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Original Article

Clinical Manifestation, Imaging Features and Treatment Follow-up of 29 Cases with Hepatic Tubercolosis

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Abstract. To understand the clinical and imaging manifestations and the treatment and follow-up of hepatic tuberculosis (HTB), we retrospectively analysed the clinical and imaging data of 29 patients with HTB who had been diagnosed clinically or by biopsy, and the clinical and imaging data had been summarised. Patient characteristics were followed up after anti-TB drug treatment. The median age of the 29 patients with HTB was 37 years, and most were male (58.6%). The patient's symptoms included fever (48.2%), respiratory symptoms (27.5%), abdominal pain (24.1%), and abdominal distension (10.3%). Elevated erythrocyte sedimentation rate (79.3%), elevated serum C-reactive protein (75.8%) and hypoalbuminemia (62.0%) were common features. Three patients were serologically positive for acquired human immunodeficiency syndrome, and two were serologically positive for hepatitis B surface antigen with normal tumour markers. The 29 patients with HTB included 17 with serous HTB, 9 with parenchymal HTB (8 with parenchymal nodular HTB and 1 with parenchymal miliary HTB), 1 with intrahepatic abscess type HTB, and 2 with hilar HTB. Approximately 86% of the patients also had pulmonary TB. Most of the serous HTB patients also had tuberculous peritonitis. Enhanced computerized tomography scans of the serous and parenchymal HTB cases showed the progressive development of lesions. Abnormal blood perfusion was observed in the hepatic artery, and the clearest evidence of TB was observed in the hepatic portal vein. Magnetic resonance imaging indicated that the lesions returned a high signal in the diffusion-weighted imaging sequence. However, the lesions' apparent diffusion coefficient values reflected high signals. The Xpert MTB/RIF test detected Mycobacterium TB complex in the liver biopsy fluid from 10 patients.

Regarding histopathology, one patient showed granulomatous inflammation, and one patient's acid-fast bacillus (AFB) stain was positive. The treatment of two patients was stopped due to their adverse reactions to the drugs and the risk of creating drug-resistant TB. The remaining patients received anti-TB treatment, but one subsequently died, and two were unavailable for follow-up. The clinical symptoms of HTB are difficult to detect, and it has diverse manifestations by imaging, with no obvious specificity in terms of pathological results. Therefore, follow-up of liver lesions for checking anti-TB therapy is another method for diagnosing HTB. In addition, early active anti-TB treatment can achieve good curative results.

Keywords: Hepatic tuberculosis, CT, Clinical features, X-PERT, Imaging diagnosis.

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Introduction. Hepatic tuberculosis (HTB) refers to TB resulting from a liver infection by Mycobacterium tuberculosis, a rare extrapulmonary TB that accounts for less than 1% of TB cases. Bristowe reported the first documented case of HTB in 1858. More than 20 years after Koch's discovery of Mycobacterium tuberculosis, lleston and McNee classified HTB into miliary (disseminated) and local (isolated) types in 1905, as reported by Chien et al. Miliary HTB is more common than local HTB in literature reports, where it represents 79% of HTB cases.

The main clinical manifestations of HTB are fever, cyanosis, jaundice, shortness of breath, cough, moist lung rale, hepatomegaly, splenomegaly, and abdominal distension. These indicators lack characteristic clinical symptoms and specific imaging manifestations, which can easily lead to a missed or misdiagnosis.⁵ A retrospective study by Longxin et al. found a misdiagnosis rate of up to 91% for HTB.⁶ Several clinical studies have found that HTB can easily be misdiagnosed as liver cancer, cholangiocarcinoma, or other malignant diseases.^{5,7-8}

The diagnosis of HTB is challenging, even in areas where TB is endemic, due to the non-specificity and diversity of its clinical symptoms. Statistically, HTB accounts for 1.5%-4.2% of digestive system diseases manifested by fever and approximately 2.7% of active TB autopsies. Garmpis et al. 10 found that HTB was characterized by central caseous necrotic granuloma with or without anti-acid bacteria, indicating that a liver biopsy of suspected cases of HTB may be useful for the timely diagnosis and treatment of the disease. A study conducted by Freitas et al. 11 also indicated the important role of a liver biopsy in correctly diagnosing HTB in patients with significant liver injury factors but atypical

clinical manifestations. Simultaneously Mycobacterium tuberculosis complex detection and testing for rifampicin resistance could be performed on this specimen using the Xpert MTB/RIF assay.¹²

The current paper explores the clinical and imaging manifestations, treatment, and follow-up of HTB to provide a practical basis for suspecting and then diagnosing HTB.

Data and Methods.

General data. Twenty-nine HTB patients, 17 males and 12 females, who each underwent a biopsy with effective diagnostic and anti-TB treatment in our hospital between April 2012 and May 2021, were selected for this study. The age of the patients ranged from 16 to 81 years, with a median age of 37 years. There was no significant difference in the patients' geographical distribution. Among the participants, 14 (48.2%) had a fever as the first clinical manifestation, 7 (24.1%) had abdominal pain, and 8 (27.5%) had cough and sputum symptoms. The total number of patients with TB at additional sites other than the lungs was 25 (86.2%). Among these, seven had TB peritonitis, three had splenic TB, six had lymph TB, three had spinal TB, and six had tuberculous pleuritis. In addition, three patients had acquired immunodeficiency syndrome, two had type 2 diabetes, two presented with fatty livers, and two had chronic viral hepatitis B. Additionally, 23 patients (79.3%) had elevated erythrocyte sedimentation rates (ESRs), 22 (75.8%) had elevated C-reactive protein (CRP) levels and 18 (62.0%) had hypoalbuminemia (see **Tables 1** and 2). The disease course ranged from 6 to 24 months.

Methods. The demographic data, clinical, laboratory, and imaging examinations, and the pathological and

Table 1	General	data and	clinical	symptoms (of the patients.

General data	Number		Clinical Symptoms	Numbe	r
Male	17 (number)	58.6	Fever	14	48.3
Female	12 (number)	41.4	Abdominal pain	7	24.1
Median age	37 (years old)	-	Abdominal distension	3	10.3
course of disease	6-24 (month)	-	Cough and expectoration	8	27.6
Regional differences	No	-	Chest tightness and chest pain	2	6.9

Table 2. Clinical and laboratory characteristics of 29 patients with HTB.

Clinical manifestation	Number	Percentage (%)	Laboratory result	Number	Percentage (%)
Fever	14	48.2	Erythrocyte sedimentation rate	23	79.3
Respiratory symptoms	8	27.5	Hypoalbuminemia	18	62.0
Abdominal pain	7	24.1	CRP	22	75.8
Abdominal distension	3	10.3	Aminopherase	4	13.7
Chest tightness and chest pain	2	6.8	T-spot	20	68.9

microbiological outcomes of 29 patients with HTB were analyzed. All patients were examined by computerized tomography (CT) of the liver; some also had a magnetic resonance imaging (MRI) scan for comparison. Plain and three-phase dynamic contrast enhancement scans were performed using a LightSpeed or a Bright Speed Pro-16layer scanner (GE Healthcare, USA). The CT scanning requirements were set as follows: 120 kV, 200-250 mA, and a pitch of 1.375. Some patients underwent concurrent CT and MRI examinations. The MRI was performed using a **Philips** Achieva superconducting-type MR instrument and an abdominal surface coil for routine MRI examinations. In addition, multiphase dynamic enhancement scanning performed using the THRIVE circum phase gradient echo sequence.

Statistical methods. Descriptive statistics (mean, standard deviation, percentage, frequency count) were calculated using the SPSS Statistics 17.0 software program. Categorical data were examined using the chisquare test, and continuous data were analysed using the analysis of variance.

Results.

General data and clinical results. Between April 2012 and May 2021, 29 patients in our hospital were diagnosed with HTB. The median age in this cohort was 37 years (range = 16-81 years), and most patients were male (58.6%). Among the 29 patients, three had a history of close contact with pulmonary TB patients, six (20.6%) had previously developed pulmonary TB, three were seropositive for HIV, and two were positive for hepatitis B surface antigen. Fever (48.2%), respiratory symptoms (27.5%), abdominal pain (24.1%) and abdominal distension (10.3%) were common clinical features. Common laboratory abnormalities included elevated ESR (79.3%), elevated blood CRP (75.8%) and hypoalbuminemia (62.0%). Furthermore, 20 patients had positive r-interferon tests (68.9%). All patients had normal tumour markers (alpha foetoprotein [AFP] and carcinoembryonic antigen). Initially, all patients received anti-TB therapy, but two patients discontinued this due to their inability to tolerate the side effects. Subsequently, one patient died of other causes, and two were unavailable for follow-up (see **Table 2**).

The manifestations of hepatic tuberculosis seen by imaging. The CT scans of the 29 patients showed primarily low-density foci, including the 17 patients with serohepatic HTB showing mostly single but sometimes multiple nodular lesions or hypertrophy on the liver envelope. Abnormal perfusion can occur in the liver tissue adjacent to a lesion, which may be associated with altered local vascular compression. The lesions observed during the enhanced scanning of the delayed arterial

phase showed progressive intensification. The perihepatic parenchyma was compressed. The nine patients with parenchymal HTB included eight with parenchymal nodular HTB and one with parenchymal miliary HTB (Figure 1). The images of these two types of HTB are the same, except that the miliary lesions are approximately 0.5-1 cm and the nodular lesions are about 2-3 cm. 14-15 In plain CT scan images, the lesions showed low or equal density shadows, blurred margins, and lowdensity changes due to liquefaction or caseous necrosis at the centre of the lesion. Abnormal peripheral blood perfusion or irregular enhancement of blood pressure was observed during the enhanced scanning arterial stage, and clearer lesions were indicated during the portal phase. Two patients with enlarged lymph nodes in the hilar area (Figure 2) had no lesions in the liver parenchyma or subcapsular region. The patients in this group included one with parenchymal abscess type TB for whom the lesion was distributed through the right lobe of the liver. There was no enhancement in the central liquefied necrosis area of the lesion, and a mild annular enhancement was observed around the lesion during the

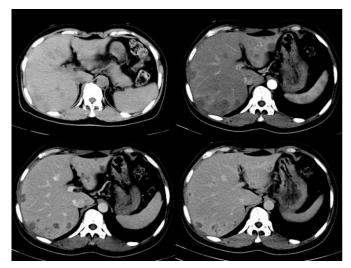


Figure 1. Diffusing parenchymal hepatic tuberculosis.

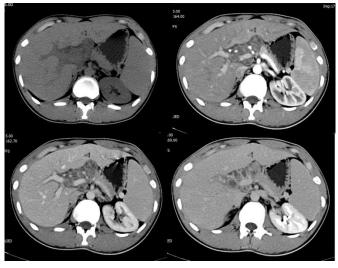


Figure 2. Lymph node tuberculosis in the hepatic portal area.

delayed phase of the CT scan. The lesion showed a low signal in the T1 weighted image (T1WI) and a high signal in that T2 weighted (T2WI). Restricted focal diffusion on the diffusion-weighted (DW) sequence produced a high alert, but the apparent diffusion coefficient (ADC) value was also increased, suggesting a benign condition.

Pathological diagnosis of hepatic tuberculosis. Of the 29 patients included in the study, 10 underwent an ultrasound-guided liver biopsy for suspected HTB. The tissue (liquid) samples were submitted for the Xpert MBT/RIF assay. Seven patients tested positive. One had rifampicin-resistant TB, and one had TB that was resistant to isoniazid and streptomycin. Two patients each underwent a liver biopsy for pathology. One of these was found to have granulomatous lesions; the other had no specific lesions. One patient tested positive for AFB staining. Finally, ten patients underwent biopsies (liquid) for Mycobacterium TB culture. Two patients tested positive, and the remaining patients tested negative.

Treatment and follow-up. Among the participants, 27 patients underwent 4-5 anti-TB drug treatments (ATT) for 6-9 months. Two became resistant to anti-TB drugs after 18 months of treatment. Six patients with a previous history of TB and three with HIV received ATT for 12 months. One died of organ failure before follow-up (not associated with TB). Two patients were removed from the controls. Two patients refused further ATT due to drug intolerance. At the end of the treatment phase, a low-dose CT scan was performed on 25 patients, and the results indicated absorption of lesions in all patients and improvement in their symptoms. No significant adverse events related to treatment were observed in these 25 patients.

Discussion. Immunosuppressed patients are more susceptible to Mycobacterium tuberculosis infection, and in recent years, TB, particularly in the hepatic manifestation, has become more common in HIV-infected patients, ¹⁶⁻¹⁷ indicating a close link between cellular immunity and HTB. There were three cases of HIV infection among the participants in the current study. The HTB patients were mostly aged 30-50 with a median age of 37, and there were more men than women. ¹⁸⁻²⁰ According to the literature, HTB patients with TB and TB contact history are uncommon. ²⁰⁻²¹ In our study, five patients had a TB history, and three had close contact with TB patients.

Many cases of HTB start slowly. In most cases, HTB patients have TB at additional sites, but the primary tuberculosis focus has been absorbed or overcome by fibrosis and calcification when HTB is found. Most reports suggest that fever, abdominal pain, weight loss,

and a loss of appetite are common symptoms of HTB, ²³-²⁴ and a few patients present with jaundice. ²⁵⁻²⁶ In our data, fever was the most common clinical symptom (48.2%), followed by respiratory symptoms (27.5%) and abdominal pain (24.1%). A higher number of respiratory symptoms than digestive tract symptoms reported at the initial hospital visit may be related to the department the patient attended, which is considered a referral bias. However, lung localization, present in 86% of HTB may cause respiratory patients, symptoms. Hepatosplenomegaly was the most common symptom of HTB.²⁷ Unfortunately, hepatomegaly was not recorded in our data, and three patients were thought to have splenic TB (one of whom had this confirmed by a routine PET-CT examination). In our study, more than half of the patients had elevated ESR and CRP and reduced albumin. Tumour markers were within the normal range. Tuberculin tests showed nine patients were strongly positive, six were moderately positive, and five were negative. The r-interferon release test showed 20 patients were positive and 9 negative (including 3 HIV patients). Therefore, a negative tuberculin test result may not rule out TB in clinical practice. In contrast, a positive rinterferon test should be considered an alert for the possible presence of a TB infection, either internal or external to the lungs.

All study patients showed low-density liver lesions on abdominal CT scans. Several cases of mild enhancement of the lesions' peripheral edges after contrast injection have been reported in the literature.²⁸⁻²⁹ The study's CT and MRI results revealed that low-density shadows of elliptical nodules were observed on CT scans in cases of serous HTB. A progressive enhancement was observed between the artery and delayed periods in enhanced scanning. The focal margin was blunt at the liver parenchyma margin. The clinical findings for TB peritonitis and ovarian cancer can overlap, leading to potential misdiagnoses.³⁰

The parenchymal HTB lesion was often surrounded by abnormal triangular high-density shadows due to abnormal blood perfusion caused by an inflammatory response. All TB nodules in the liver were clearer during the portal phase, and enhancement was still visible around the lesion. Their MRI often showed low T1WI and high T2WI and DW signals. However, the ADC map showed a high signal. The enhanced scanning lesion had no enhancement in the centre and a mild circular enhancement around it. Intrahepatic bile duct TB is rare among HTB patients and was not found in our study. Atypical HTB is characterized by irregular bile duct wall enhanced thickening and expansion, scanning enhancement and delayed enhancement, and diffuse punctate calcification of the bile duct wall.³¹ In some cases, the imaging sign appeared in liver abscesses, tumours, and other lesions. In contrast, non-specific inflammation is not evident in tumour lesions and could

be considered an indirect sign of HTB progression.³² The enhanced scan portal stage showed increased clarity around the lesions, and the delayed period showed mild enhancement around the lesions, which are common manifestations of the disease detected by MRI.

Study limitations. The present study was limited by the lack of Xpert MTB/RIF assay results, cultures, and pathological specimens for some patients from the clinical work used in this research. This omission may have led to some patients with HTB remaining undiagnosed. Symptoms of the digestive tract are frequently misdiagnosed as tumours or liver abscesses. Since most patients refused a second biopsy procedure, imaging served as the primary means of follow-up. Our experiments also have statistical issues caused by small sample sizes due to the rarity of HTB.

Conclusions. In conclusion, HTB is a rare disease with hidden clinical symptoms and diverse imaging manifestations. Patients with pulmonary TB and an existing history of TB or HIV infection should be made aware of the possibility of HTB. Histopathology (diagnostic examination) showed granuloma necrosis with giant cells. In all suspected cases diagnosed by liver biopsy, Xpert MTB/RIF assay, and mycobacterium culture. AFP is normal, so this test should be carried out whenever possible to distinguish primary malignant liver tumours from HTB.

Ethics approval and consent to participate. This study was conducted according to the Declaration of Helsinki and approved by Wenzhou Central Hospital. All participants signed an informed consent form for inclusion in the study.

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