JOURNAL
OF HEPATOLOGY

# Multiple hepatic cysts in an adult male

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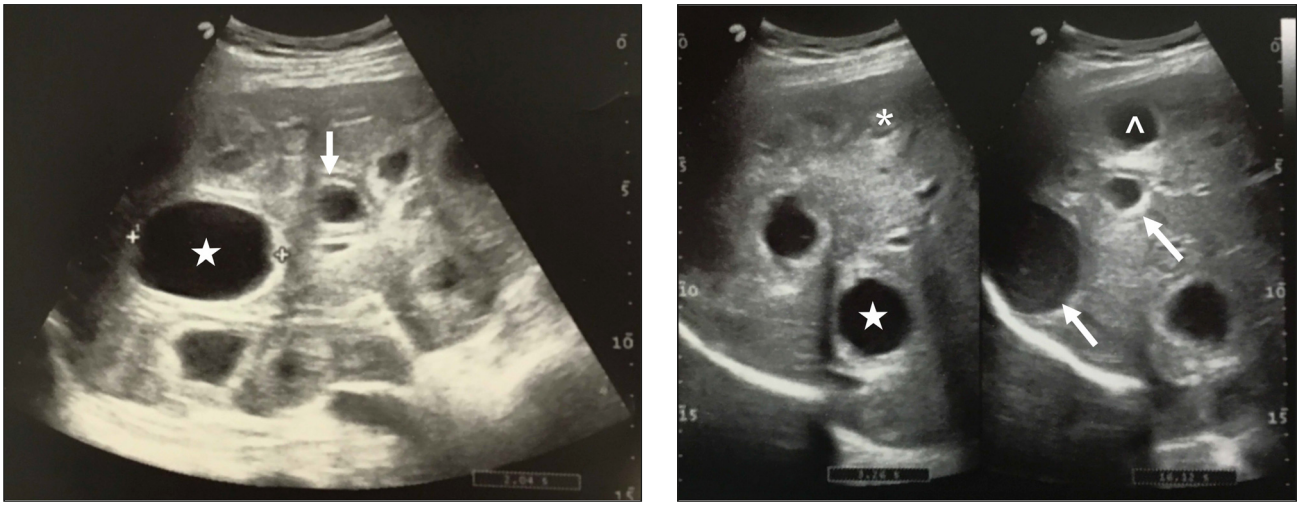

**Fig. 1. Liver ultrasound.** Liver ultrasound performed by an expert hepatologist showed multiple spheric lesions between 1 and 6 cm, some appearing as unilocular anechoic spaces with thin walls (star); others appearing as relatively hypoechoic lesions with mural thickening, hyperechoic walls, and debris-containing fluid (arrow). Cist aspiration (^) and targeted liver biopsy were performed (*).

## Description

A 59-year-old male with an uneventful past medical history was admitted to our service due to epigastric pain, inappetence, and weight loss. The symptoms started after a recent trip to Morocco to visit his family. He denied any exposure to unusual plants or animals. Vitals were normal. Physical examination showed an enlarged liver. Labs demonstrated normocytic anemia (hemoglobin 12 g/dl), slight elevation of AST (70 U/L, with an upper limit of normal [ULN] of 45 U/L), normal ALT, a significant increase in GGT (1,137 U/L; ULN: 65 U/L) and ALP (428 U/L; ULN: 128 U/L), normal bilirubin, and a modest increase in C-reactive protein (21 mg/L; ULN: 6 mg/L). CEA, AFP, and CA 19-9 were normal, while HBV and HCV serology were negative. Upper endoscopy was normal; colonoscopy showed a single 10 mm adenoma in the caecum. Liver ultrasound showed multiple spheric lesions measuring between 1 and 6 cm, some appearing as unilocular anechoic spaces with thin walls reminiscent of simple hepatic cysts, whilst others appeared as relatively hypoechoic lesions with mural thickening, hyperechoic walls, and debris-containing fluid, without signal flow on color Doppler (Fig. 1, left). An extensive microbiological work-up including Echinococcus, Entamoeba, and TBC was ordered. Based on the clinical picture and liver ultrasound suggestive of hepatic cyst infection, the patient was treated with metronidazole and underwent cyst aspiration (with evacuation of dense, chocolate-colored fluid) and percutaneous biopsy of one of these lesions (Fig. 1, right). The C-reactive protein decreased to normal values, and he was discharged to the outpatient service.

## What is your diagnosis?

1. Echinococcus cyst infection.
2. Liver metastases from unknown primary.
3. Primary liver cancer.
4. Hepatic tuberculosis.

Keywords: GIST; liver ultrasound; cKIT; liver metastases.
*Received 20 April 2023; received in revised form 5 May 2023; accepted 9 May 2023;*
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https://doi.org/10.1016/j.jhep.2023.05.006

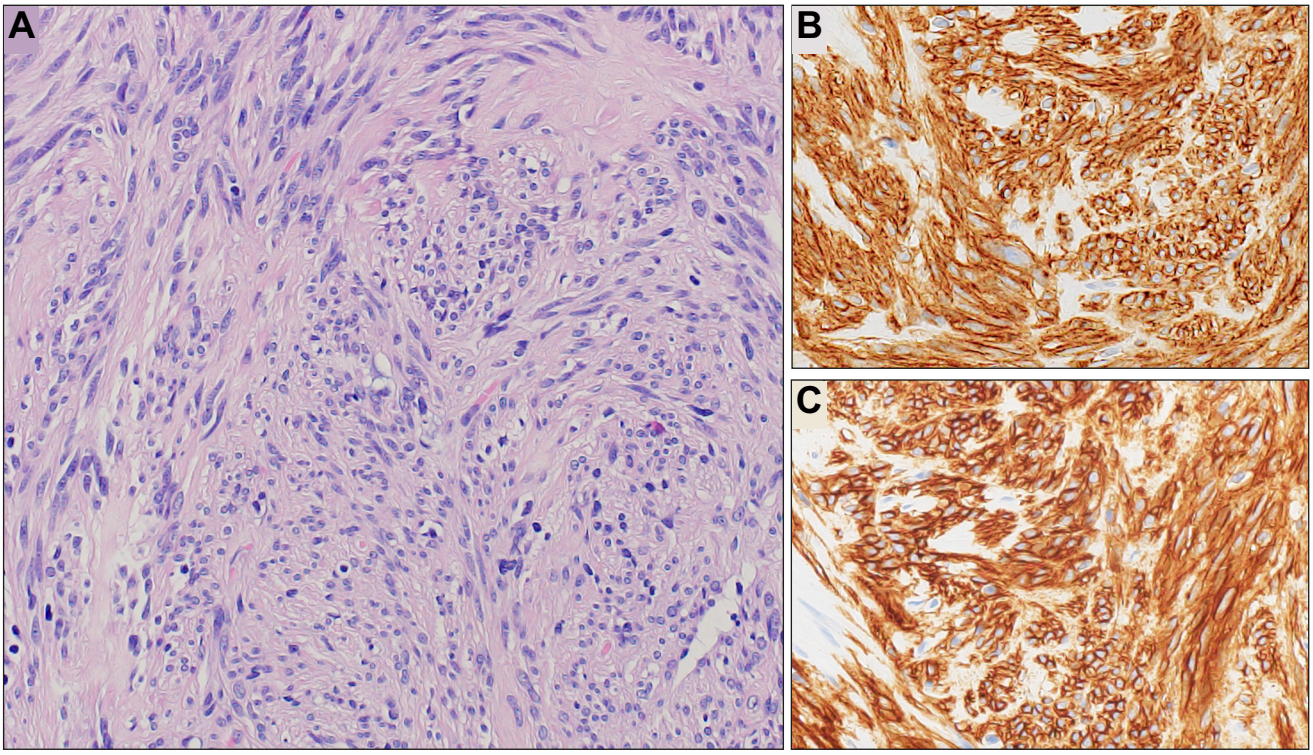


**Fig. 2. Histologic images of the liver biopsy sample showing morphologic and immunohistochemical features of GISTs.** Short fascicles composed of spindle to epithelioid cells with moderate eosinophilic cytoplasm, undefined cellular borders, coarse nuclear chromatin and indistinct small nucleoli. No presence of necrosis. (A) H&E 20x. Diffuse immunopositivity for (B) CD117 and (C) DOG1, 20x. GIST, gastrointestinal stromal tumor.

## Diagnosis and patient's outcome

The cytologic examination of the cystic fluid aspirate demonstrated some red and white blood cells (*i.e.*, inconclusive). The microbiological report was negative. The microscopic examination of the biopsy cores showed a spindle to epithelioid cell proliferation walled off by a thick fibrous pseudocapsule from the normal hepatic parenchyma. Microscopically, the tumor cells were arranged in short fascicles and displayed a modest amount of eosinophilic cytoplasm, undefined cellular borders with coarse nuclear chromatin, and small nucleoli (Fig. 2A). There were no mitotic figures or necrosis. Multiple areas of collagenous degeneration were present (Fig. 2A). The tumor was diffusely positive for CD34, CD117 (Fig. 2B) and DOG1 (Fig. 2C), whereas S100 and MDM2 were negative. Molecular analysis was carried out by DNA extraction from several 10 μm thick sections, followed by PCR amplification and Sanger sequencing, which detected a *cKIT* gene mutation involving exon 11 (V560D).

The histopathological and molecular findings were consistent with the diagnosis of a gastrointestinal stromal tumor (GIST). Therefore, the patient was referred to the oncologist for further management and treatment. A PET scan demonstrated that the primitive site of the GIST was the small bowel. The patient received systemic treatment with imatinib and achieved a complete oncological response.

## GIST as a potential cause of liver metastases

GISTs are presumed to originate from the interstitial cells of Cajal, which are located in the myenteric plexus and are responsible for intestinal peristalsis.[1] GISTs are rare tumors with an annual estimated incidence of up to 1.5 cases/100,000 person-years.[2] GISTs are mostly diagnosed in older adults with a median age of 60–65 years, with a slight male predominance. The stomach (50-60%) and small bowel (30-35%) are the most commonly affected sites, followed by the colon/rectum (5%), esophagus (<1%) and appendix. Rarely, GISTs may be found in the retroperitoneal space or within the omental layers (*i.e.*, extra-intestinal GIST).[2]

Symptoms can be heterogenous depending on tumor site and/or complications including gastrointestinal bleeding and/or chronic anemia, abdominal pain, dyspepsia, nausea/vomiting, diarrhea/stypsis, and rarely bowel perforation or occlusion.[3]

The typical endoscopic appearance of GISTs is that of a rounded parietal protuberance with normal overlying mucosa and a central depression or umbilication. In larger tumors, the central area may become ulcerated. Since GISTs are *submucosal* tumors, biopsies of the intestinal mucosa are often negative. As such, the most accurate method of biopsy retrieval for diagnosis of a suspected GIST is via endoscopic ultrasound. Percutaneous and/or laparoscopic biopsy of a GIST should be avoided due to the potential risk of dissemination.[3] The radiological appearance of a GIST may vary depending

on imaging technique, anatomical site, and growth pattern. In CT scans, GISTs may present as exophytic masses with heterogeneous enhancement. Exophytic, gastric GISTs can be misinterpreted as pancreatic mucinous tumors or pseudocysts.[1]

The pathologist plays a key role in the diagnosis of GISTs, which requires morphologic and immunohistochemical characterizations of the lesions. Over 90% of GISTs show cytoplasmic immunoreactivity for c-KIT (CD117), a tyrosine kinase receptor, whereas only 5% are CD117 negative. Up to 50% of c-KIT-negative cases will stain for DOG1, which is equally sensitive and specific for GISTs. Spindle cell GISTs also show CD34 positivity and, more rarely, smooth muscle actin and protein S100 positivity. Genetically, GISTs present *c-KIT* mutations which lead to uncontrolled cellular growth and resistance to apoptosis. As such, GISTs have a specific sensitivity to imatinib, a tyrosine kinase inhibitor.[1] *PDGFRA* mutations may also be encountered; albeit *PDGFRA* and *c-KIT* mutations are almost always mutually exclusive (unless related to treatment resistance).

At diagnosis, up to 50% of patients will have metastatic disease. The liver is the most common site of GIST metastases (70-80%). Compared with the background liver parenchyma, metastases from GIST usually appear as relatively hypoechoic lesions on liver ultrasound, whereas they are generally hypervascular on CT and MRI. However, liver metastases may also be mixed with both hypo- and hyper-vascular masses.

Purely cystic liver metastases are commonly found in patients with GIST receiving imatinib treatment.[1] By contrast, only few cases of hepatic GIST with mostly cystic features (prior to treatment) have been described so far.[4] The factors responsible for cystic transformation of hepatic GIST metastases have not yet been thoroughly investigated; however, it could be speculated that spontaneous tumor necrosis and/or intralesional bleeding due to uncontrolled tumor growth may be involved. This hypothesis would be indirectly supported by [a] the ultrasound appearance (some lesions were hypoechoic with debris-containing fluid, Fig. 1); [b] the characteristics of the fluid evacuated through cyst aspiration, which was dense and chocolate-colored.

Surgical resection is the treatment of choice for localized GISTs. Imatinib can be used as neo-adjuvant therapy in patients with larger tumors harboring tyrosine kinase mutations. In patients with locally advanced or metastatic disease (either at diagnosis or in the case of recurrence after surgery), target therapy with imatinib is the standard of care. The introduction of imatinib has significantly improved patient survival from less than 16 months to up to 5 years. In patients who progress despite initial tyrosine kinase inhibitor therapy (imatinib), sunitinib (second-line) and regorafenib (third-line) can be considered.[3]


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## Financial support

The authors received no financial support to produce this manuscript.


## Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contribution

All the authors contributed to the conceptualization, writing and revision of the manuscript; AZ and MS: final revision and approval.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2023.05.006.

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