

Case Report

Diagnosis and treatment of hepatic tuberculosis: report of five cases and review of literature

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Abstract: Hepatic tuberculosis is uncommon, lack of specific clinical manifestations and imaging features, so it can easily be misdiagnosed in clinical. Herein, we discuss variety of its forms and summarize the diagnosis and treatment of hepatic tuberculosis in this paper. Five cases of hepatic tuberculosis are described. The diagnosis, treatment and outcome of the patients are discussed. Image examination associated with image-guided fine needle aspiration biopsy is the best diagnostic method. In our center, three patients underwent needle biopsy and confirmed hepatic tuberculosis. In addition, two patients preoperative misdiagnosed as cholangiocarcinoma were confirmed hepatic tuberculosis by postoperative pathology. Three patients underwent surgical procedures along with anti-tubercular drug therapy, two patients received only anti-tubercular drug therapy. The renal post-transplantation patient with hepatic tuberculosis eventually died of multiple organ failure (MODS). The other four patients were followed for 48~120 months, yielding no recurrence of hepatic tuberculosis. In conclusion, hepatic tuberculosis usually associated with atypical clinical manifestations. Image examination associated with image-guided fine needle aspiration biopsy is the best diagnostic method. Anti-TB treatment is effective in most of cases. However, if there are indications for surgery or difficult to diagnose, surgical procedures along with anti-tubercular drug therapy could be adopted.

Keywords: Liver mass, tuberculoma, tuberculosis, TB, anti-TB

Introduction

Although the prevalence of tuberculosis (TB) decreased quickly worldwide after the widespread use of anti-TB drugs in the 1940s, the incidence rates have increased in recent years owing to government complacency regarding the TB problem, inadequate public health measures, HIV coinfection, intravenous drug abuse, multidrug resistance, and an increased number of immunocompromised patients [1-3]. Tuberculous involvement of liver as a part of disseminated tuberculosis is seen in up to 50-80% cases, with the increasing resurgence of TB, the incidence of hepatic TB has also been increasing [4].

Hepatic TB lacks typical clinical symptoms and imaging diagnosis, so can easily be misdiagnosed and delayed treatment in clinical. Our

literature review have found that the vast majority of articles are case reports, and lack of experience of the diagnosis and treatment of hepatic tuberculosis. In this study, five cases of hepatic tuberculosis are described. The diagnosis, treatment and outcome of the patients are discussed and a review of literature of hepatic TB is also presented.

Materials and methods

Patients

Five cases of hepatic TB patients were referred to our hospital from 1 January 2000 to 31 December 2011. The medical records were reviewed retrospectively and data were obtained concerning demographics, the clinical presentation, diagnoses, treatment and follow-up.

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Table 1. Clinical characteristics of the 5 cases of hepatic tuberculosis

clinical characteristics	n	patient number
Epigastric pain	5	1, 2, 3, 4, 5
Lethargy	4	2, 3, 4, 5
Mild fever	3	1, 4, 5
Jaundice	2	2, 3
Previous TB infection	3	2, 3, 5
Hepatomegaly	3	1, 2, 5
Splenomegaly	1	5
Raised ALP	3	1, 3, 4
Raised WBC	2	1, 2
Raised γ GT	3	1, 3, 4
Raised ESR	2	2, 5
FNA	3	1, 4, 5
Classification		
TLGT	3	2, 3, 5
Primary tuberculoma	1	1
Primary tuberculous abscess	1	4
Treatment		
Surgical procedures along with anti-TB	3	1, 2, 3
Anti-TB	2	4, 5

ALP: alkaline phosphatase; WBC: white blood cell count; γ GT: γ -glutamyl transpeptidase; ESR: erythrocyte sedimentation rate; FNA: ultrasound-guided fine needle aspiration biopsy; TLGT: tuberculosis of the liver associated with generalized miliary tuberculosis.

Classification of hepatic TB

Hepatic TB was classified according to the classification proposed by Reed [5]. The 5 cases were classified as shown in **Table 1**. According to his modified classification, three cases belong to tuberculosis of the liver associated with generalized miliary tuberculosis (TLGT) and the other two cases are primary tuberculoma or abscess of the liver.

Management after admission

Hospital examination of the patients included blood biochemistry, chest x-ray, electrocardiography, percutaneous ultrasonography (US), helical computed tomography (CT) or magnetic resonance imaging (MRI) scan of the chest and abdomen and ultrasound-guided fine needle aspiration biopsy (FNA) to confirm the diagnosis and to identify the location of the lesions. In our study, three patients underwent needle biopsy and confirmed hepatic tuberculosis. In addition, taking into account the special lesion site and risk of biopsy, two patients didn't perform needle biopsy and were misdiagnosed as cholangiocarcinoma. But they were confirmed

hepatic tuberculosis by postoperative pathology.

The mean time of duration of presentations is 6 (1~14 days) days. The clinical presentations of the patients included abdominal pain, lethargy, mild fever, jaundice, raised alkaline phosphatase level and erythrocyte sedimentation rate. Clinical characteristics of the 5 cases of hepatic TB were shown in **Table 1**. Two patients' past medical history included lung tuberculosis and one included intestinal tuberculosis. They were resolved successfully by anti-TB therapy and remained well until this presentation. Quadruple therapy (isoniazid, rifampin, pyrazinamide, and ethambutol) was adopted anti-tuberculosis protocol in our hospital. All

patients required at least 1 year of medical therapy.

Three patients underwent surgical procedures along with anti-tubercular drug therapy. One of the three patients who belongs to primary tuberculoma presented with a 3-day history of epigastric pain and mild fever (case one). Physical examination of the abdomen revealed hepatomegaly, of three finger-breadths, which was slightly tender. Her chest X-ray was normal and human immunodeficiency virus (HIV) status was negative. Ultrasonography (US) of the abdomen revealed acute calculous cholecystitis and a septated echogenic mass measuring 5×4.6 cm, lying in the right anterior lobe of the liver. Abdominal computed tomography (CT) showed the hypodense mass with no evidence of any other intra-abdominal masses. A liver mass was obtained by ultrasound-guided fine needle aspiration biopsy (FNA), showed features consistent with tuberculosis: multiple epithelioid cell granulomas with Langhans giant cells and caseation. Alcohol and acid fast bacilli were also demonstrated in the specimens. After anti-inflammatory therapy, the pain and fever were not alleviated. The patient received

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cholecystectomy and primary tuberculoma enucleation along with anti-tubercular therapy. Another patient who belongs to miliary tuberculosis of the liver associated with previous intestinal tuberculosis presented with a 1-week history of lethargy, generalized pruritics, jaundice and epigastric pain (case two). On physical examination, she was noted to be mild jaundice and hepatomegaly, of three finger-breadths, which was slightly tender. Her chest X-ray was normal and HIV status was negative. US scan of the liver revealed multiple round hypodense lesions between 1.5 to 2.5 cm in diameter and abdominal CT showed the hypodense masses in the left lobe of the liver. No other intra-abdominal masses were seen in the abdomen. The patient was misdiagnosed as cholangiocarcinoma with intrahepatic metastasis. In consideration of the patient's lesions were located in the left lobe and accompanied by biliary obstruction, so the patient underwent left liver resection, the postoperative pathology confirmed hepatic tuberculosis. She received anti-tubercular therapy for one year. The other patient presented with a 1-week history of lethargy, poor appetite, jaundice and epigastric pain (case three). His chest X-ray revealed calcified TB foci and HIV status was negative. US scan of the liver revealed hepatolithiasis accompanied by hilar mass measuring 3×2 cm. Enhanced abdominal CT appears as an un-enhancing, low density lesion. No other intra-abdominal masses were seen in the abdomen. Taking into account the risk of biopsy, the patient didn't perform needle biopsy and was misdiagnosed as hilar cholangiocarcinoma, but confirmed hepatic tuberculosis by intra- and postoperative pathology. He received anti-tubercular therapy post operation.

In addition, there were two patients received only anti-TB therapy. In particular, one of the two patients was a 45-year-old worker presented with a 1-day history of lethargy, mild fever and epigastric pain (case four). There was no evidence of hepatomegaly, splenomegaly and lymphadenopathy. She underwent renal transplantation two months ago and was taking immunosuppressant. There was no history of previous contact with tuberculosis. Her chest X-ray was normal and HIV status was negative. US scan of the abdomen revealed a low-density lesion with abscess measuring 4×4.8 cm, lying in the right posterior lobe of the liver. Enhanced

abdominal CT appears as an un-enhancing, central, low density lesion with a slightly enhancing peripheral rim corresponding to surrounding tissue, and no evidence of any other intra-abdominal masses. US-guided FNA of lesion showed hepatic tuberculoma associated with abscess. Alcohol and acid fast bacilli were also demonstrated in the specimens. After multidisciplinary consultation, the patient received anti-tubercular therapy. Unfortunately, during the treatment process the patient suffer from incomplete intestinal obstruction, electrolyte disturbance, sepsis, and ultimately lead to multiple organ failure (MODS) and died. The other patient who belongs to miliary tuberculosis of the liver associated with previous lung tuberculosis received only anti-tubercular therapy and received better clinical result (case five).

Outcomes

Three cases underwent surgical procedures along with anti-tubercular drug therapy and the other two cases received only anti-tubercular drug therapy. Except for the post-renal-transplant patient died of MODS. The other four patients recovered without complications and clinical complaint disappeared. The patients were followed for 48~120 months (median 72 months), yielding no recurrence of the hepatic TB.

Discussion

Hepatic TB is reported to occur in 50–80% of patients who are dying of pulmonary TB [6]. But most of cases are usually clinically silent. Therefore, it is possibly under-diagnosed and under-reported in clinical practice. The clinical classification and nomenclature of hepatic TB is confusing in the literature [5, 7-9]. It classified by Levine as miliary tuberculosis, pulmonary tuberculosis with hepatic involvement, primary liver tuberculosis, focal tuberculoma or abscess, or tuberculous cholangitis [9]. However, Reed divided it into three forms: tuberculosis of the liver associated with generalized miliary tuberculosis, primary miliary tuberculosis of the liver, and primary tuberculoma or abscess of the liver [5]. In our study, we adopt Reed's classification. According to his classification, three cases belong to tuberculosis of the liver associated with generalized miliary tuberculosis and the other two cases are primary tuberculoma or abscess of the liver.

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Liver is a common site for granuloma formation owing to its rich blood supply, lying at the distal end of portal circulation and large number of reticuloendothelial cells. A majority of granulomas are usually located near the portal tract and there is only mild perturbation of hepatic function, so most patients are minimally symptomatic or asymptomatic. Primary hepatic TB is rare because low oxygen tension in the liver is unfavorable for growth of mycobacteria [8]. Hepatic TB secondary to pulmonary or intestinal tuberculosis is more common. In our study, three cases belong to secondary to pulmonary or intestinal tuberculosis. But primary hepatic tuberculosis should be brought to our attention. There were two cases of primary tuberculoma or abscess of the liver in our center.

Hepatic TB lack typical clinical manifestations and imaging diagnosis, it may follow common clinical complaints with mild fever, right upper quadrant pain, hepatomegaly, weakness, night sweats, and so on. Hepatomegaly is usually found with an increase in alkaline phosphatase and normal transaminase levels [4, 5, 7, 8, 10-12]. Jaundice caused by tuberculosis invasion and oppression bile duct, is easy to be confused with hilar tumors, and some liver tuberculoma patients may associated with portal hypertension or biliary tract bleeding [13, 14]. In our center, two patients were misdiagnosed as cholangiocarcinoma. Imaging techniques (US, CT and MRI) are useful in making the diagnosis of tuberculoma or tubercular abscess. On CT, the liver tuberculoma appears as an un-enhancing, central, low density lesion owing to caseation necrosis with a slightly enhancing peripheral rim corresponding to surrounding granulation tissue [9, 15, 16]. One of the typical CT features of hepatic tuberculosis might be multiple lesions of varying density, indicating that there are lesions in different pathologic stages coexisting in hepatic TB, including tuberculous granuloma, liquefaction necrosis, fibrosis or calcification [17]. MRI of hepatic tuberculosis shows a hypointense nodule with a hypointense rim on T1-weighted imaging and hypointense, isointense or hyperintense with a less intense rim on T2-weighted imaging, and peripheral enhancement or internal septal enhancement on post-contrast MRI [15, 18]. In our study, most of the patients met the above image results. Cao et al, reported that contrast-enhanced ultrasonography may

be helpful in differentiating the diagnosis of hepatic TB from other hepatic focal lesions [19]. In recent years, the F-18 FDG PET/CT is widely used in the diagnosis and staging of malignant tumors, but prone to misdiagnosis in the diagnosis of hepatic tuberculosis, because the hepatic tuberculosis also showed FDG-avid [20]. These findings, although suggestive of tuberculosis, have also been seen in necrotic tumors such as cholangiocarcinoma, hepatocellular carcinoma and metastatic carcinoma. Therefore, a high degree of clinical suspicion is required to diagnose this entity which can be medically managed easily but if not treated can lead to hepatic failure and ultimately death [6, 14]. Summary of the literature and our data, the following conditions should be suspected hepatic TB: (1) previous medical history of tuberculosis or contact with tuberculosis and complaint mild fever, night sweat, fatigue, weight loss, epigastric pain, jaundice, hepatomegaly with or without splenomegaly or lymphadenopathy, liver tenderness; (2) an elevated levels of ESR, ALP, serum globulin, adenosine deaminase but normal transaminase; positive tuberculin test; (3) US and CT scan showed intrahepatic hypodense lesions or associated with point linear high-density calcific lesions, enhanced CT may reveal slightly enhance. In our center, three patients underwent needle biopsy and confirmed hepatic tuberculosis. However, taking into account the special lesion site and risk of biopsy, two patients didn't perform needle biopsy and were misdiagnosed as cholangiocarcinoma. But they were confirmed hepatic tuberculosis by postoperative pathology. Therefore, image examination associated with image-guided fine needle aspiration biopsy is the best diagnostic method [5, 17, 19, 21].

Coexistence of HIV with mycobacterium tuberculosis should not be underestimated and evidence of HIV infection or other immunodeficiency states should be paid high attention to [22, 23]. But all of our patients' HIV status were negative.

Quadruple therapy (isoniazid, rifampin, pyrazinamide, and ethambutol) is recommended anti-tuberculosis protocol because of the increasing incidence of drug-resistant tuberculosis. At least 1 year of medical therapy is generally required [24]. Extra-pulmonary tuberculosis had a high incidence and high mortality in post-transplant population [25]. Therefore, high

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attention should be given to its differential diagnosis in clinical practice. Balancing anti-tuberculosis and anti-rejection therapy is important for this specific population. In our transplantation center, we have found that the classical anti-tuberculosis protocol shows high hepatotoxicity incidence and should be cautiously selected. Fluoroquinolones combined with first-line anti-tubercular drugs is a new protocol with satisfactory effect and low hepatotoxicity incidence, and therefore might be safer in the treatment of post-transplant tuberculosis [26]. With early diagnosis and prompt effective treatment, the prognosis of hepatic tuberculosis is usually good. However, if there are indications for surgery or difficult to diagnose, surgical procedures along with anti-tubercular drug therapy could be adopted. In our study, three patients underwent surgical procedures along with anti-tubercular drug therapy and received better results. Summary of the literature and our data, indications of surgical treatment of hepatic tuberculosis include: (1) isolated tuberculoma, liver tuberculous abscess while anti-TB treatment effect is not obvious; (2) oppression of biliary tract causing obstructive jaundice; (3) concurrent portal hypertension or biliary tract bleeding or acute abdomen; (4) confusion with malignant lesions. Surgical procedures contain enucleation, local excision, liver segment or lobe resection, abscess drainage and biliary drainage. Owing to the development of laparoscopic techniques in recent years, surgical procedures for hepatic TB is more conducive.

In conclusion, hepatic tuberculosis usually associated with atypical clinical manifestations. Image examination associated with image-guided fine needle aspiration biopsy is the best diagnostic method. Anti-TB treatment is effective in most of cases. However, if there are indications for surgery or difficult to diagnose, surgical procedures along with anti-tubercular drug therapy could be adopted.

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Disclosure of conflict of interest

The authors declare that they have nothing to disclose.

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