

## Original Research Article

# Primary hepatic tuberculosis mimicking malignancy

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**Received:** 13 May 2019

**Revised:** 05 July 2019

**Accepted:** 08 July 2019

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### ABSTRACT

**Background:** One of the most serious health issues in developing regions is tuberculosis (TB), which has high prevalence worldwide. We aimed to investigate 6 cases of primary hepatic tuberculosis that mimics malignancy and to emphasize that differential diagnosis should be considered in Turkey, which is still an endemic region for tuberculosis.

**Methods:** Data of 14 patients who were diagnosed with primary hepatic tuberculosis between January 2008 and January 2018 were retrospectively evaluated.

**Results:** There were 11 females and 3 males among the cases with an average age of 51.3 years old. The most frequent presentations were the upper right quadrant pain and weight loss. Although laboratory values of 12 patients were normal, isolated gamma-glutamyl transferase (GGT) height was found in 2 patients. Granulomatous inflammation was diagnosed with applying percutaneous needle biopsy in 12 patients and laparoscopic liver biopsy in 2 patients. Tissue culture was positive in 2 patients. No recurrence was detected in any of the patients after medical treatment.

**Conclusions:** When abdominal pain, fever, weight loss complaints, and malignancy-like masses in liver are detected during the differential diagnosis of patients who live in endemic areas such as Turkey; hepatic tuberculosis should be considered as a diagnosis.

**Keywords:** Hepatic tuberculosis, Malignancy, Granulomatous inflammation

### INTRODUCTION

One of the most serious health issues in developing regions is tuberculosis (TB), which has high prevalence worldwide. Up to 50%–80% of cases with disseminated TB have hepatic involvement. In case the absence of miliary TB, hepatic TB is seen rarely, which is less than 1% of TB cases.<sup>1</sup> Clinical manifestations are usually very few in hepatic TB. Therefore primary hepatic TB is usually misdiagnosed with distinguishing hardly from other malignancies such as intrahepatic cholangiocarcinoma (iCCA), hepatocellular carcinoma, metastasis, klatskin tumor and liver abscess using

imaging modalities.<sup>2</sup> There is a positive correlation between the increasing incidence of hepatic HB and prevalence of HIV/AIDS.<sup>3</sup> Transmission occurs either hematogenous from lungs or local from intestine.<sup>4</sup> The involvement can be in types of disseminated, focal, or cholangitic.<sup>4,5</sup> Hepatic TB has non-specific clinical presentation.<sup>6</sup> Its clinical findings are mostly upper abdominal pain, high-grade fever, hepatomegaly and weight loss. Jaundice is uncommon; it has been reported in 35% of the cases and is usually obstructive in nature, simulating other conditions causing extrahepatic biliary obstruction and makes the diagnosis more challenging. TB is diagnosed when there caseating epitheloid

granuloma or acid-fast bacilli (AFB) is found in the aspirated pus or biopsy.<sup>7</sup>

In this study, we aimed to investigate 14 cases of primary hepatic TB that mimics malignancy and to emphasize that differential diagnosis should be considered in Turkey, which is still an endemic region for TB.

## METHODS

In this study, data of 14 patients who were diagnosed with primary hepatic TB in the General Surgery Department of Afyonkarahisar Health Sciences University between January 2008 and January 2018 were retrospectively evaluated. They had antituberculosis treatment. Hepatic TB cases, which were detected with other organ involvement, were excluded from the study. Patients were evaluated in terms of age, gender, history of TB, complaints, physical examination findings, laboratory tests, radiological findings, pathology results, culture results, treatment algorithms and follow-up periods. Patients applied with complaints were examined with USG, CT and MRI. Gastroscopy, colonoscopy and PET-CT were performed for the diagnosis of malignancy. The diagnosis was given with laparoscopic biopsy in patients who could not diagnose with percutaneous needle biopsy and needle biopsy. After a routine follow-up of the formol fixation, hematoxylin eosin was stained and examined. In the sections, granuloma structures were seen which were separated by sharp margins in the surrounding liver tissue, with a large caseous necrosis in the middle, and in the tendency to merge with each other (Figure 1A). These granuloma structures included epithelioid histiocyte and rare Langhans type giant cells (Figure 1B).

### Differential diagnosis

Infectious conditions such as leprosy, sarcoidosis, Hodgkin's disease, brucellosis, inflammatory bowel disease and liver tumours were the differential diagnosis of hepatic TB.

### Treatment

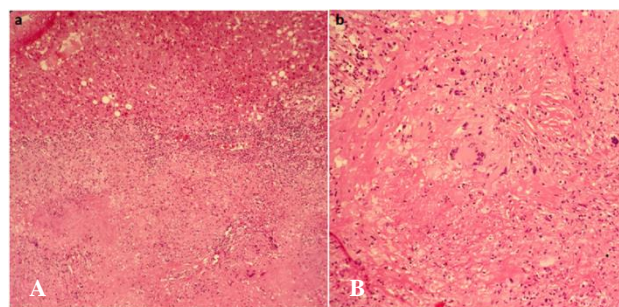
Antitubercular drug therapy was used for the treatment of patients during 2 months with an intensive phase of four drugs: isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). Afterwards a continuation phase of three drugs (HRE) was applied during 4 months.

### Outcome and follow-up

Clinical improvements were observed within the 4 weeks of starting drug therapy. All symptoms seen at the time of onset started resolving. Patients gained some weight. After the 2 months of intensive phase drug therapy, repeat ultrasounds of the liver were performed. Complete resolutions of the lesions from both lobes of the liver were observed in the ultrasound images.

## RESULTS

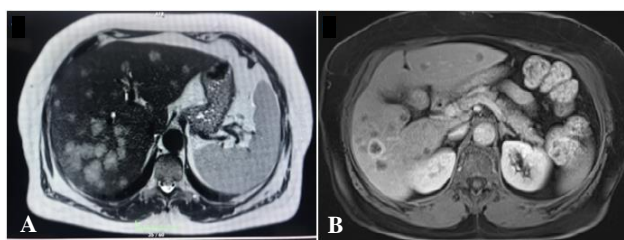
There were 11 females and 3 males among the cases with an average age of 51.3 years old. None of the patients had a history of TB. The most frequent presentations were the upper right quadrant pain and weight loss. Physical examination of all patients was normal. Although laboratory values of 12 patients were normal, isolated gamma-glutamyl transferase (GGT) height was found in 2 patients. Chest X-ray was normal in all patients. When Ultrasonography (USG) findings were evaluated, hypoechoic mass was detected in all patients. Contrast-enhanced CT revealed suspicious hypoechoic mass lesions (Figure 2). MRI of the upper abdomen showed hypointense in T1-weighted sections, mild heterogeneous hyperintense in T2-weighted sequence, and cystic necrotic lesions in the centre of the contralateral series (Figure 3A and B). In PET-CT lesions, hypermetabolically increased fluorodeoxyglucose (FDG) involvement was detected (Figure 4). Granulomatous inflammation was diagnosed with applying percutaneous needle biopsy in 12 patients and laparoscopic liver biopsy in 2 patients. Tissue culture was positive in 2 patients. No recurrence was detected in any of the patients after medical treatment. Average follow-up period was 32.1 months (Table 1).



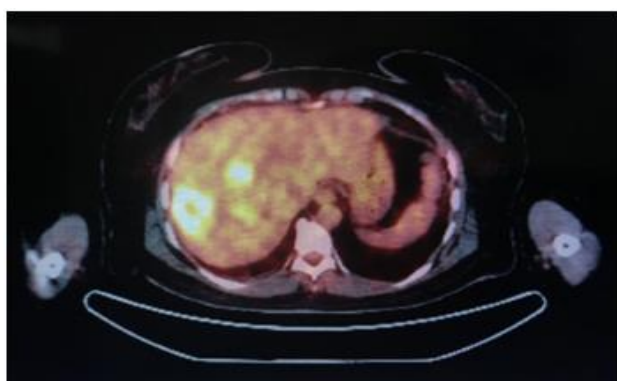
**Figure 1: (A) Granulomatous structures with a sharp transition to liver tissue and containing large necrosis (X40HE); (B) multi-nucleus giant cells forming granuloma structures, epithelioid histiocytes (x100 HE).**



**Figure 2: Suspicious hypodense lesions with 4.5x4 cm diameter metastasis in the 7<sup>th</sup> segment of the liver right lobe shown using contrast CT.**



**Figure 3: (A) Multiple lesions following slight heterogeneous hyperintensities in T2A images by applying MRI imaging of upper abdomen; (B) multiple lesions showing mild peripheral contrast involvement in some of T1 dynamic contrast series in upper abdomen MR imaging.**



**Figure 4: Lesions showing multiple FDG involvement in PET-CT (SUVmax: 12.4).**

**Table 1: Results of patients.**

<b>Age (average)</b>	51.3
<b>Gender (F/M)</b>	11/3
<b>Complaint (n)</b>	
Upper right quadrant pain	12
Nausea	4
Dyspepsia	3
Weight loss	11
<b>PET-CT (average SUVmax)</b>	12.2
<b>Mass diameter (n)</b>	
>3 cm	6
<3 cm	8
<b>Location (n)</b>	
Right lobe	2
Bilobar	12
<b>Mantoux test(n)</b>	
Negative	14
Positive	-
<b>Percutaneous needle biopsy (n)</b>	
Negative	2
Positive	12
<b>Laparoscopic biopsy (n)</b>	2
<b>Tissue culture (n)</b>	
Negative	12
Positive	2
<b>Follow-up period (months)</b>	32.1

## DISCUSSION

TB is a global disease that one third of the world's population is exposed to, and 2 billion people are latentemic, seen 8 million new cases per year.<sup>8</sup> Abdominal TB is a seldom manifestation considering various extrapulmonary TBs. Haematogenous or lymphatic spread from current active TB; direct extension from adjacent involved tissues; reactivation of a dormant focus in the abdomen following haematogenous spread during an earlier primary infection; or ingestion of the pathogen might cause TB.<sup>9</sup> Hepatic TB has been detected rarely within abdominal TB patients. TB is always seen in liver as secondary to other locations. Primary hepatic TB is used in the sense that a TB lesion in the liver may result from tubercle bacilli gaining access to the portal vein from a microscopic or small TB focus in the bowel, with subsequent healing taking place at the site of entry and leaving no trace of it.<sup>10</sup>

Nomenclature and clinical classification of hepatic TB are ambiguous in the literature. According to Levine, TB is classified as miliary TB; pulmonary TB with hepatic involvement; primary liver TB; focal tuberculoma or abscess; and TB cholangitis. Military TB is the most commonly seen type. Mycobacteria growth is affected negatively with low oxygen tension in liver so 1% of hepatic TB cases are primary hepatic TB. However almost 70% of disseminated cases of TB show hepatic involvement.<sup>11</sup> All cases in our study were primary hepatic TB and no other focus was detected in the tests.

The diagnosis of extrapulmonary TB is difficult. These types are usually in hardly reachable areas so it is difficult to get a tissue sample. The diagnosis is usually made in conjunction with clinical and radiological imaging. Abdominal pain, fever and weight loss are the most common clinical findings. Alkaline phosphatase in bilirubin values and minimal elevation in GGT values may be detected in laboratory findings.<sup>12</sup> All patients in our study had upper right quadrant pain and weight loss complaints. Laboratory values of 12 patients were normal. Isolated GGT height was found in 2 patients.

Most of the lesions are small in hepatic TB. Giant nodular lesions, which have larger diameter than 3cm, are seen rarely. By Bristowe described macronodular tuberculoma first time in 1858.<sup>13</sup> Debray et al also used the term "pseudotumour".<sup>13,14</sup> Beside single solitary lesions, the literature has reported multiple nodules or abscesses. Diagnosis in such polymorphous appearances that mimic primary or metastatic malignancy is difficult especially before pathological examination. Hypoechoic lesions are seen in ultrasonography findings of hepatic TB. CT scans of hepatic TB reveals non-enhancing, central, and low-density lesion, which has caseation necrosis with slightly enhancing peripheral rim corresponding to surrounding granulation tissue. Hypointense nodule with a rim on T1-weighted images was observed in MRI of hepatic TB. However,



hypointense, isointense or hyperintense nodule with a less intense rim was seen with T2-weighted imaging. Image features of hepatic TB may belong to multiple lesions of varying density. This indicates that there are lesions in different pathologic stages coexisting in hepatic TB, including TB granuloma, liquefaction necrosis, fibrosis or calcification. Therefore differential diagnosis of primary hepatic TB and malignancies is very ambiguous with using imaging modalities. Such as other malignant tumours, hepatic TB shows FDG-avidity on F-18 FDG PET/CT. FDG-avidity is also seen in necrotic tumours like hepatocellular carcinoma, iCCA, and metastatic carcinoma so F-18 FDG PET/CT is not useful in differentiating hepatic TB from other hepatic necrotic masses.<sup>15-17</sup> Radiological imaging findings of all patients in our study has been mimicking malignancy. In PET-CT imaging of all patients, pathological FDG involvements were observed. The lesion diameter was measured larger than 3 cm in 6 cases. The lesions were bilobar in 12 cases and unilobar in 2 cases.

Pathologic examinations of liver lesions are important for the diagnoses of hepatic TB because images, laboratory findings, and clinical manifestations are ambiguous. Therefore we can mention the percutaneous fine needle biopsy as a right diagnostic method. It is used as a diagnostic tool in the study of mycobacteria culture in biopsy material. However, its reproductive rate is low with a rate between 10% and 60%.

PCR has been reported as a useful tool for the diagnosis of hepatic TB. With using PCR tool, the identification rate of hepatic granulomas, which is caused by TB, was at least 57% in the study.<sup>18</sup> In our study, only two patients had a culture of reproduction. Twelve patients were diagnosed as granulomatous inflammation with percutaneous needle biopsy. However two patients were diagnosed with laparoscopic biopsy because we could not give their diagnosis with percutaneous needle biopsy. Since PCR analysis has not been performed in our clinic, it could not be used for the diagnosis.

When the cases in our study are examined, patients with primary hepatic TB have complaints such as abdominal pain and weight loss rather than specific complaints, which may be seen in malignancy cases. In addition, similar findings with malignancy were found in the images. Percutaneous biopsy has always been performed. When the first biopsies did not give any results, repeated percutaneous biopsies and even laparoscopic biopsies were taken. Otherwise, unnecessary liver resections can be performed for these patients. In our case series, two patients were diagnosed with tissue culture, but in other cases, diagnosis was given as granulomatous inflammation in the pathological examinations. Other granulomatous diseases were excluded in the differential diagnosis. All patients have been monitored after anti tuberculosis treatment and they are healthy. The lack of PCR analysis during diagnosis is the limitation of our study.

As a result, when abdominal pain, fever, weight loss complaints, and malignancy-like masses in liver are detected during the differential diagnosis of patients who live in endemic areas such as Turkey; hepatic TB should be considered as a diagnosis.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Akıcı M, Bozkurt E, Özdemir C, Kaya F. Primary hepatic tuberculosis mimicking malignancy. *Int Surg J* 2019;6:3078-82.