Imaging aspects and differential diagnosis of hepatic tuberculosis lesions in immunosuppressed patients

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Learning objectives

The aims of our presentation are:

- to review the imaging features of hepatic manifestations in tuberculosis disease (TB);
- to establish the current role of imaging in the detection and characterization of these lesions;
- to describe and illustrate the most important differential diagnosis.

Background

INTRODUCTION

Tuberculosis (TB) is a common disease transmitted by inhaling airborne bacilli from a person with active TB. [7] The bacilli multiply in the alveolus and are carried by macrophages, lymphatics and blood to distant sites (lung pleura, brain, kidney, bone) [7,8].

Causes: Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium africanum.

Organ involvement. Although the respiratory system is most frequent involved, TB may involve any organ or system:

- heart
- central nervous system (CNS)
- head and neck
- musculoskeletal system
- genitourinary system
- adrenal
- lymphadenopathy

INCIDENCE/PREVALENCE

The prevalence of tuberculosis has continued to decline in the US over the past few years (5,1/100 000), but there has been an increase in global prevalence, particularly in immunocompromised patients, with a rate of increase of approximately 1.1% per year [1,7].

Age:

- primary infection - any age, especially pediatric;
- recrudescent disease - adult and elderly [6,7].

Predominant sex: male > female.
SIGNS AND SYMPTOMS

- cough;
- hemoptysis;
- fever and night sweats;
- weight loss;
- malaise;
- adenopathy;
- pleuritic chest pain;
- hepatosplenomegaly;
- renal, bone or CNS diseases are late findings [7].

RISK FACTORS

- for infection: urban, homeless, minority, migrant workers, institutional (prison, nursing home), close contact with infected individual;
- for disease: HIV, recent infection, IV drug abuse, lymphoma, chronic renal failure, malnutrition, steroids, immunosuppressive drugs, gastrectomy and cancer [7].

A prompt diagnosis of TB is imperative for community public health.

ABDOMINAL TUBERCULOSIS

- **Gastrointestinal (GI) tuberculosis**: ileocecal involvement (80-90% of cases) - thickening of the valve lips or wide gaping of the valve with narrowing of the terminal ileum; fistulas are rare;
- **Tuberculous peritonitis**: is usually associated with other forms of gastrointestinal tuberculosis [7]. Type Peritonitis: wet, dry, fibrotic [1].
- **Hepatosplenic tuberculosis**: is exceptional and it usually occurs on an immune suppressed background.

- The main clinical manifestations are fever, shiver, weight loss, hepatosplenomegaly and anorexia.

- Tuberculosis is known to involve the liver in different ways. Generally, tuberculosis of the liver is classified as either a military form, which is part of generalized military tuberculosis, or a local form, which is further subdivided into focal or nodular tuberculosis (tuberculous hepatic abscess and tuberculoma) and tubular or hepatobiliary tuberculosis (tuberculosis involving the intrahepatic ducts) [3]. The liver parenchyma can be either homogenous or heterogeneous [5].

- **Lymphadenopathy.** Abdominal lymphadenopathy is the most common manifestation of abdominal tuberculosis, being seen in 55%-66% of patients [1].
Imaging findings of liver tuberculosis

- **Miliary tuberculosis of the liver** is most frequent and is usually not detected at imaging, hepatomegaly being the only imaging anomaly. In the healing stage of TB, computed tomography may show diffuse hepatic calcifications (50% of cases) [3].
- In the **macronodular form**, CT findings are nonspecific and include the presence of hypoenhancing lesions both before and after intravenous administration of contrast material. Hepatic tuberculomas eventually tend to calcify. At magnetic resonance (MR), the lesions are hypointense on T1-weighted images and hypointense to isointense on T2-weighted images [3].

Findings and procedure details

**TECHNIQUES**

**Ultrasonography** (US): convex probe (3.5 MHz) for the evaluation of deeper structures.

**Computed tomography** (CT) protocol: we used a 16, 64-slice CT system, performing acquisitions before and after intravenous administration of iodinated contrast material (1.5 ml/kgc, injected with a rate of 3 ml/sec via power injector), with a thickness of 5 mm per slice and reconstructed images of 1.5 mm per slice. The scan was triggered via bolus tracking. Postcontrast CT acquisition:

- arterial phase - performed 35-40 sec or 15-20 sec after bolustracking;
- portal phase - performed 70-80 sec or 50-60 sec after bolustracking;
- equilibrium/delayed phase - performed at about 3-5 minutes after contrast injection.

CT was also used when the liver biopsy was performed.

**Magnetic resonance imaging** (MRI) protocol: was performed using a 1.5T magnet with Torsopa coil and three-plane localizer, using multiplanar T1 and T2-weighted sequences with respiratory gating, with or without fat suppression (FS) and 3DT1-weighted sequences before and after intravenous administration of gadolinium (0.1 ml/kg Gd-BOPTA).

**IMAGING FINDINGS**

In liver tuberculosis contrast enhanced CT shows multiple hypodense, hypovascular lesions, randomly spread throughout the entire parenchyma. Because of the rather nonspecific features with all imaging modalities in hepatic tuberculosis, percutaneous biopsy is needed in almost all patients with suspected liver TB, along with appropriate clinical information (Fig. 1 on page 7, Fig. 2 on page 8).

Diagnosis can be established by showing caseating granuloma, a positive acid-fast bacillus or culture for Mycobacterium species, or a positive polymerase chain reaction [3].
Associated findings like adenopathy, ascites and peritoneal disease suggest disseminated TB [5].

**DIFFERENTIAL DIAGNOSIS**

Because of the wide-ranging imaging aspects of hepatic involvement in tuberculosis, an accurate differential diagnosis is imposed in all immune suppressed patients.

1. **Malignant lesions**

- **Leukemia.** A heterogeneous group of malignant neoplasms developing from hematopoietic (blood-forming) cells. The proliferating cells accumulate in bone marrow primarily. Infiltration of leukemic cells into other organ systems may produce the varied clinical manifestations of advanced leukemia [9].

  **US:**
  - hypoechoic nodular hepatic lesions;
  - hepatosplenomegaly; lymphadenopathy *(Fig. 3 on page 8).*

  **CT:**
  - focal, nodular, hypovascular lesions in the liver +/- spleen;
  - hepatosplenomegaly; lymphadenopathy *(Fig. 4 on page 9, Fig. 3 on page 8).*

- **Lymphoma.** Primary hepatic lymphoma is very rare and hepatic lymphoma is usually seen in association with systemic disease, both Hodgkin's disease and non-Hodgkin (NHL) [5].

  **CT:**
  - focal, poorly visualized, low attenuation masses on unenhanced scans, hypoattenuating after intravenous administration of iodine material;
  - frequently associated with splenic involvement (Hodgkin's disease);
  - hepatosplenomegaly;
  - concomitant lymphadenopathies help suggest the diagnosis. *(Fig. 5 on page 10)*

- **Recurrence of hepatocellular carcinoma.** Immunosuppression can lead to opportunistic bacterial infections and increased incidence of malignant disorders. Recurrence of hepatocellular carcinoma (HCC) after liver transplantation can have similar imaging features as hepatic tuberculosis:
  - **CT:** hypodense, hypovascular, multiple nodular lesions, opposed to the typical aspect of HCC;
• MRI: numerous small hepatic nodules, hypointense in T1, hyperintense in T2, hypovascular, with intense restricted diffusion;
• Final diagnosis: liver biopsy - histopathological report; poor prognosis. (Fig. 6 on page 11)

- Metastatic disease. Hepatic metastatic disease is the most common malignancy of the noncirrhotic liver, surpassed in incidence of focal lesions only by hemangioma, focal fatty change and simple cysts. The most common primary neoplasms to cause hepatic metastases are colon, stomach, pancreas, breast and lung [4].

CT appearance:
• depends on tumor size, vascularity, hemorrhage, necrosis, as well as the timing of scanning;
• hepatomegaly;
• iso-/hypodense nodules on unenhanced CT, hypoattenuating with early peripheral enhancement;
• the site of the primary tumor (Fig. 7 on page 12).

2. Infections

- Fungal disease. Hepatosplenic fungal infection is a clinical manifestation of disseminated fungal disease in patients with hematologic malignancies or compromised immunologic system. Most hepatic fungal involvement occurs in leukemia patients and are caused by Candida albicans; other fungus-relates diseases include Cryptococcus infection, histoplasmosis, mucormycosis and Aspergillus [3].

CT patterns:
• microabscesses (Fig. 8 on page 13): multiple round, discrete areas of low attenuation ranging from 2-20 mm;
• bull's eye configuration: well-defined hyperdense lesions surrounded by hypodense rim on the native phase, with early central enhancement and tendency to homogenize in the delayed phase. (Fig. 9 on page 14).

- Bacterial abscesses. Pyogenic abscesses, particularly when multiple may be caused by hematogenous dissemination, ascending cholangitis or superinfection of necrotic tissue. Early diagnosis and imaging-guided percutaneous drainage have markedly reduced both the mortality rates and the need for surgery [3]. In adults, Escherichia Coli is most commonly isolated, while Staphylococcus is most often isolated from pediatric liver abscesses [4].

CT aspects:
• low attenuation rounded masses on both noncontrast and contrast-enhanced scans; (Fig. 10 on page 15, Fig. 11 on page 16)
• possible enhancing peripheral rim or capsule.

3. Rare differential diagnosis

Other more unusual differential diagnosis for hepatic tuberculosis in immunosuppressed patients are:
- **Sarcoidosis.** Most commonly the disease produces hepatosplenomegaly. Nodules, ranging from 2-20 mm in size can be identified in 5-30% of patients. Nodules are hypodense at noncontrast CT and show no substantial enhancement. Lymphadenopathy is often present in the porta hepatic or around the celiac axis [5].
- **Parasitic diseases** *(schistosomiasis, toxoplasmosis)*. Liver involvement shows a characteristic pattern of capsular and parenchymal calcification perpendicular to the liver capsule. The liver surface can be nodular and fibrosis may show increased periportal fat. There is an increased risk for HCC [5].
- **Viral involvement of the liver** *(infectious mononucleosis, cytomegalovirus)*
- **Others** *(syphilis)*

**Images for this section:**

![Imagery showing various liver conditions related to differential diagnosis.](attachment:image-url)
**Fig. 1:** 31-year-old man with aplastic anemia. Hypoattenuating, ill-defined, nodular hepatic lesions and cystic splenic lesions both before and after intravenous administration of iodinated material. Histopathological report: hepatosplenic tuberculosis.

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**Fig. 2:** Hepatosplenic tuberculosis. a. CT-guided liver biopsy; b-c. Atypical appearance for tuberculosis because of the immune suppressed background (suppurative necrosis); Ziehl-Neelson stain.

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Fig. 3: Chronic myeloid leukemia; 32-year-old woman. a-b. Abdominal ultrasonography (US); c-d. Contrast-enhanced computed tomography: multiple hepatic hypovascular lesions; voluminous inhomogeneous expansive process developed in the spleen with consecutive splenomegaly.

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**Fig. 4:** Acute myeloid leukemia; 60-year-old man. Hepatosplenic lesions with different morphology: some cystic-like, others hypoattenuating; peripheral, wedge-shaped hypo-enhancing splenic regions, typical for infarction; bilateral pleural effusion; right lower lobe consolidation.

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**Fig. 5:** Burkitt lymphoma; 29-year-old woman. Contrast-enhanced CT scan, venous phase. a-b. Axial acquisitions: multiple focal hypovascular hepatic lesions spread throughout both lobes; c. Coronal reconstruction: extensive retroperitoneal adenopathies.

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Fig. 6: 58-year-old man with liver transplantation for hepatocellular carcinoma 4 months prior the imaging investigation. a. CECT arterial phase; b-c. Diffusion weighted imaging (DWI) + apparent diffusion coefficient (ADC); d. Axial T2-weighted MR image with fat-suppression; e. Axial T1 after intravenous administration of Gd - hepatobiliary phase: numerous small hepatic nodules, hypointense in T1, hyperintense in T2, hypovascular, with intense restricted diffusion; f. CT guided liver biopsy: histopathological report - microglandular adenocarcinoma.

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Fig. 7: Rectal cancer; 72-year-old man. a-b: Soft-tissue density mass that narrows the bowel lumen, invading mesorectal fat; c-f: multiple hypovascular nodular lesions spread throughout both liver lobes, evocatory for hepatic metastases.

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Fig. 8: Fungal disease; 50-year-old woman known with acute myeloid leukemia. CECT scan shows innumerate small non-enhancing liver nodules, typical for fungal microabscesses.

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Fig. 9: Fungal disease (nodular type); 38-year-old male known with acute myeloid leukemia. a-d: CECT scan native and after intravenous administration of iodine contrast (arterial-venous-equilibrium phases): bull's eye configuration: well-defined hyperattenuating lesions surrounded by hypoattenuating rim that tend to homogenize in the delayed phase; e-f: tomography aspect after 4 months of antifungal treatment: complete remission.

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Fig. 10: Acute myelomonocytic leukemia; 25-year-old man. a-b. Well-formed cavity of the superior left lobe, with a central soft-tissue mass surrounded by a crescent of air - typical CT aspect of asperigilloma; c-d. Multiple small non-enhancing nodules that involve hepatic parenchyma. Given the nature of the pulmonary cavity, the first diagnosis of the liver lesions was fungal disease. Ultrasonography guided liver biopsy was performed giving the final diagnosis of bacterial infection (Escherichia Coli).

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**Fig. 11:** Acute liver failure; 31-year-old man. a-c: Nodular non-enhancing hepatic lesions, ascites; d-e: An external biliary drainage catheter was used. Bacteriological investigation: Klebsiella pneumoniae.

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Conclusion

1. Tuberculosis is one of the most common infectious diseases, with a variety of clinical manifestations and radio-imaging features.
2. Deep analysis of imaging findings (US, CT, MR), correlated with complete clinical information allow an accurate and noninvasive evaluation of the hepatic parenchyma.
3. Given the rather nonspecific features of hepatic tuberculosis, a rigorous differential diagnosis is imposed, hepatic biopsy remaining the "gold-standard".

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