Letter to the Editor

Ectopic hepatocellular carcinoma in the gallbladder

Da-Long Wan[1#], Chen-Guang Hua[1#], Xu Yang[2], Chen Hu[1], Qing-Hong Ke[1], Yan Shen[1]

[1]Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [2]Department of Pathology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Yan Shen, PhD. Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, No. 79 Qingchun Road, Hangzhou 310003, China. Email: Shenyan1965@163.com.

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Ectopic hepatocellular carcinoma (EHCC) is hepatocellular carcinoma (HCC) occurring in ectopic hepatic parenchyma (1). EHCC is a rare clinical entity, and preoperative diagnosis poses significant challenges (2). This study reports an unusual case of EHCC located on the serosa of the gallbladder, distinct from the liver.

A 40-year-old female was admitted to our hospital with a complaint of elevated alpha fetoprotein (AFP) levels in Oct 2022. Within a span of 3 months, the patient exhibited an elevation in her AFP level from 60 to 120 ng/mL, while carcinoembryonic antigen (CEA), carbohydrate antigens (CA) 125, CA 199, CA 153 remained within the normal range. The patient reported no discomfort, weight loss, fever or night sweats. She presented with an 8-year history of cholecystitis and experienced a dull pain in the right upper quadrant following consumption of greasy food, which demonstrated relief upon administration of levofloxacin and traditional Chinese medicine. Furthermore, she had a prolonged 40-year history of chronic hepatitis B infection without consistent adherence to antiviral therapy against the hepatitis B virus (HBV). The physical examination was normal. The hepatitis B surface antigen was 1,427.94 IU/mL and HBV-DNA was 1.36×10E2 IU/mL. The abdominal ultrasound revealed a solid lesion measuring 1 cm × 1 cm in close proximity to the hepatic fissure. The computed tomography arteriography (CTA, *Figure 1A,1B*) and magnetic resonance imaging (MRI) both revealed an exogenous nodule measuring approximately 1.6 cm in diameter in segment IV, projecting into the gallbladder fossa, suggestive of HCC.

Prior to the surgical procedure, liver three-dimensional visualization imaging examination was employed to further acquire detailed anatomical information of the patient's liver, as well as the shape and spatial distribution of the mass, facilitating precise determination of the surgical boundaries (*Figure 1C*). The surgical findings revealed a 1.5-cm yellow mass on the serosa of the gallbladder, while the liver exhibited normal morphology and texture (*Figure 1D*). No other enlarged lymph nodes or abnormal nodules were observed in the abdominal cavity. Resection of a partial of hepatic tissue, including the gallbladder, was subsequently performed.

Histologically, the mass exhibited moderate differentiation consistent with HCC, while the gallbladder showed chronic inflammation and cholesterol deposition (*Figure 1E*). The resected liver tissue displayed mild steatosis in hepatocytes, and no neoplastic or preneoplastic changes were identified in the neck of the gallbladder. Immunohistochemical analysis confirmed positive staining for hepatocyte (*Figure 1F*), arginase-1, glypican (GPC)-3, and P53 markers, further supporting the diagnosis of HCC. The postoperative course was uneventful. The serum AFP levels exhibited a decrease to 55.2 ng/mL within three days postoperative. Up to now, the patient was followed up for twenty-seven months without any signs of recurrence of HCC.

By conducting a comprehensive search on PubMed using the keywords "ectopic hepatocellular carcinoma" and "gallbladder", we identified five case reports of EHCC associated with the gallbladder (3-7). However, after full-text evaluation, three of these cases were not definitively located on the gallbladder. For instance, Leone *et al.* described a mass connected by a thin stalk to the liver, unrelated to the gallbladder, which was initially misdiagnosed as gallbladder carcinoma preoperatively (5). Similarly, Cheng *et al.* reported

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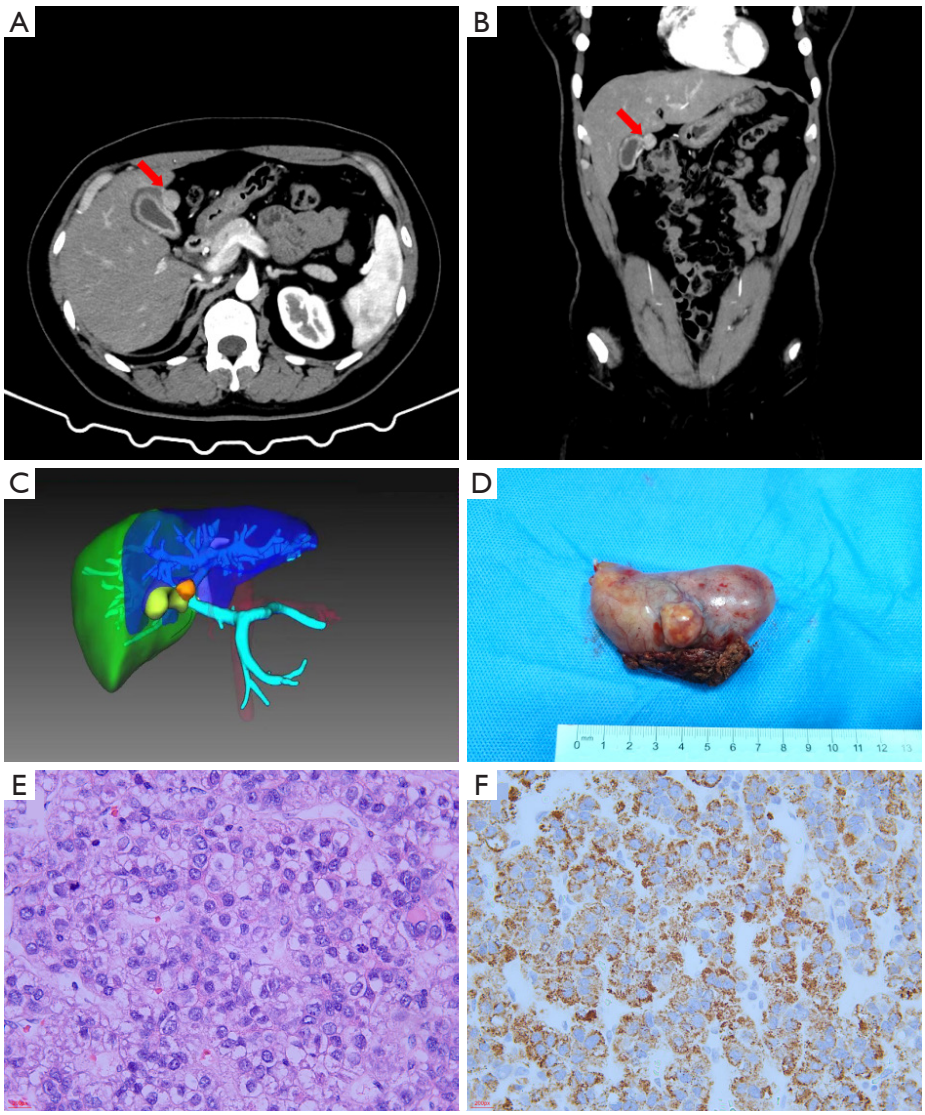

Figure 1 Imaging, macroscopic, and microscopic characteristics of the lesion. (A,B) The CTA revealed an exogenous nodule (red arrow) measuring approximately 1.6 cm in diameter in segment IV, projecting into the gallbladder fossa. The tumor (red arrow) exhibited arterial enhancement during the arterial phase. (C,D) Three-dimensional visualization imaging of the liver showed that the mass appeared to have originated from the gallbladder, with no evident vascular invasion in the surrounding area. The gross specimen revealed a yellow mass arising from the serosal layer of the gallbladder. (E,F) Histologically, the mass exhibited moderate differentiation HCC (hematoxylin and eosin stain, 400×). Immunohistochemical analysis confirmed positive staining for hepatocyte-specific markers (×400). CTA, computed tomography arteriography; HCC, hepatocellular carcinoma.

a case originating from the intrahepatic bile duct, extending secondarily to the gallbladder (3). Additionally, Ikeda *et al.* documented ectopic liver tissue on the gallbladder but not EHCC (4). Thus, previous review articles contained inaccuracies. Strictly speaking, only two reports have been documented where EHCC occurred exclusively within the gallbladder. In one case, a 12-cm polypoid mass was observed in the mucosal layer of the gallbladder in a female patient aged 49 years (7). Another case involved a patient with gallstones and cholecystitis, in whom a 1-cm HCC was incidentally discovered within the thickened gallbladder wall during pathological examination post-cholecystectomy (6). In contrast to these two cases, we encountered a patient with EHCC located on the serosa of the gallbladder.

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The anatomical location may suggest distinct etiological mechanisms. For example, EHCC on the gallbladder serosa could arise from ectopic liver tissue implanted during embryonic development, whereas intramural or mucosal EHCC might involve alternative pathways.

According to recent literature summarizing previously reported EHCC cases, the pancreas and diaphragm are the predominant sites for EHCC (2). This raises a critical question: Why is the gallbladder not the most common site for EHCC? Previous studies indicate that the gallbladder is the most common site for ectopic liver tissue due to its proximity to the liver during embryogenesis (8). Ectopic liver tissue is also reported to be more susceptible to HCC development (9). Paradoxically, one might expect the gallbladder to be the most common site for EHCC. We hypothesize that EHCC in the gallbladder is often incidentally detected during postoperative pathological analysis, leading to underreporting despite its relative prevalence among pathologists. To address this gap, we strongly encourage pathologists to publish additional data to improve the recognition and understanding of this disease.

Surgery is the most effective diagnostic and therapeutic approach for EHCC, with favorable prognoses observed in most patients (6). From a prognostic perspective, patients with EHCC typically exhibit a more favorable clinical prognosis and lower recurrence rates compared to those with conventional HCC (6). Surgical resection often achieves complete tumor excision. Our case aligns with this observation: the patient remains recurrence-free for 27 months post-resection of the gallbladder and adjacent hepatic tissue.

In conclusion, the precise etiology of EHCC warrants further investigation, and its rarity continues to pose diagnostic challenges preoperatively. Moreover, active surgical intervention often yields favorable outcomes for patients.

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Footnote

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