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CASE REPORT

Hepatic inflammatory pseudotumor: educational value of an incorrect diagnosis at contrast-enhanced ultrasound

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Abstract Hepatic inflammatory pseudotumor (IPT) is a rare lesion that is frequently confused with malignant tumors. According to the latest guidelines on contrast-enhanced ultrasound, hypoenhancement of solid lesions in the portal and late phases corresponds to the wash-out phenomenon that characterizes malignancies. IPT may show rapid arterial enhancement and portal or late phase hypoenhancement, falsely suggesting malignancy. We report a case of a diagnostic error in which a multifocal IPT was misdiagnosed as hepatic metastases. The IPT developed after an endoscopic retrograde cholangiography was investigated by close follow-up with CEUS and contrast-enhanced CT.

Keywords Contrast-enhanced sonography · Hepatic inflammatory pseudotumor · Focal liver lesion · Diagnostic error

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Introduction

Inflammatory pseudotumor (IPT) of the liver can mimic abscesses, metastases, peripheral cholangiocarcinomas, and hepatocellular carcinoma. This condition can occur at all ages, and its common presenting features include low-grade fever, weight loss, hepatomegaly, jaundice, and leukocytosis. Histologically, it is characterized by proliferating fibrous tissue infiltrated by inflammatory cells, but the exact etiology of IPT remains unknown [1–3]. It is difficult to make a specific diagnosis based on the laboratory or imaging findings because there is no specific laboratory marker and radiographic appearance.

We report a case of incorrect diagnosis of an IPT confused with hepatic metastases. It developed after endoscopic retrograde cholangiopancreatography (ERCP) and disappeared spontaneously. By contrast-enhanced ultrasound (CEUS), we identified the typical pattern of malignancy, i.e., early and intense wash-in with rapid and marked wash-out. This led us to an incorrect diagnosis. The case was proven at biopsy and investigated by close follow-up with CEUS and contrast-enhanced CT until resolution.

Case report

The patient was a 66-year-old woman who had suffered from symptomatic cholelithiasis treated with cholecystectomy a few years before. Due to the development of right upper quadrant pain and obstructive jaundice, the patient had first undergone MR-cholangiography and then ERCP with removal of choledochal lithiasis. In addition to the biliary stones, the unenhanced MR images showed multiple, coalescent hyperattenuating lesions in the liver dome

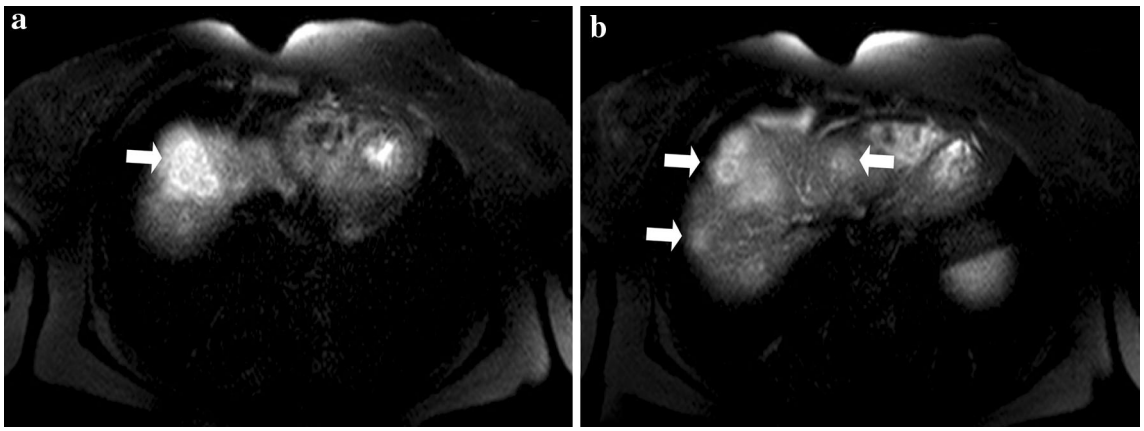

Fig. 1 Cross-sectional MR. **a**, **b** Axial, fat-suppressed T2-weighted images. Multiple and confluent hyperintense round areas in the hepatic dome (*arrows*)

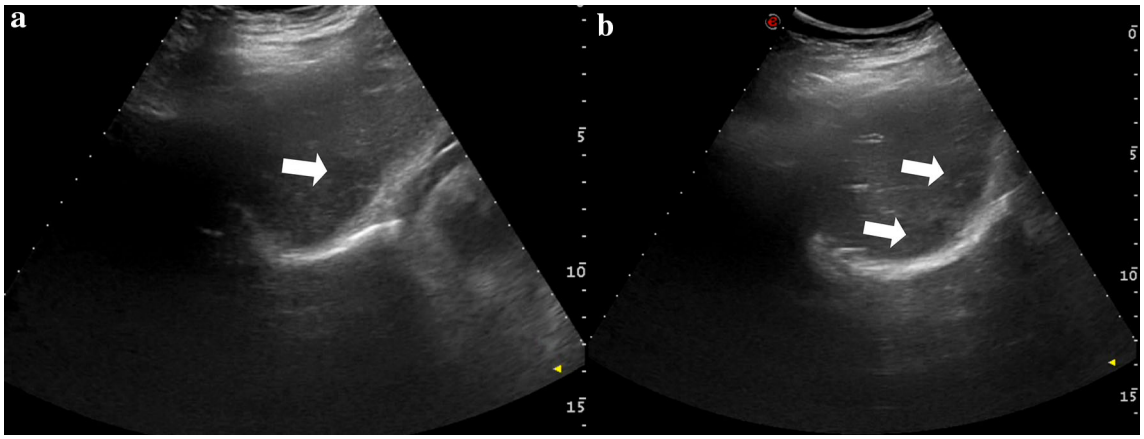

Fig. 2 Plain B-mode US images. (**a**, **b**) High-quality gray-scale pictures showing the presence of multiple poorly defined hepatic lesions with slightly heterogeneous and hypoechoic appereance (*arrows*)

(Fig. 1). Consequently, after ERCP and sphincterotomy, the patient was referred to our oncologic institution.

On admission, physical examination revealed scleral icterus and pruritus. There were no clinical signs of an abdominal mass. Her liver and spleen were not enlarged. No stigmata for chronic liver disease were identified. Superficial lymph nodes were not palpable. The lungs were normal on auscultation. A chest radiograph and an electrocardiogram were normal.

Laboratory investigations revealed that the hemoglobin level was 9.8 g/dL, and the white blood cell count was 8660/μL with segmental neutrophilia (79.2 %). There was no eosinophilia. The erythrocyte sedimentation rate was elevated to 100 mm/h (normal range 0–15 mm/h), and the serum C-reactive protein level was also elevated to 8.78 mg/dL (normal range 0–0.8 mg/dL). Serum direct bilirubin (1.6 mg/dL, normal range 0–0.3 mg/dL), aspartate (60 IU/L, normal range 10–36 IU/L) and alanine aminotransferases (62 IU/L, normal range 7–35 IU/L), alkaline phosphatase (360 IU/L, normal range 44–147 IU/L), and γ-glutamyltransferase (240 IU/L, normal range 0–51 IU/L) levels were also elevated. There were no other relevant abnormalities in the laboratory tests. Tests for serum alpha-fetoprotein (αFP), carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19–9, and serology for hepatitis A, B, or C were also all within normal ranges.

Abdominal ultrasound (US) was performed with a MyLab 70 XVG GOLD scanner (Esaote, Genoa, Italy) using a multifrequency (2.5–5 MHz) convex probe. It confirmed the presence of multiple poorly defined hepatic lesions with a slightly heterogeneous and hypoechoic appereance, but the differential diagnosis was quite difficult based exclusively on the US imaging findings (Fig. 2). There was no associated biliary dilatation.

To better assess the liver lesions, the patient was submitted to contrast-enhanced low-MI real-time ultrasound (CEUS) imaging with Sonovue® (Bracco, Milano, Italy). Sonovue® was injected into the antecubital vein in a bolus

fashion, followed by a flush of 10 mL of 0.9 % normal saline solution. After contrast injection, continuous scanning began immediately and lasted 4–5 min. On CEUS, these lesions were characterized by a diffuse and homogenous hypervascularity in the arterial phase and by a rapid wash-out with internal microcirculation in the portal phase (Fig. 3). This enhancement pattern was heavily suggestive of malignancy, probably of metastatic origin. Consequently, the patient was submitted to esophagogastroduodenoscopy and colonoscopy to identify the unknown primary tumor. However, both examinations were negative.

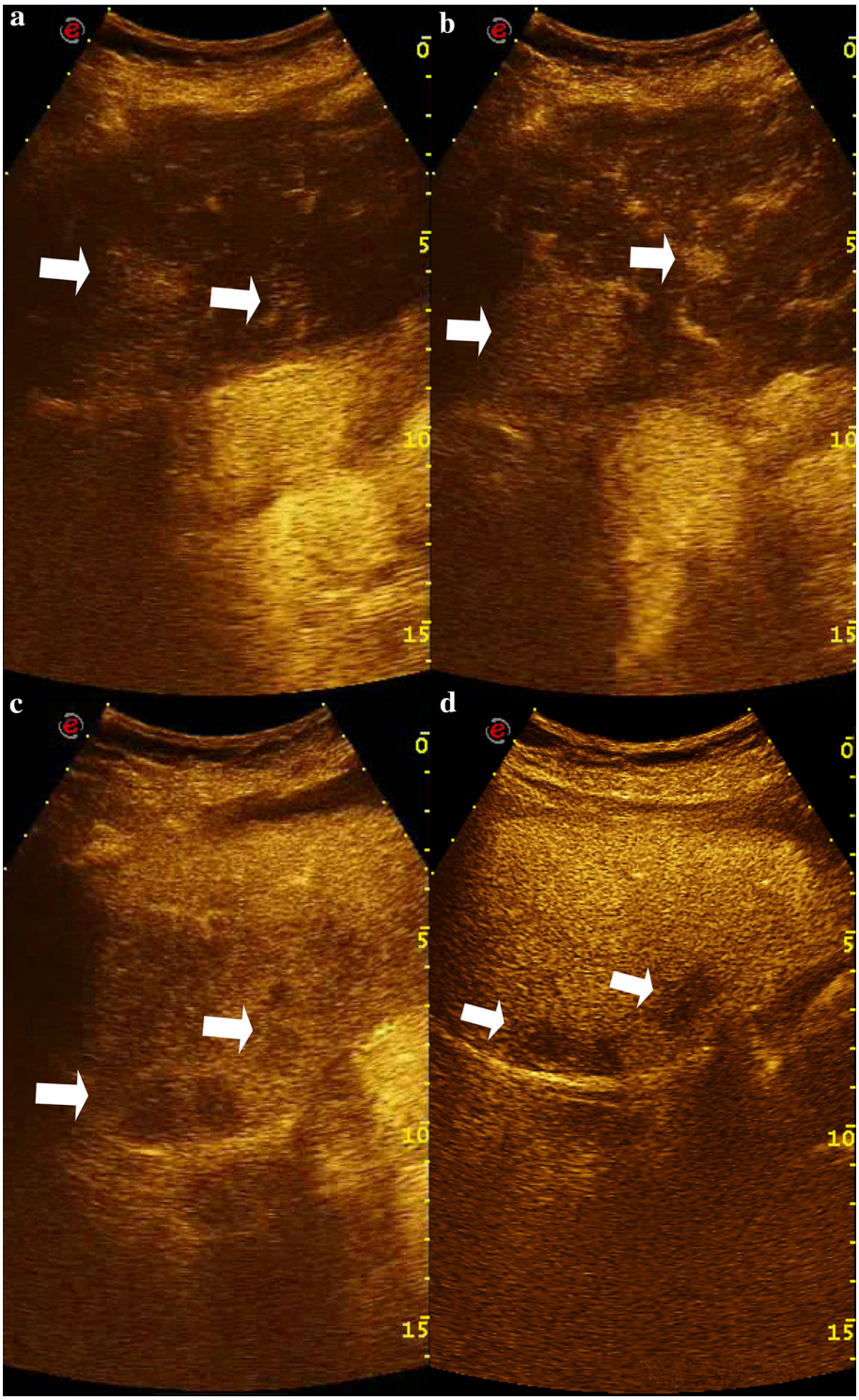

Fig. 3 CEUS images in the principal vascular phases. **a**, **b** Early and late arterial phase image taken 18 and 28 s after contrast injection showing lesions characterized by diffuse and homogeneous hypervascularity (*arrows*). **c**, **d** The enhancement wash-out rapidly depicted as hypoenhancement in the portal (**b**, 55 s) and late (**c**, 93 s) phases after contrast injection (*arrows*)

Additionally, contrast-enhanced computed tomography (CT) with a 16-detector row MSCT scanner (Somatom Volume Zoom; Siemens Medical Solutions, Erlangen, Germany) was performed. A frontal 512-mm scout view was first obtained with 120 kVp and 50 mA. This was followed by helical scanning from the top of the liver to the symphysis pubis with 4 × 2.5-mm collimation, 120 kVp, and 100 mA s (effective). The table feed was 15 mm per 0.5 s of 4-scanner rotation (30 mm/s), resulting in a pitch of 1.5:1. From the raw data of the acquisition, 3-mm-thick transverse sections were reconstructed with 1.5-mm increments. Arterial, portal, and late phase acquisitions were performed with fixed scan delays of 35, 80, and 180 s after i.v. bolus injection (2.5 cc/s) of only 100 cc of non-ionic iodinated contrast media (Ultravist 370; Bayer, Berlin, Germany) followed by 200 cc of saline solution with a dualhead injector (Stellant Injection System, Medrad Inc., United States). CT images clearly depicted the liver lesions, which showed a moderate to marked enhancement in the arterial phase. However, there was increasing contrast enhancement of the lesions and a characteristic target-like appearance was evident during the portal and late phases (Fig. 4). No other abnormalities were found on CT examination. These CT findings were felt to be nonspecific, and could indicate a malignancy such as metastatic disease, hepatocellular carcinoma, peripheral cholangiocarcinoma, or a benign lesion such as hepatic abscess.

Finally, [18F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) was performed in order to confirm the presence of metastatic disease. Transmission data were acquired prior to injection. The fasting patient was then injected intravenously with 240 MBq 18 F-FDG and emission data were acquired 50 min later. PET images were visually compared with the corresponding CT images, using anatomic landmarks for localization. For quantitative analysis, a ROI was placed over the area of maximum activity in the lesions to generate an SUV. However, FDG-PET scan revealed no abnormal metabolic activity or hypermetabolism in the liver lesions.

Due to the discrepancy among the various imaging studies, we attempted ultrasound-guided percutaneous needle biopsy (FNAB). Histologically, the biopsy specimens contained macrophages with a foamy cytoplasm, multinucleated giant cells, and neutrophilic infiltration in a background of stroma composed of interlacing bundles of myofibroblasts and collagen bundles. Immunohistochemical studies showed staining for CD68-positive cells with a foamy shape. Positive staining for SMA, CD10, and CD34 was also evident, and IgG-positive plasma cells were abundantly observed. The surrounding liver parenchyma showed no evidence of cirrhosis. A final histopathological diagnosis of IPT-Fibrohistiocytic type was established.

CEUS examination was repeated after a month. Compared to the previous exam, CEUS depicted a lower hypervascularity in the arterial phase of the focal lesions, but still there was the same "hyper- to hypo-perfusion" pattern. Three months later, the patient was submitted to whole-body contrast-enhanced CT, which showed complete regression of the focal hepatic lesions (Fig. 5). The patient had not received any therapy during this time.

Discussion

IPT is a rare benign lesion that develops in an acute way. It is difficult to make a specific diagnosis based on laboratory or imaging findings because there is no specific laboratory marker or radiographic appearance. Therefore, most

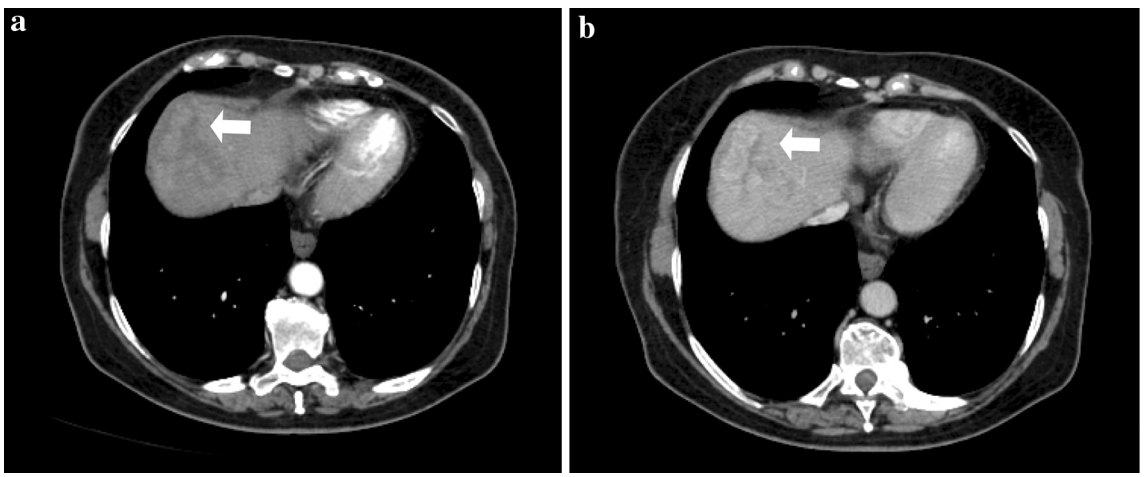

Fig. 4 Contrast-enhanced CT. **a** Arterial phase scan showing confluent, focal areas with moderate to marked enhancement (*arrows*). **b** Portal phase scan showing increasing contrast enhancement of the lesions (*arrows*). A characteristic target-like appearance was clearly evident in this phase. Images taken 33 s and 81 s after contrast injection

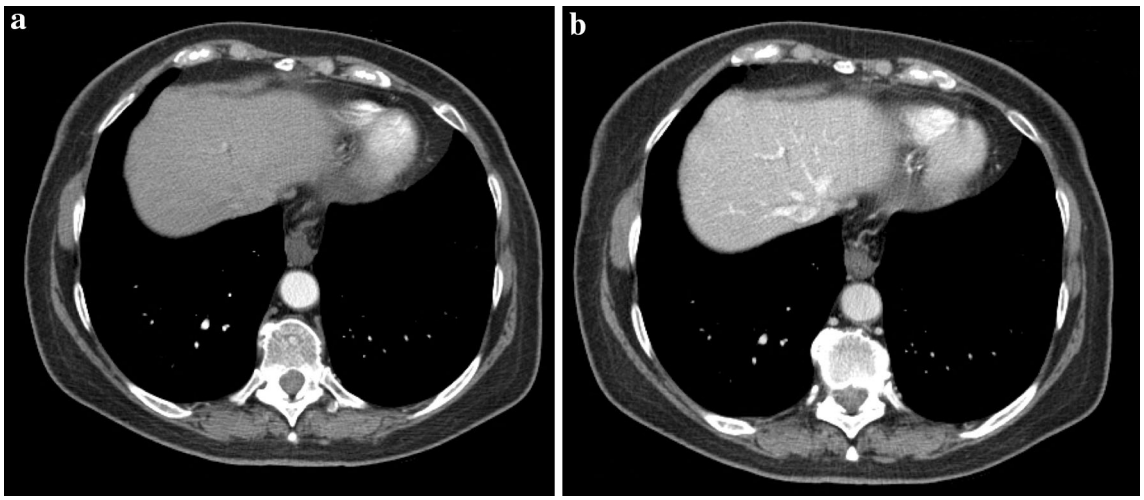

Fig. 5 Contrast-enhanced CT. **a**, **b** Arterial and portal phase 3 months later showed complete regression of the focal hepatic lesions without any therapy

reported cases of IPT of the liver were diagnosed after surgery [4]. Recently, ultrasonography-guided percutaneous liver biopsy has been reported to be more useful than CT or MRI [1].

According to the latest version of the international guidelines on CEUS [5], hypoenhancement of solid lesions in the late and portal phases corresponds to the wash-out phenomenon that characterizes malignancy. Almost all metastases show this enhancement feature, while less constant is their arterial enhancement pattern [6]. So a hypoperfused lesion in the portal phase has to be considered malignant until proven otherwise (positive predictive value 92–93 %) [7]. However, there are some exceptions: poorly vascularized benign lesions, such as necrotic-inflammatory lesions (focal eosinophilic hepatitis, hemorrhagic necrotic nodule, nodular tuberculosis), and some types of hepatocellular adenomas can be hypoperfused during the portal-sinusoidal phase, mimicking a malignant lesion [8]. Most listed lesions appear to be isoperfused or hypoperfused in the arterial phase, while in the case of adenomas, as well as in our case of IPT, there is an intense wash-in and a rapid, marked wash-out that may mislead for diagnostic purposes.

A study [9] of 36 cases of IPT diagnosed with CEUS showed a variety of enhancement patterns of hepatic inflammatory lesions, particularly in the arterial phase. A more constant CEUS behavior is displayed in the portal phase. This variety of enhancement patterns is due to the pathological changes in the course of disease progression.

In our clinical case, the CEUS behavior of the lesions strengthened the malignant diagnostic hypothesis much more than the contrast-enhanced CT and MRI findings. In fact, IPT presented as an enhancement defect in the portal phase, preceded by a rapid and homogeneous filling in the arterial phase. Only after biopsy and follow-up with CEUS and contrast-enhanced CT was it possible to make a specific diagnosis without surgery.

In most cases, CEUS allows us to distinguish malignant lesions from benign ones and also from pseudolesions, often providing information for an appropriate diagnosis, being more sensitive and specific than CT and MRI, which are not real-time diagnostic imaging techniques [6]. However, in radiological practice, there are some interpretative pitfalls to be considered. Although the guidelines suggest taking a kind of orientation in certain situations, the information yielded by CEUS should be framed and contextualized in a group of other satellite symptoms. In our experience, the lack of a primary cancer and the negativity of tumor markers should have led us to also consider an inflammatory nature.

In conclusion, automatic application of standard guidelines may sometimes lead to a misdiagnosis, while having a more critical attitude in borderline situations can help us avoid falling into insidious diagnostic pitfalls.

Conflict of interest Antonio Corvino, Benedetta Guarino, Orlando Catalano, Fabio Corvino, Alfonso Amore, and Antonella Petrillo declare that they have no conflict of interest.

Human rights statements and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.Informed consent was obtained from the patient for being included in the study.Written informed consent was obtained from the patient according to the Ethical Committee of our Institution.

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