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Case Report

A case of multiple macronodular hepatic tuberculosis difficult to differentiate from hepatocellular carcinoma with intrahepatic metastasis: CT-guided fine needle aspiration biopsy confirmed the diagnosis

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Abstract: Multiple macronodular hepatic tuberculosis is difficult to be differentiated from hepatocellular carcinoma with intrahepatic metastasis in clinical practice, especially when hepatitis B with or without liver cirrhosis coexists with it. Herein, we report a 30-year-old man with a 10-year history of hepatitis B and a family medical history of hepatocellular carcinoma related with hepatitis B that was finally diagnosed as multiple macronodular hepatic tuberculosis. Abdominal B-mode ultrasonography (US) and plain computed tomography (CT) revealed multiple unequal-sized nodules in the liver. CT-guided fine needle aspiration biopsy (FNAB) of the liver demonstrated a caseating granuloma with lymphocytes, multinucleate giant cells and epithelioid cells compatible with the diagnosis of tuberculosis and no hepatoma cells were detected. Thus, the diagnosis of hepatic tuberculosis was confirmed and hepatocellular carcinoma with intrahepatic metastasis was excluded.

Keywords: Multiple macronodular hepatic tuberculosis, hepatocellular carcinoma, intrahepatic metastasis, FNAB

Introduction

Tuberculosis (TB) infection remains a significant cause of morbidity and mortality, particularly in developing and underdeveloped nations [1]. It mainly affects lungs and rarely invades the liver. Most hepatic involvement of tuberculosis, called hepatic tuberculosis (TB), belong to the category of systemic miliary tuberculosis secondary to pulmonary tuberculosis and intestinal tuberculosis [1]. Due to lack of specificity, clinical manifestation and laboratory analysis show limited value in diagnosing hepatic TB. Although ultrasonography (US) and computed tomography (CT) are very useful radiological tools in suggesting the possibility of hepatic TB, histopathological examination of the liver biopsy is usually the final resort for the diagnosis of hepatic TB in clinical practice. Although it has some disadvantages, CT-guided fine needle aspiration is a common method to obtain liver specimen for biopsy. Compared with widely reported isolated hepatic tuberculosis, such as abscess [2], nodule [3], biliary invasion [4], serosal invasion [5] and miliary hepatic tuberculosis, multiple macronodular hepatic tuberculosis is first reported. Here, we describe a case of multiple macronodular hepatic tuberculosis, difficult to differentiate from hepatocellular carcinoma with intrahepatic metastasis and present our diagnostic experience.

Case report

A 30-year-old Chinese man was admitted to the hospital with complaint of weight loss (up to 10 kg), poor appetite and weakness for 10 months, abdominal distension and chest congestion for 3 months. Five years ago, he suffered from pulmonary tuberculosis in right pulmonary lobes,

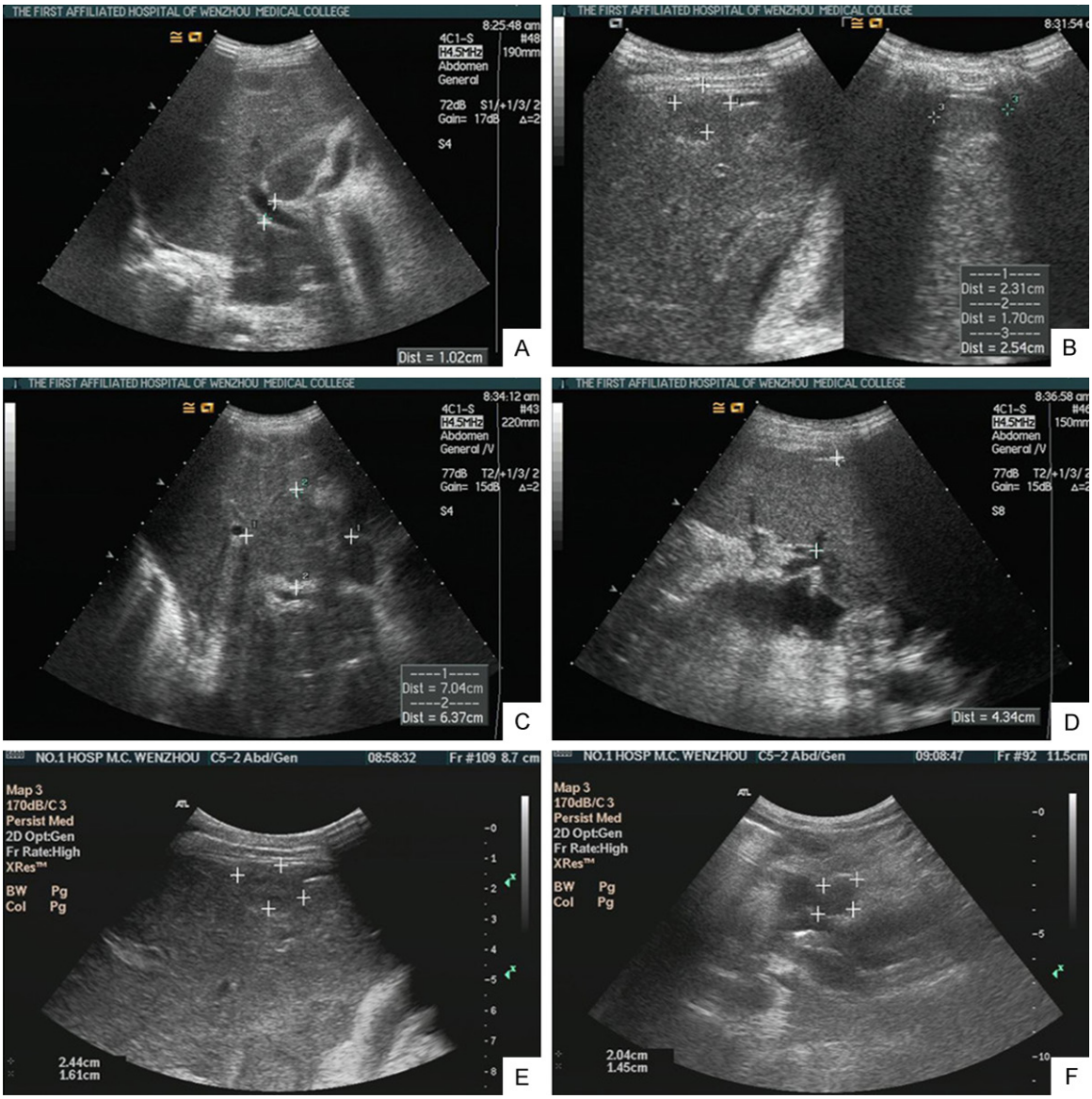

Figure 1. High-resolutions B-mode ultrasonography of the liver showed multiple unequal-sized hypoecho nodules with an unclear boundary in the capsule of right hepatic anterior and posterior lobe and the posterior peritoneum. Detailed data about their sizes were listed. A: 1.02 cm; B: 2.31 cm × 1.70 cm × 2.54 cm; C: 7.04 cm × 6.37 cm; D: 4.34 cm; E: 2.44 cm × 1.61 cm; F: 2.04 cm × 1.45 cm.

but was cured with complete anti-tuberculous therapy. He had a 10-year history of hepatitis B and his father died of primary hepatocellular carcinoma related with hepatitis B. He had no past medical history of diabetes, hypertension, cardiovascular diseases, hyperlipidemia, cancers, etc. Physical examination revealed the following characteristics: temperature 36.9°C, pulse rate 78 beats/min, blood pressure 120/75 mmHg, respiratory rate 17 breaths/min, emaciation, mild jaundice of skin and mucosa, mild tenderness in right upper quadrant, splenomegaly, but there was no palpable hepatomegaly. Blood biochemistry revealed the following data: haemoglobin 96 g/L (normal range 120-160 g/L for males), white blood cells 14,200/mm^3 (normal range 4,000-10,000/mm^3), blood platelets 283,000/mm^3 (normal range 100,000-300,000/mm^3), erythrocyte sedimentation rate 102 mm/h (normal range 0-15 mm/h for males), adenosine deaminase 43 U/L (normal range 4-22 U/L), alanine aminotransferase 31 U/L (normal range 5-40 U/L), aspartate aminotransferase 40 U/L (normal

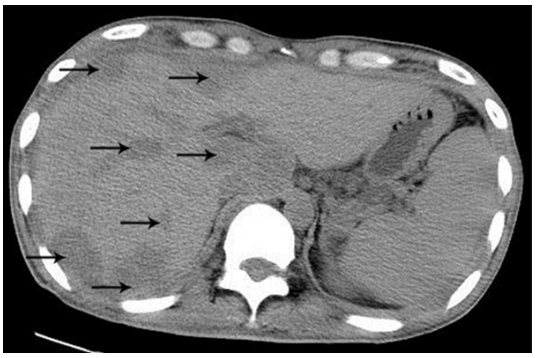

Figure 2. Abdominal computed tomography revealed multiple hypodense lesions of the liver (black arrows).

range 8-40 U/L), alkaline phosphatase 159 U/L (normal range 40-150 U/L), γ-glutamyl transpeptidase 86 U/L (normal range 11-50 U/L), total bilirubin (TBiL) 33 μmol/L (normal range 0-22 μmol/L) with a direct bilirubin of 21 μmol/L (normal range 0-6.8 μmol/L), total protein 59.6 g/L (normal range 60-80 g/L), albumin 25 g/L (normal range 35-50 g/L), albumin/globulin rate 0.8 (normal range 1.5-2.5). Detection of HBV antigen in serum revealed: HBsAg (+), HBsAb (-), HBeAg (-), HBeAb (+), HBcAb (+); HBV DNA 3.6×10^2 copies/ml. The level of α-fetoprotein was 283 μg/L (normal range ≤ 20 μg/L), but the levels of other tumor markers, such as carcinoembryonic antigen and carbohydrate antigen 19-9, were within the normal limits. The patient was non-reactive in HIV serology and his tuberculin test was strongly positive. A chest CT scan showed multiple calcification foci in right pulmonary lobe, bilateral hydrothorax (obvious on the right), mild hydropericardium. US scan of abdomen revealed multiple flaky or nodular asymmetrical hypoecho nodules in the capsule of right hepatic anterior and posterior lobe with an unclear boundary, multiple unequal-sized partly interfused hypoecho nodules of the posterior peritoneum, moderate liquid dark area (**Figure 1**). Abdominal plain CT revealed multiple hypodense lesions of the liver, multiple retroperitoneal lymphadenectasis in the peritoneal cavity, ascites, splenomegaly (**Figure 2**). Taken CT, US image findings, clinical manifestation and past medical history into consideration, the diagnosis of hepatocellular carcinoma with intrahepatic metastasis was suspected. In order to establish the diagnosis, liver specimens were obtained by CT-guided fine needle aspiration biopsy (FNAB). Histopathological examination showed features consistent with tuberculosis: central caseous necrosis surrounded by lymphocytes, multinucleate giant cells and epithelioid cells (**Figure 3**) and no hepatoma cells were detected. Although acid-fast bacilli (AFB) could not be detected on smear examination, and polymerase chain reaction (PCR) for Mycobacterium tuberculosis was negative in the biopsy specimen, the diagnosis of hepatic tuberculosis was confirmed. Peritoneal tuberculosis and TB of retroperitoneal lymph nodes were suspected. Taking into account the risk, difficulty, lack of necessity, the patient didn't perform puncture for biopsy.

Quadruple anti-tuberculous therapy with rifampicin, isoniazid, pyrazinamide and ethambutol was started. To enhance the curative effect, prednisone and ofloxacin were added. At the two-month follow-up, he got a gain weight of 3 kg and ameliorative appetite. At the six-month follow-up, the patient had no abnormal laboratory parameters and no hypodense lesions on abdominal CT. His enlarged spleen and lymph nodes in the posterior peritoneum returned to be normal size. He received another six months treatment to finish 1 year anti-tuberculous therapy.

Discussion

Hepatic tuberculosis (TB) is caused by liver involvement of Mycobacterium tuberculosis and it is a rare clinical entity. Due to lack of specific clinical presentation and imaging findings, the diagnosis was often overlooked [6]. Though its classification was confusing in the literature, hepatic TB was usually categorized into 5 types: miliary, abscess, nodule, biliary invasion and serosal invasion [7]. Isolated nodular hepatic tuberculosis had been reported [3], but multiple macronodular hepatic tuberculosis was rarely reported. Multiple macronodular hepatic tuberculosis was defined as multiple unequal-sized nodules in the liver, commonly greater than 2.0 cm [8]. As we can find in **Figure 1**, hepatic nodules in our case were asymmetrical and often greater than 2.0 cm. It was different from miliary hepatic tuberculosis, which was defined as multiple, miliary, micronodular lesions with size ranging from 0.6 cm to 1.8 cm [5].

Yu et al. considered that one of the typical CT features of hepatic tuberculosis might be mul-

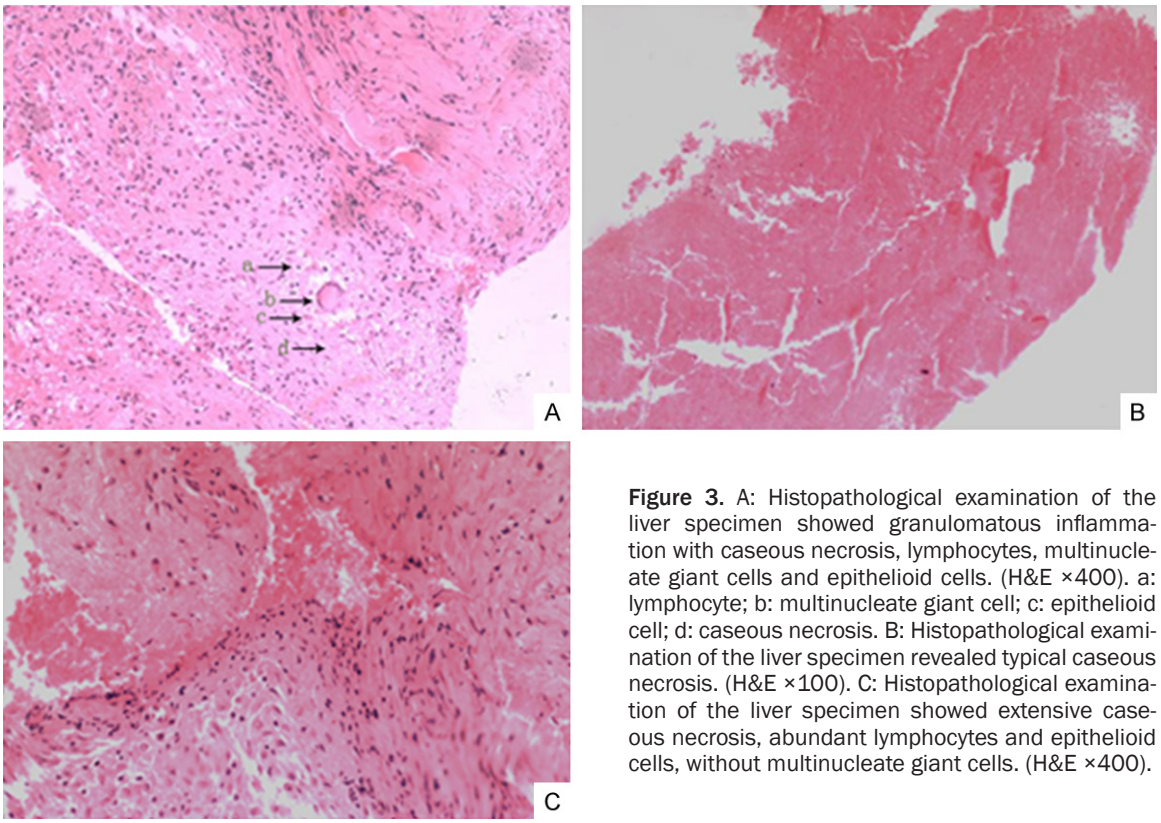

Figure 3. A: Histopathological examination of the liver specimen showed granulomatous inflammation with caseous necrosis, lymphocytes, multinucleate giant cells and epithelioid cells. (H&E ×400). a: lymphocyte; b: multinucleate giant cell; c: epithelioid cell; d: caseous necrosis. B: Histopathological examination of the liver specimen revealed typical caseous necrosis. (H&E ×100). C: Histopathological examination of the liver specimen showed extensive caseous necrosis, abundant lymphocytes and epithelioid cells, without multinucleate giant cells. (H&E ×400).

tiple, various-dense lesions, indicating that there are lesions developed in different pathologic stage coexisting in hepatic tuberculosis, including tuberculous granuloma, liquefaction necrosis, fibrosis or calcification [5]. These features may be helpful for suggesting the diagnosis of tuberculosis, but they can also be found in necrotic tumors such as metastatic carcinoma and hepatocellular carcinoma [5, 9]. Considering his major complaint of weight loss is one of the major symptoms of malignant tumor, his CT findings were accorded with imaging features of metastatic carcinoma and his father died of primary hepatocellular carcinoma, the diagnosis of hepatocellular carcinoma with intrahepatic metastasis is highly suspected. However, histopathological examination of liver biopsy finally confirmed the diagnosis of hepatic tuberculosis.

Due to lack of specific clinical manifestations and imaging findings, hepatic tuberculosis is often misdiagnosed as primary or metastatic hepatocellular carcinoma and lymphoma, especially when it coexists with these malignancies [10]. Laboratory analyses showed limited value in suggesting the possibility of hepatic tuberculosis and image examination associated with image-guided fine needle aspiration biopsy is the best diagnostic method for hepatic tuberculosis [11, 12]. CT-guided fine needle aspiration biopsy is taking a more and more important role to confirm the diagnosis of hepatic tuberculosis in current clinical practice, since it has many advantages over the percutaneous puncture biopsy of the liver guided by B-mode ultrasonograph [1]. CT has a high resolution and can clearly show not only the size and location of the lesions but also adjacent relationships of intrahepatic blood vessels and bile ducts around them. Therefore, CT-guided fine needle aspiration biopsy has a lot of advantages such as accurate positioning, high puncture success rate, and low occurrence rate of complications including bleed, infection etc. Especially, there exists the possibility of hepatocellular carcinoma in our case, CT-guided fine needle aspiration biopsy can decrease the risk of implantation metastasis of tumor cells along the puncture pathway. These advantages explain why we take CT-guided fine needle aspiration instead of US-guided percutaneous puncture for biopsy, though it has some disadvantages, including more radioactive than US-guided per-

cutaneous puncture biopsy, a little inconvenient to implement and cost comparatively much. As reported, CT-guided fine needle aspiration biopsy has a nearly 100% of specificity and 90%-100% of sensitivity [13]. Recently, Positron Emission Tomography/Computed Tomography shows a promising future in identifying the correct site for biopsy [14, 15], especially for the special location or extremely small lesions [7].

Histopathological examination of the liver specimen showing caseating granulomas with epithelioid cells, lymphocytes and Langhan giant cells is the gold standard for the diagnosis of hepatic tuberculosis. Based on that, positive acid-fast bacilli (AFB) detection, positive polymerase chain reaction (PCR) for Mycobacterium tuberculosis or positive T-SPOT TB test [7] can further confirm the diagnosis.

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Disclosure of conflict of interest

None.

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References

[1] Liao JR, Zhang D and Wu XL. Pulmonary tuberculosis combined with hepatic tuberculosis: a case report and literature review. Clin Respir J 2014; [Epub ahead of print].

[2] Hassani KI, Ousadden A, Ankouz A, Mazaz K and Taleb KA. Isolated liver tuberculosis abscess in a patient without immunodeficiency: A case report. World J Hepatol 2010; 2: 354-357.

[3] Vimalraj V, Jyotibasu D, Rajendran S, Ravichandran P, Jeswanth S, Balachandar TG, Kannan DG and Surendran R. Macronodular hepatic tuberculosis necessitating hepatic resection: a diagnostic conundrum. Can J Surg 2007; 50: E7-8.

[4] Chong VH and Lim KS. Hepatobiliary tuberculosis. Singapore Med J 2010; 51: 744-751.

[5] Yu RS, Zhang SZ, Wu JJ and Li RF. Imaging diagnosis of 12 patients with hepatic tuberculosis. World J Gastroenterol 2004; 10: 1639-1642.

[6] Hassan I, Brilakis ES, Thompson RL and Que FG. Surgical management of abdominal tuberculosis. J Gastrointest Surg 2002; 6: 862-867.

[7] Yu HY and Sheng JF. Liver Tuberculosis Presenting as an Uncommon Cause of Pyrexia of Unknown Origin: Positron Emission Tomography/Computed Tomography Identifies the Correct Site for Biopsy. Med Princ Pract 2014; 23: 577-9.

[8] Karunanithi S, Sharma P, Jain TK, Vijay MK and Kumar R. Multiple hepatic lesions in a case of isolated hepatic tuberculosis simulating metastases on 18F-FDG PET/CT imaging. Nucl Med Rev Cent East Eur 2014; 17: 108-109.

[9] Zhang XZ and Lu Y. CT-guided transcutaneous fine-needle aspiration biopsy. A report of 350 cases. Chin Med J (Engl) 1990; 103: 599-603.

[10] Limaiem F, Gargouri F, Bouraoui S, Lahmar A and Mzabi S. Coexistence of Hepatocellular Carcinoma and Hepatic Tuberculosis. Surg Infect (Larchmt) 2014; 15: 437-40.

[11] Reed DH, Nash AF and Valabhji P. Radiological diagnosis and management of a solitary tuberculous hepatic abscess. Br J Radiol 1990; 63: 902-904.

[12] Cao BS, Li XL, Li N and Wang ZY. The nodular form of hepatic tuberculosis: contrast-enhanced ultrasonographic findings with pathologic correlation. J Ultrasound Med 2010; 29: 881-888.

[13] Zhang XZ, Lu Y. CT-guided transcutaneous fine-needle aspiration biopsy. Chin Med J 1990; 103: 599-603.

[14] Shejul Y, Chhajed PN and Basu S. 18F-FDG PET and PET/CT in Diagnosis and Treatment Monitoring of Pyrexia of Unknown Origin Due to Tuberculosis with Prominent Hepatosplenic Involvement. J Nucl Med Technol 2014; 44: 1-3.

[15] Sellam Karunanithi PS, Jain TK, Vijay MK, Kumar R. Multiple hepatic lesions in a case of isolated hepatic tuberculosis simulating metastases on 18 F-FDG PET/CT imaging. Nuclear Medicine Review 2014; 17: 108-109.