



Radiological Approach to Liver Infections

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Abstract

Liver infections are a common and appropriate management depends on the accurate diagnosis. Imaging is an important part of the workup of patients with suspected liver infections. The imaging appearances depend on the causative agent. When imaging features are seen in context of the clinical presentation, biochemical features, and predisposing condition, a specific diagnosis is possible in a significant proportion of patients. In this review, we discuss the imaging-based approach to liver infections.

Keywords

- ▶ liver
- ▶ infection
- ▶ imaging

Introduction

Hepatic infections are common. Liver may be involved by bacteria, parasites, mycobacteria, fungi, and viruses.¹ The clinical and radiological presentation of liver infection depends on the body's immune response to hepatotropic organisms. Patients may present with symptoms ranging from nonspecific upper abdominal complaints with an indolent course to an acute rapidly progressive condition. Imaging has an important role in the diagnosis as well as management of liver infections. Ultrasound (US) is the most common imaging test employed in patients with suspected liver infections. Computed tomography (CT) and magnetic resonance imaging (MRI) are employed for patients with complicated disease course. The radiologists need to be aware of the mimics of liver infection like cysts, neoplasm, and autoimmune diseases.¹ To ensure an accurate diagnosis and appropriate antimicrobial therapy, image-guided culture from aspirated fluid as well as tissue samplings may be needed. In this review, we discuss the imaging features of liver infections.

Bacterial Infections

Pyogenic Liver Abscesses

Liver is the most common site of visceral abscess and over half of the abscesses are polymicrobial.² Pyogenic infection most commonly involves the middle-aged patients. There is

no gender predilection. Pathogenesis is multifactorial including hematogenous dissemination from a gastrointestinal infection via portal vein, disseminated sepsis by hepatic artery, ascending cholangitis, inoculation from either a penetrating trauma or invasive procedure, or from contiguous spread from diseases like cholecystitis. Most common bacterium responsible is *Escherichia coli*.

Clinical presentation is variable ranging from the nonspecific symptoms or “unwellness” to fever, rigors, and right upper abdominal pain. Nonspecific biochemical abnormalities include hypoalbuminemia, raised aminotransferases, and hyperbilirubinemia.

Early diagnosis reduces the need for surgery and mortality.² While larger abscesses (>5 cm) need drainage, smaller abscesses can be treated by antibiotic use alone with or without aspiration.³ The imaging features of pyogenic liver abscesses (PLA) are discussed below.

US: Pyogenic abscesses may be visualized as ill-defined or well-defined hypoechoic solitary or multiple lesions.⁴ Internal echoes and air may be seen (→ Fig. 1A). Acoustic enhancement and absence of Doppler signal can help in exclusion of neoplasm.

CT: The most common finding at CT is a low attenuation lesion with enhancing peripheral rim (→ Fig. 1B, 1C). Low attenuation fluid attenuation area surrounded by high attenuation peripheral inner rim that represents pyogenic membrane and low attenuation outer rim representing parenchymal edema can give rise to “double target sign.”⁵

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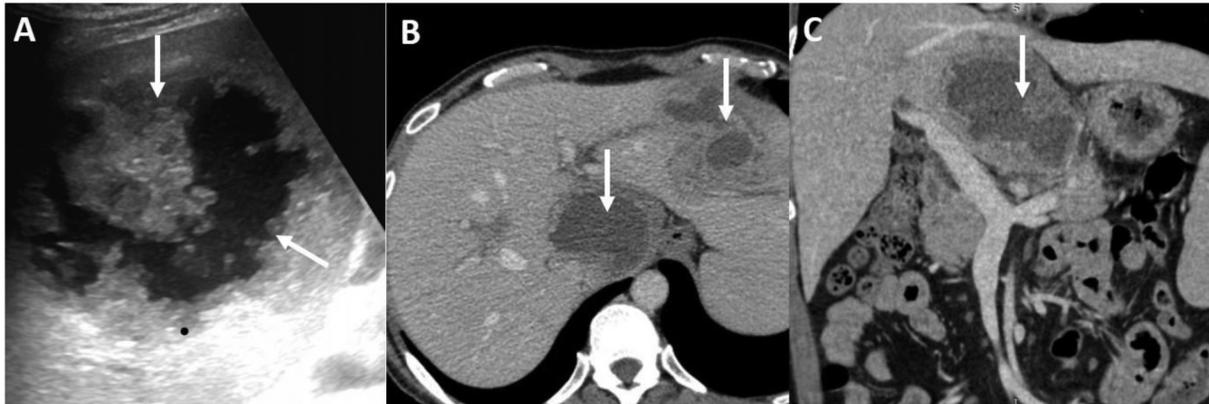


Fig. 1 Pyogenic liver abscess in a 29-year-old male. Ultrasound image (A) shows a well-defined heteroechoic lesion with thick shaggy wall (arrow). Axial (B) and coronal (C) computed tomographic images show peripherally enhancing hypodense lesions in left lobe of liver (arrows).

When multiple low attenuation lesions are seen in a localized area and coalesces to give rise to single abscess cavity, it gives rise to “cluster sign.”

MRI: The signal intensity on T1-weighted and T2-weighted images may vary depending on the content of the lesion.⁶ However, most lesions are hypointense on T1-weighted and hyperintense on T2-weighted images. Double target sign may be seen on T2-weighted images as an iso- to hypointense inner layer surrounded by hyperintense outer layer. Diffusion restriction (hyperintensity on high b-value diffusion-weighted images [DWI] low signal intensity on apparent diffusion coefficient maps) is seen.

Other features: Transient hepatic attenuation or intensity difference may be associated with liver abscesses. Gas may be seen within abscesses (more common in *Klebsiella*) either in bubble form or as an air fluid level. In *Klebsiella Pneumoniae* infection, numerous thin arborizing bands resembling turquoise mineral are seen (“turquoise sign”).⁷

Differential Diagnosis

Amebic liver abscess: This is discussed in the section below.

Hepatic tumors: Necrotic tumors (e.g., mesenchymal hamartoma and undifferentiated embryonal sarcoma) may mimic a liver abscess. Enhancement characteristics of an inflammatory capsule with double target appearance including progressive uptake in the outermost layer favors abscess over neoplasm.⁸ Aspiration/biopsy must be performed when differentiation is not possible on imaging.

Liver cysts: Cholangitic abscesses may mimic cysts because they can be markedly hyperintense on T2-weighted imaging. Perilesional edema, faint enhancing rim, or diffusion restriction is the feature that favors cholangitic abscesses.

Parasitic Infections

Amoebic Liver Abscess

Amoebic liver abscesses (ALA) are an extraintestinal manifestation of *Entamoeba histolytica* infection. Amebiasis is endemic in Asia, Africa, South and Central America and is more common in adult male.⁹ Trophozoites from intestine migrate up the portal vein and invade the hepatic parenchy-

ma. Clinically, ALA presents as fever, right upper quadrant pain, and hepatomegaly. Patients are younger in comparison with the pyogenic abscesses. Classically, ALA are solitary and unilocular, but in approximately 30% of the cases, septa may be present.¹⁰ ALA are commonly located in the right lobe of liver typically in the subcapsular location. Diaphragmatic disruption is common in the amoebic abscesses. Patient with ALA responds well to metronidazole and aspiration is generally not acquired. When diagnosis is uncertain or there are signs of impending rupture, aspiration may be considered. The imaging features of amoebic liver abscesses are discussed below.

US: ALA are round-to-oval hypoechoic lesions with low level internal echoes and acoustic through transmission.¹¹ No significant wall echoes are seen.

CT: ALA are seen as well-defined rounded hypoattenuating lesion with thick peripheral enhancement and perilesional edema.¹¹ Associated circumferential thickening of the ascending colon and caecum suggesting amoebic colitis may be seen (→ Fig. 2).

MRI: Lesions are hypointense on T1-weighted images and hyperintense on T2-weighted images.¹² Perilesional T2-weighted hyperintensity due to edema is seen. On DWI, the lesion shows central areas of diffusion restriction.

Differential Diagnosis

PLA: As discussed above, the ALA are most solitary and seen in young patients in endemic countries. However, when these are multiple, the differentiation from PLA may be difficult. Although some previous studies have suggested some differences in the echo pattern within the lesions, these are nonspecific.

Infected hydatid cyst: This is discussed below.

Echinococcus

Cystic and alveolar echinococcosis are the commonest forms caused by *Echinococcus Granulosus* and *E. Multilocularis*, respectively. Cystic echinococcosis (hydatid cyst) is the most common form seen in India. Hydatid cysts has three layers, innermost live germinal endocyst, multilamellated ectocyst, and fibrous outer pericyst representing host

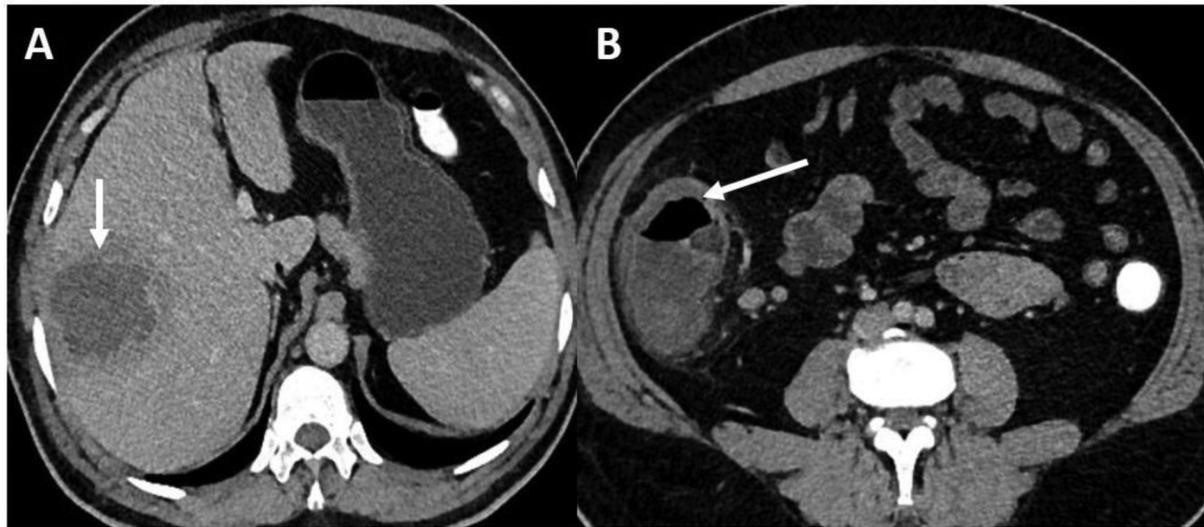


Fig. 2 Amebic liver abscess in a 42-year-old male. Axial images at the level of liver (A) and lower abscess (B) show a well-defined peripherally enhancing lesion in right lobe (arrow, A) and circumferentially mural thickening of the caecum s/o amebic liver abscess with amebic colitis.

response of the liver parenchyma. Daughter cysts are the result of endocyst invagination. Smaller cysts are asymptomatic, while larger cysts present with upper abdominal mass, pain, or jaundice. Ruptured cysts can cause anaphylaxis and seeding of the other parts of the body.¹³

US: US appearance ranges from cystic lesion to solid appearing pseudotumors. US-based World Health Organization classification of hydatid cysts is useful for the assessment of stage and guiding appropriate management. Six stages have been described (→**Fig. 3**) in the following text.

Cystic lesion (CL): Unilocular cyst with uniform anechoic content, and not clearly visible cystic wall.

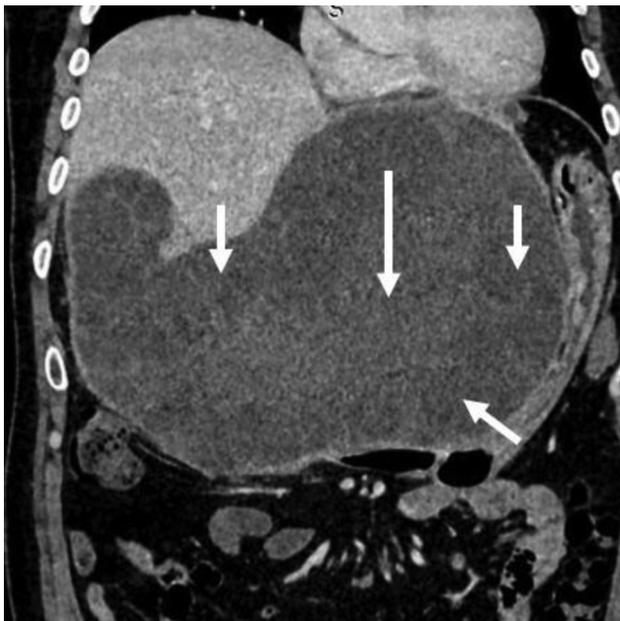


Fig. 3 Hydatid cyst: Computed tomography (CT). Axial CT image shows a large exophytic liver hydatid cyst showing multiple daughter cysts (short arrows). Note that the daughter cysts have lower attenuation (short arrows) compared to the central part of the cyst (arrow).

Cystic echinococcosis (CE) 1: Unilocular cyst with uniform anechoic component and well visualized cystic wall. On repositioning the patient, hydatid sand in the form of fine mobile echoes can be seen (“snowstorm sign”).

CE 2: Multiseptated multivesicular cyst due to multiple daughter cysts.

CE 3: Inner detached floating membrane within an active unilocular cyst gives “water lily sign” appearance.

CE 4: Mixed hypoechoic and hyperechoic cyst with absent daughter cysts give rise to “pseudotumor” or “ball of worms” appearance.

CE type 5: Partially or complete calcified lesion is seen.

CT: CT is less sensitive than US in the depiction of the hydatid cyst characteristics. Imaging findings vary based on the stages. It can be unilocular, with daughter cyst, partially or densely calcified. Daughter cysts has lower attenuation than the main cysts (→**Fig. 4**). Detached endocyst can be seen as linear area of high attenuation.

MRI: On MRI, pericyst is well delineated as hypointense rim on T1-weighted and T2-weighted images. Daughter cysts are more T2 hyperintense than the rest of the cyst. Collapsed membrane appears T2 hypointense on all sequence giving rise to “serpent” sign. No post-contrast enhancement of the cyst component is seen; however, fibrous pericyst may show delayed enhancement. MRI with magnetic resonance cholangiography allows better depiction of the cysto-biliary communication.¹⁴

Differential Diagnosis

- 1) Simple hepatic cyst: It may mimic unilocular hydatid cyst. Imaging findings that provide clue for diagnosis are hydatid sand, segmental cyst wall thickening, coexistent hydatid cyst elsewhere, pericystic dilatation of the biliary radicle, or satellite cysts.
- 2) Biliary cystadenoma or cystadenocarcinoma: Enhancement of septa or mural nodule is seen in these tumors.
- 3) Abscess: Infected hydatid cyst can mimic abscess, especially, if no daughter cysts and membranes are seen.

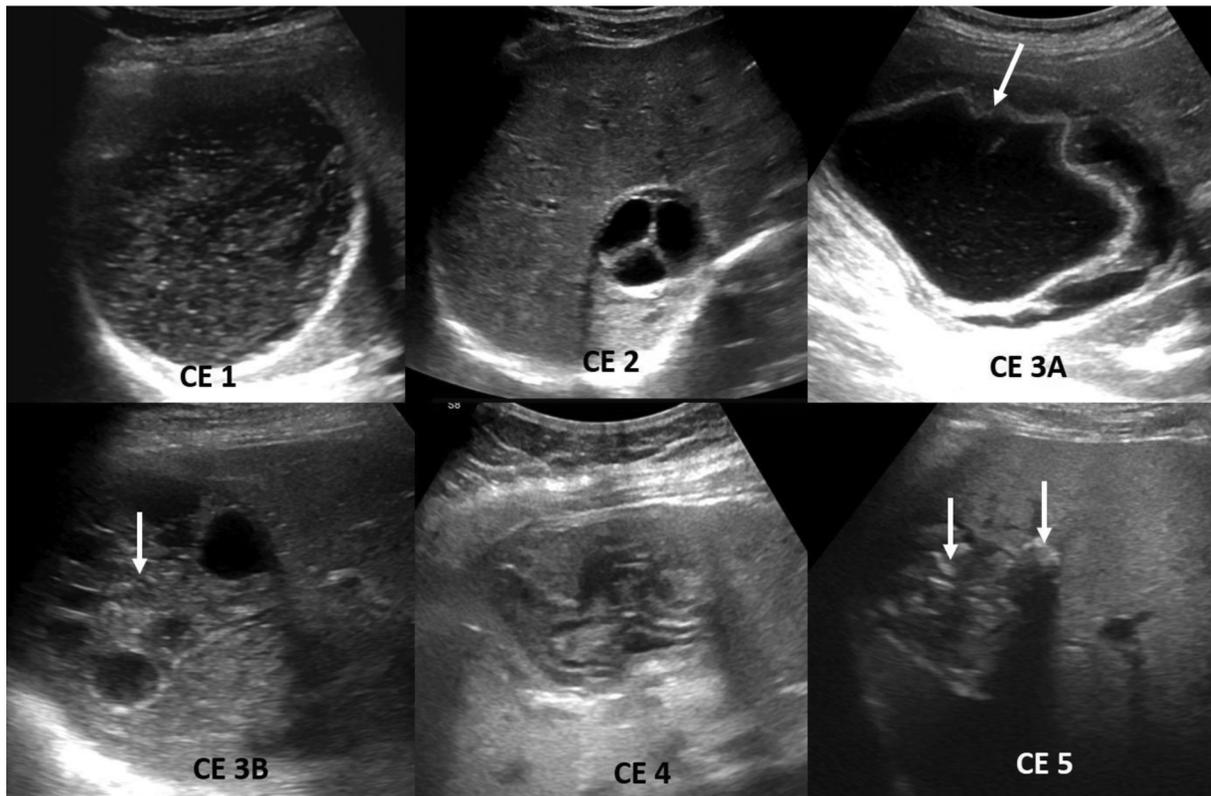


Fig. 4 Hydatid cyst: Ultrasound. Multiple stages of hydatid cyst are shown. Cystic echinococcosis (CE 1): The cyst wall is well visualized and there is fine echogenic debris suggestive of hydatid sand. CE 2: Cyst with daughter cysts. CE 3a: Undulating membrane (arrow). CE 3b: Cyst with central matrix (arrow) and few daughter cysts. CE 4: Heteroechoic solid cystic lesion. CE 5: Solid lesion with calcifications (arrows).

Complications

- 1) Infection: Infected hydatid cyst wall enhances on contrast administration. Intracavitary air-fluid level may be seen.
- 2) Rupture: Various types of ruptures have been reported. Rupture into the biliary ducts can lead to cholangitis. Rupture into the peritoneal cavity, surrounding viscera, and thorax, though less common, may be fatal.

Visceral Larva Migrans

It is caused by *Toxocara canis*. The lesions may be incidentally detected during workup of nonspecific upper abdominal complaints or peripheral eosinophilia. Abdominal discomfort, nausea, and vomiting are the other reported features. Visceral larva migrans lesions present as variable sized hypo or isoechoic lesion with an ill or well-defined margin on US. Multiple oval or elongated hypoattenuating lesions may be seen on contrast-enhanced CT images (► Fig. 5). MRI features correspond with the CT finding and lesions show T1-weighted hypointensity and T2-weighted heterogeneously hyperintense signal. Due to migration of larva, the lesions change their location.¹⁵

Most important differential diagnosis is metastasis. Lack of peripheral enhancement on venous phase, ill-defined margin, and subtle hypodensity favors the diagnosis of visceral larva migrans.

Fascioliasis

Fascioliasis is a foodborne infection in humans caused by a parasite *Fasciola hepatica*. Humans are the definitive hosts

and infection occurs due to accidental ingestion of parasitic metacercaria cysts along with freshwater plants.¹⁶ These metacercariae cysts are formed from the cercaria released by the water snails, which are its intermediate host. When accidentally ingested by humans, metacercariae cyst exists

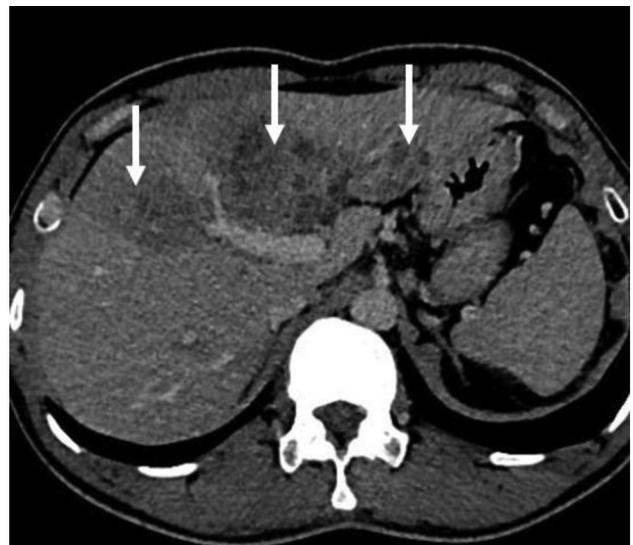


Fig. 5 Visceral larva migrans in a 29-year-old female with blood eosinophilia and vague upper abdominal symptoms. Axial computed tomography shows multiple clustered hypodense lesions in both lobes (arrows).

within the duodenum and traverses across its wall into the peritoneal cavity. It further reaches the liver parenchyma via its capsule and finally infects the biliary ducts where they mature into adult flukes and lay eggs in few months. These are released in the stool, hatch into miracidia in freshwater, and again infect intermediate hosts. These adult flukes can survive in the liver for a decade. Human infections are usually in developing countries. The infection presents with nonspecific symptoms of right hypochondrium pain, fever, vomiting, and urticaria in early stage of the disease. Various immunological tests and direct parasitology from stools are available for diagnosis.^{17,18} There is high incidence of negative stool sampling as the eggs are excreted in later stage of disease. Radiological modalities can not only help in early noninvasive diagnosis of the disease but also help to rule out other focal liver lesions.^{16,17}

Early parenchymal phase of disease: On US, multiple focal or diffuse small hypoechoic as well as hyperechoic lesions are seen scattered in liver parenchyma. On CT, they appear as clusters of hypodense lesions predominantly at the periphery in subcapsular location and progressing toward the center. They show mild peripheral enhancement. Mild adjacent capsular thickening and perihepatic fluid can be seen, likely representing entry of parasite within the parenchyma. On MRI, they appear as cluster of small peripherally enhancing, T2W hyperintense lesions in subcapsular region with multiple variable intensity linear lines representing their migration tracts in the parenchyma.^{19,20}

Late ductal phase of disease: On US, features of intrahepatic as well extrahepatic biliary duct dilatation with echogenic walls and periportal linear hypoechoic lines can be seen along with the above describe liver lesions. Rarely, live fluke may be seen within the gallbladder and biliary ducts. CT may demonstrate ductal dilatation with mural thickening and enhancement. Multiple hypodense lesions in clusters radiating from peripheral subcapsular location in biliary distribution may be seen. On MRI, linear filling defects may be seen within the gallbladder or biliary ducts representing adult flukes.²⁰

Hepatic Tuberculosis

Liver involvement in tuberculosis is seen in the immunocompromised patients. The incidence is higher in human immunodeficiency virus (HIV) patient with a CD4 counts less than 200 cells/ μ L.²¹ Manifestation can be micronodular or macronodular. Micronodular involvement is the most common.²² The lesions in micronodular tuberculosis are less than 2 mm and are often missed at US. High-resolution US may help detect lesions as multiple tiny hypoechoic nodules scattered throughout the liver. Hepatomegaly is the only manifestation. On CT, multiple tiny hypodense nodules with no discernible enhancement are seen (**Fig. 6**). On MRI, these nodules are T1 hypointense and T2 hyperintense.²³ When there is extensive caseous necrosis, these lesions manifest as tubercular abscesses. Sometimes, these lesions may be relatively hypointense on T2-weighted images.

The macronodular tuberculosis presents as variable sized nodules usually 1 to 3 cm in size. The nodules are lesser than



Fig. 6 Hepatic tuberculosis in an 18-year-old female with a past history of treated pulmonary tuberculosis. Axial computed tomography image shows multiple tiny (2–4 mm) nodules scattered diffusely in both lobes of liver (arrows).

micronodular tuberculosis. The lesions are hypoechoic on US and hypoattenuating at CT.

Differential diagnosis includes fungal infections, sarcoidosis, lymphoma, and metastases. The presence of necrotic lymphadenopathy and cavitary pulmonary lesions favors tuberculosis.

Fungal Infections

Prevalence of the fungal infection in immunocompromised high-risk patients ranges from 20 to 40% with risk factors including immunosuppression due to prolonged neutropenia, hematological malignancies, solid organ or stem cell transplant recipients or due to any other factor.²⁴ Some of the commonest fungi responsible are *Candida*, *Aspergillus*, and *Cryptococcus neoformans*, histoplasmosis, and mucormycosis. To initiate appropriate therapy and avoid fat complications, early diagnosis of the infection is crucial. Because of the similar imaging appearance of different infections, complementary studies like galactomannan assay and tissue sampling are necessary.

Candidiasis

Candida is the most common fungal species to infect the liver and spleen. *Candida* species evoke response ranging from no or little inflammation to granuloma formation and suppuration. In immunocompromised high-risk patients, including those with prolonged neutropenia, hematological malignancies, solid organ, or stem cell transplant recipients, the presence of multiple hepatic lesions should raise suspicion of fungal infection.

US pattern of hepatic candidiasis²⁵: -

- a) Uniformly hypoechoic nodule: This consists of fibrotic area that has replaced inflammation and is the most common but nonspecific appearance of candidiasis.

Table 1 Imaging appearances of various liver infections

Sr. no	Infection	Ultrasound	CT	MRI
1	Pyogenic liver abscess	Solitary /multiple hypoechoic lesions, thick walls, internal echoes	Hypoattenuating lesions with peripheral enhancing shaggy wall with surrounding edema— <i>double target sign</i> Multiple— <i>cluster sign</i>	Solitary/multiple T2 hyperintense lesions showing diffusion restriction
2.	Amoebic liver abscess	Mostly solitary, more common in right lobe, round to oval hypoechoic with low level internal echoes	Round hypoattenuating lesion, peripheral enhancement, associated cecal and ascending colon thickening	Usually solitary, T2W hyperintense lesion with central diffusion restriction
3.	Echinococcus	Appearance depends on WHO stage. Specific appearances: cyst with daughter cysts, floating membrane	Daughter cysts are hypoattenuating compared to main cyst, detached membranes, wall calcification	T1/T2W hypointense rim-pericyst T2 hypointense collapsed membrane— <i>serpent sign</i>
4.	Visceral larva migrans	Multiple variable size isoechoic to hypoechoic lesions	Multiple hypodense lesions changing locations, no peripheral enhancement, ill-defined margins	Multiple T2W hyperintense lesions, lack of peripheral enhancement
5.	Fascioliasis	-Multiple small hypoechoic/hyperechoic lesions in parenchymal phase -Biliary duct dilatation, periportal echogenic lines, flukes in gallbladder in biliary phase	-Hypodense lesions progressing from periphery to center, mild peripheral enhancement in parenchymal phase -Biliary duct dilatation with enhancing thick walls along with parenchymal lesions in biliary phase	-T2W hyperintense lesions progressing from periphery to center, migration of lesions in parenchymal phase -Biliary duct dilatation, filling defects in ducts/gallbladder in biliary phase
6.	Tuberculosis	Micro/macronodular involvement seen as small hypoechoic lesions scattered in liver	Multiple tiny hypodense lesions in both lobes, no discernible enhancement	T2W hyperintense lesion, tubercular abscesses
7.	Fungal—Candidiasis	Hypoechoic nodule, bull's eye appearance wheel within wheel appearance	More pronounced on arterial phase, variable appearance, hypo/hyper attenuating lesion, hypodense with hyperdense rim	Acute microabscess, T1W hypointense T2W hyperintense, no perilesional edema, subacute: T1/T2W hyperintense Chronic: Mildly hyperintense on T2W, no post contrast enhancement
8.	Acute viral (normal imaging does not exclude acute viral hepatitis)	Reduced parenchymal echogenicity— <i>starry sky</i> Gallbladder wall thickening	Heterogeneous liver, periportal edema, gallbladder wall thickening and periportal lymph nodes	Periportal edema <i>HIV cholangiopathy</i> —sclerosing cholangitis, papillary stenosis, biliary stricture

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; T1W, T1-weighted.

- b) Bull's eye appearance: This involves central echogenic area surrounded by a hypoechoic rim.
- c) Wheel within a wheel appearance: The central hypoechoic area is surrounded by an echogenic rim.
- d) Echogenic foci with posterior acoustic shadowing.

CT: Arterial phase has the greatest sensitivity for diagnosis of the candidiasis. Some of the described patterns are²⁶: -

- a) Hypoattenuating lesions.
- b) Lesions with hypoattenuating center and hyperattenuating rim.
- c) Lesions causing transient hepatic enhancement.
- d) Hyperattenuating lesion

MRI is superior in sensitivity to US and CT for the detection of fungal infection. In the acute stage, microabscesses are generally mildly T1 hypointense and T2 hyperintense. Absence of perilesional edema differentiates the fungal

infection from others. In the subacute phase, lesions are hyperintense on T1-weighted and T2-weighted images. In chronic stage, abscesses show subtle T1 hypointensity and are iso to mildly hyperintense on T2-weighted imaging with no post-contrast enhancement.²⁷

Differential diagnosis includes other diseases that manifest as multiple hepatic nodules, including tuberculosis, lymphoma, leukemia, sarcoidosis, metastasis, and sometimes even focal fatty infiltration. Associated neutropenia is the most important pointer toward the possibility of fungal infection. Sometimes sampling may be needed for confirmation of diagnosis.

Viral Infections

Hepatotropic viruses like hepatitis A, B, C, and E, herpes simplex virus, HIV, and coxsackie virus are the commonest to infect the liver.²⁸ The clinical manifestations range include acute presentation with abdominal pain and jaundice, and subclinical infection that gradually leads to cirrhosis and occasionally acute fulminant hepatic failure.

Diagnosis is made by correlating clinical presentation with the serology, and biochemistry. Imaging finding in viral infections is nonspecific. Its main role is to exclude other pathological condition like biliary tract obstruction, diffuse metastasis, and cirrhosis.

US: Findings in a case of acute hepatitis include hepatomegaly with decreased parenchymal echogenicity and “starry sky” appearance due to relatively increased periportal echogenicity.

CT: Findings are nonspecific. The most common pattern is heterogeneous enhancement with periportal edema. Well-defined area of hypoattenuation may be seen.²⁹ When complications like portal hypertension develops, dilated portosystemic collaterals along with splenomegaly and ascites are seen. Edematous gallbladder wall thickening and periportal lymphadenopathy may also be seen.

MRI: Periportal T2 hyperintensity representing edema may be seen. Ill-defined areas of T1 hypointensity and T2 hyperintensity may also be seen.³⁰ HIV cholangiopathy may manifest as sclerosing cholangitis, papillary stenosis with upstream dilatation, or combined forms. Long segment biliary stricture may also be seen.

It is important to stress that normal imaging does not exclude viral hepatitis.

► **Table 1** enumerates the imaging manifestations of various liver infections.

Conclusion

Imaging is critical to the diagnosis and management of patients with liver infections. Although the imaging findings are specific only in a small proportion of patients, imaging findings and image-guided sampling allow appropriate treatment and follow-up in most cases.

Conflict of Interest
None declared.

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