.*

***Discussion**: Tuberculosis presenting with an isolated hepatic presentation is a rare entity. This case proves to be unique, as our patient had experienced primary isolated hepatic TB in the absence of pulmonary TB.*

***Conclusion**: A PUO case presenting as isolated hepatic tuberculosis, liver biopsy led to the correct diagnosis.*

***Keywords:** Extrapulmonary tuberculosis, Granulomatous hepatitis, Liver, PUO (Pyrexia of unknown origin).*

Introduction

Liver involvement may occur in primary and secondary forms of tuberculosis; it is particularly frequent in patients with disseminated miliary tuberculosis [1]. The presentation of isolated form of hepatic tuberculosis is rare [2,3]. Its clinical presentation can be variable, and it is usually non-specific. Signs and symptoms include fever, hepatomegaly, night sweats, weight loss, malaise, anorexia, and abdominal pain. Occasionally, the illness can present as pyrexia of unknown origin (PUO) [3]. Extrapulmonary tuberculosis remains an important cause of PUO, and hepatic tuberculosis should be considered as a differential in such cases [3,4]. Laboratory parameters and imaging methods in the local form of hepatic tuberculosis are frequently abnormal, but non-specific. Definitive diagnosis of this condition can be very difficult; it relies on histological and/or bacteriological findings of the liver tissue obtained by biopsy [2,3]. Sometimes, clinical diagnosis of tuberculosis is only confirmed after complete recovery with specific treatment. A good outcome is generally expected with early anti tuberculous therapy [3,5]. We hereby report a case of localized hepatic tuberculosis that presented as pyrexia of unknown origin.

Case Presentation

A 48-year-old gentleman of Indian origin, has sought medical attention, with complaints of anorexia, daily bouts of fever (up to 39.5ºC) and weight loss (10 kg) over two months. He also had vague right upper abdominal discomfort over the previous two months. Physical examination revealed a cachexic state with a BMI of 17.5 kg/m2 and minimal right hypochondrial tenderness, rest of the physical examination findings were within the normal range. Laboratory investigations revealed anemia (Haemoglobin 9.3 g/dL); leucocytosis with a shift to the left (white blood cell count, 11,680 cells/mm3); elevated ESR (93 mm/hour). Liver function tests were normal except for mild hypoalbuminemia (3.05 g/dL) and mildly elevated alkaline phosphatase levels (157U/L). There was no evidence of jaundice or lymphadenopathy. Kidney function tests, urine analysis, platelets and coagulation parameters were within the normal ranges. As a part of work up for PUO, infective etiological parameters (Malarial antigen, Peripheral smear for malaria, Dengue, Leptospirosis, Weil felix antigen and brucellosis) were done, which were found to be negative. Blood and urine cultures were drawn and analysed which were negative. Mantoux test was negative and Chest x-ray was normal. 2D ECHO didn't reveal any vegetations or infective foci source. The levels of tumour markers, such as α-fetoprotein, carcinoembryonic antigen and carbohydrate antigen 19-9, were within the normal limits. The patient was nonreactive in HIV, Hepatitis B and C serology. Ultrasonography

(USG) abdomen was done which revealed Chronic calculous cholecystitis, there was no evidence of organomegaly. As a part of work up for pyrexia of unknown origin, bone marrow aspiration and biopsy were done which revealed Normoblastic Erythroid Hyperplasia, there was no evidence of fungi, mycobacteria, parasites or atypical cells. Computed tomography (CT) thorax was a normal study, there were no lesions. CT abdomen revealed suspected liver granulomas with stricture at the distal end of CBD with edema of duodenal papilla, periportal, peripancreatic and mesenteric lymphadenopathy (Figure 1). MRI abdomen showed Chronic calculus cholecystitis, well defined lesions of varying sizes in both the lobes of liver, there was no evidence of any calculi in common bile duct and intrahepatic biliary radicles were normal. Sideview endoscopy was done to look at duodenal papilla, which showed a healed duodenal ulcer. Ultrasound-guided percutaneous liver biopsy was performed, in segments V and VI, and two strips of liver tissue were extracted from the liver. Histopathological examination of the hepatic biopsy, stained by haematoxylin-eosin, Gomori and Ziehl-Neelsen, revealed a diffuse and predominantly-mononuclear cell infiltrate with caseating necrosis foci that were surrounded by epithelioid cells, suggestive of granulomatous hepatic inflammation of tuberculous aetiology, stains for AFB were positive (Figure 2). The patient was treated with 4 anti-tubercular therapies (Rifampicin, Isoniazid, Ethambutol and Pyrazinamide). Patient improved clinically and was afebrile post Antitubercular therapy and was on regular follow up. At 6 months follow up patient improved significantly, gained weight and remained afebrile.

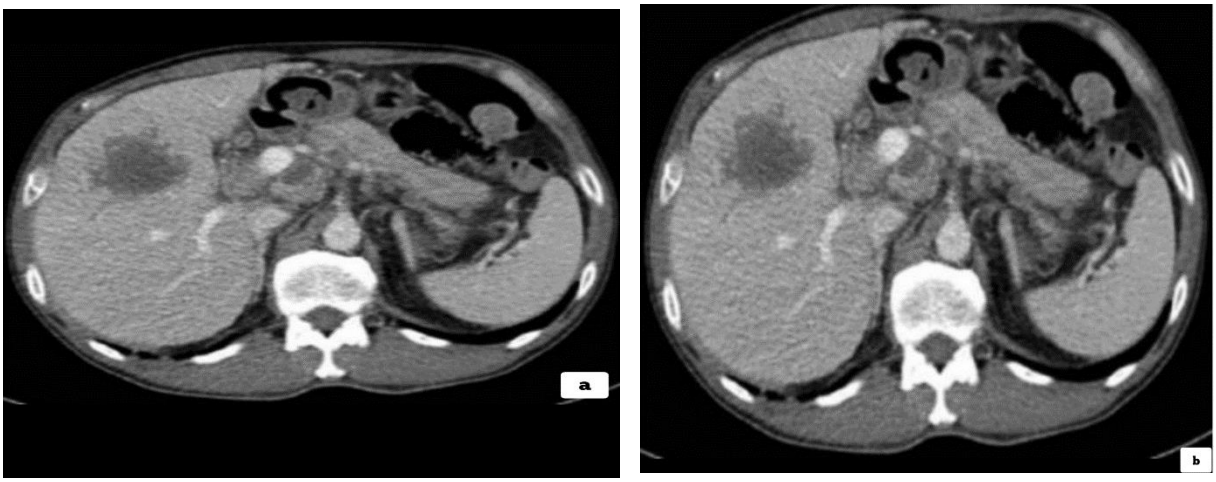

Figure 1: Contrast enhanced abdominal CT imaging (a) An ill-defined nodular lesion(granuloma) in the right anterior lobe of the liver which shows minimal enhancement of the lesion on contrast scan (b) Multiple mesenteric and peripancreatic lymphadenopathy forming a conglomerate mass. Most enlarged lymph nodes have central hyperenhancing areas due to necrosis

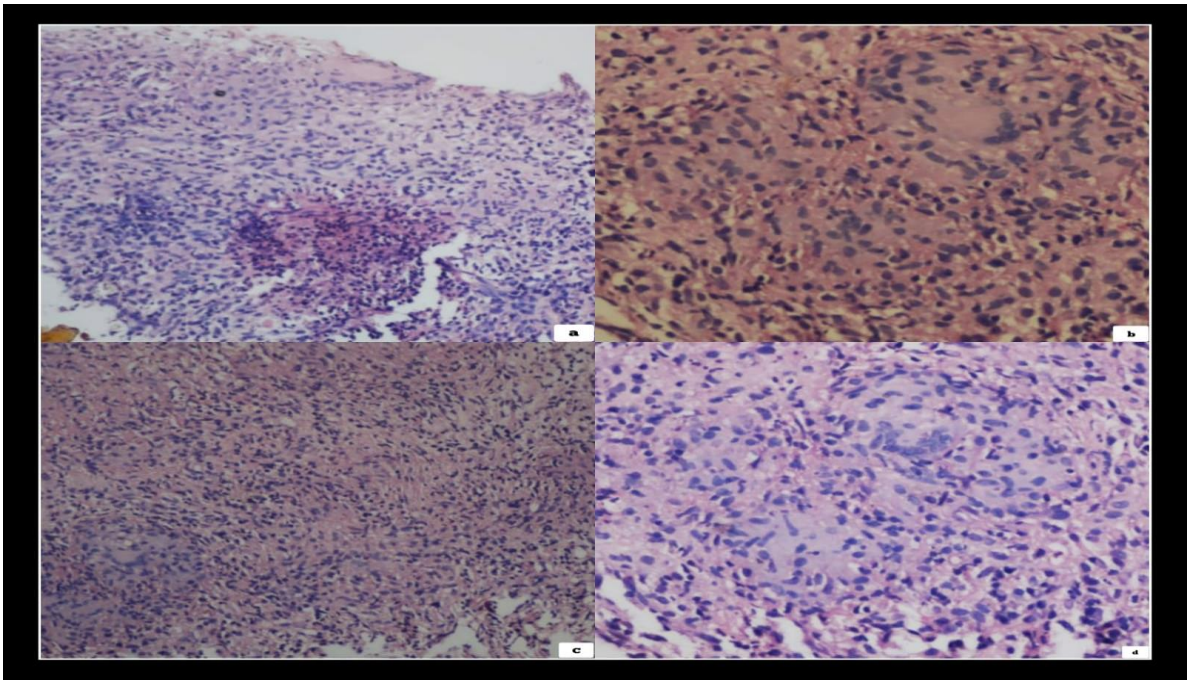

Figure 2. Histopathologic section (haematoxylin-eosin). (a). Granulomatous inflammation-epithelioid histiocytes, mononuclear infiltrate and a focus of caseous necrosis (H&E, X100) (b). Granulomatous inflammation with Langhans giant cells, epithelioid histiocytes and necrotic debris (H&E, X200) (c). Granulomatous inflammation – giant cells, mononuclear infiltrate (H&E, X100) (d). Granulomatous inflammation-langhans giant cells, epithelioid histiocytes, mononuclear infiltrate and necrotic debris (H&E stain, X200)

Discussion:

PUO constitutes one of the greatest challenges of clinical practice. It has been categorized into four variants: classic, neutropenic, HIV associated, and nosocomial. The definition of the classic type is a febrile disease lasting for more than three weeks, with fever above 38.3ºC on several occasions, which remains undiagnosed after three days of investigation in the hospital or after three outpatient visits **[**6-8**]**. Multiple etiologies should be considered when PUO is present; they can be grouped into the following categories: infection, neoplasia, collagenosis, miscellaneous, and undiagnosed causes. However, infection is the most common cause and accounts for approximately 20% to 40% of cases. Tuberculosis, mainly of extrapulmonary localization, remains an important cause of PUO **[**4,9,10**]**. For example, in a prospective study of 34 adult patients with PUO, tuberculosis, in varied clinical forms, was the most frequent disorder (40% of the patients assigned to the infectious diseases group and 17.6% of all cases in the series) **[**4**]**. In a more recent series, tuberculosis also constituted 40% of the

patients with infectious diseases as a cause of PUO [11]. Approximately 36% of the cases in reports of granulomatous hepatitis presented as PUO, and hepatic granulomas have been associated with a wide variety of diseases of diverse etiologies, with 5-36% of these remaining undiagnosed [10]. Hepatobiliary disorders can account for up to 25% of the causes of PUO [12]. The most common etiologies of these are infectious or inflammatory processes (hepatitis, cholangitis, cholecystitis), and neoplastic disorders [13].

Localized hepatic tuberculosis is a distinct clinical form of tuberculosis, with signs and symptoms related only to the hepatic injury, with minimal or no extrahepatic involvement. The clinical characterization and the nomenclature of isolated hepatic tuberculosis are not clearly defined; this disorder is referred to as atypical tuberculosis of the liver, tuberculous hepatitis, hepatic tuberculosis, hepatobiliary tuberculosis and localized or local hepatic tuberculosis. Hepatic tuberculosis constitutes less than 1% of all cases of this infection [14]. Liver involvement may occur in the primary and secondary forms of tuberculosis and is particularly frequent in patients with disseminated miliary tuberculosis. In autopsy series of disseminated tuberculosis, liver involvement was found in 80-100% of the cases [1]. On the other hand, the local form of hepatic tuberculosis, with minimal or no extrahepatic manifestations, is much less common [2,3]. Kok et al. [15] reported that hepatic tuberculosis was isolated in 0.3% of 1,678 new cases of tuberculosis.

It is believed that pathogenesis of these two forms of hepatic tuberculosis is different. Hematogenous dissemination of the bacteria seems to be the route by which the bacilli reach the liver in miliary hepatic tuberculosis; on the other hand, in local hepatic tuberculosis, the tubercle bacillus probably reaches the liver from the intestine via the portal vein. The possibility of such mechanisms is reinforced by the histopathological findings; in miliary tuberculosis, the granulomas are nearly always situated inside the lobules and in the local hepatic form they are mainly in the portal regions [3].

Patients with hepatic tuberculosis have variable clinical presentations and no consistent clinical and biochemical findings, which makes diagnosis difficult. The presenting symptoms are usually non-specific and are mainly constitutional in nature; they include fever, night sweats, malaise, anorexia, weight loss, and abdominal pain [14,15]. In general, the clue to the diagnosis of hepatic involvement is the finding of tuberculosis elsewhere. When such evidence is lacking, a correct diagnosis can be extremely difficult, as in our case study, which presented as PUO. Disturbance of bowel habit may be present, and diarrhea was about twice as common as constipation in another study [3]. Abdominal tenderness in the epigastrium or right upper quadrant is a common manifestation [15]. Hepatomegaly is observed in most cases and has been frequently associated with splenomegaly [1]; however, splenic

involvement is more common and extensive in the miliary form [16]. Jaundice may occur and is attributed mainly to the direct destruction of the liver parenchyma by tuberculosis [15], but obstructive processes may also be present [16].

The most frequent clinical-laboratory findings in tuberculosis of the liver are hepatomegaly (~90%), elevated serum alkaline phosphatase levels (~80%), fever (~70%), weight loss (~60%), and abdominal pain (~55%) [3,5]; all of them were present in our case. A moderate or marked increase in the serum levels of alkaline phosphatase, along with normal or mildly increased serum bilirubin, is considered suggestive of hepatic tuberculosis; however, these findings are not specific and may occur in other conditions, such as metastatic carcinoma, liver abscess, echinococcosis, amyloidosis, granulomatous diseases of varying etiologies, and active cirrhosis [3]. This pattern of biochemical alterations was also observed in our patient. Low serum-albumin levels and hyperglobulinaemia have also been described as suggestive of hepatic tuberculosis [2,3]. The aminotransferases can be moderately elevated or normal, and gamma glutamyl-transpeptidase levels are sometimes markedly raised. Abnormal prothrombin time has been a common finding in some series [3]. Non-specific laboratory alterations, such as anemia and leukocytosis can be found. Sometimes there is pancytopenia. Increased erythrocyte sedimentation rates are common [5,17]. Most of these laboratory abnormalities were observed in our case study.

Local and miliary forms of hepatic tuberculosis have similar biochemical presentations, but the local form is associated with more severe hepatocytic damage (higher serum ALT levels), and the miliary form is more wasting (lower serum albumin levels) [2]. The strong impairment of the general condition of our patient was probably due to the long duration of the disease condition.

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 tuberculosis, 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]. In general, tubercle bacilli are rarely encountered and the finding of caseation in the hepatic tuberculous granulomas, although variable, is not very frequent [2,17-19]. Bacteria are cultivated from the liver in only 0-10% of the cases, with the highest yield coming from granulomas with caseating necrosis [10]. Certain distinctive features can identify tuberculous granulomas in the liver; these include acid-fast bacilli within the lesion, caseating necrosis with destruction of the reticulin framework, irregular contours with a particularly dense cuff of lymphocytes surrounding the lesion, and few lesions, with a tendency to coalesce [10]. However, the etiology of hepatic granulomas can seldom be established by

histological appearance alone. Some authors suggest that, in a consistent clinical picture, which is frequently somewhat non-specific, the finding of granulomas, especially with caseating necrosis, constitutes histopathological evidence of tuberculosis, unless proven otherwise [2,20].

A high degree of suspicion is required for diagnosing localized hepatic tuberculosis, and the definite diagnosis relies on histological and/or bacteriological evidence of infection [15]. Histopathological examination of liver tissue obtained by biopsy is the most reliable diagnostic method [2,3]. Imaging methods are of little value, because the findings are non-specific. Ultrasonography, computerized tomography, and magnetic resonance imaging are very sensitive for the detection of hepatosplenic nodules, but differential diagnosis from other conditions, such as metastases, fungal abscesses and lymphomas, is difficult [14]. The tuberculin skin test is of little value as a diagnostic method. Other conditions can be associated with a positive reaction, and this test can be negative in patients with tuberculosis [10,17]. Sometimes, clinical diagnosis of tuberculosis is confirmed only after complete recovery due to antituberculous therapy. Some authors suggest that, whenever there is a lack of etiological diagnosis of a granulomatous hepatitis, patients should be considered for an empirical trial with antituberculous drugs, especially if there is clinical deterioration, particularly in areas where tuberculosis is endemic [10,17,19].

Tuberculous hepatitis is treated according to standard drug regimens. Response to treatment is less satisfactory in acutely-ill patients and in those younger than 20 years, as well as in patients with coagulopathy, high caseation scores, and those with predisposing factors, such as steroid treatment, chronic renal failure, diabetes mellitus and systemic lupus erythematosus. The success of treatment depends on early recognition of the disease, which can be very difficult, because of non-specific presentation in the great majority of cases, and because hepatic tuberculosis is easily confused with other liver diseases [5].

Conclusion: Tuberculosis of the liver should be considered in any case of unexplained hepatomegaly, hepatosplenomegaly or PUO; and, in suspicious cases, a liver biopsy should be performed without delay, since this condition responds well to early antituberculous therapy.

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