Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4357-24
Intern Med 64: 1321-1326, 2025
http://internmed.jp

【 CASE REPORT 】

Lymphangiosis Carcinomatosa of the Liver and Extrahepatic Bile Duct Due to Gastric Cancer: A Case Report and Literature Review

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Abstract:
A 78-year-old man was diagnosed with advanced poorly differentiated gastric adenocarcinoma, presenting with jaundice and diffuse thickening of the extrahepatic bile duct. No obstructive biliary sites or liver masses were observed. The serum concentrations of proteins induced by the absence of vitamin K or antagonist-II were markedly high. Samples of the extrahepatic bile duct and liver were obtained by endoscopic examination. The patient was diagnosed with lymphangiosis carcinomatosa of the liver and extrahepatic bile duct but died 28 days after hospitalization. As the disease progresses rapidly with uncharacteristic imaging findings, biopsy samples should be obtained early using several diagnostic tools.

Key words: biliary metastasis, endoscopic ultrasound-guided fine-needle biopsy, gastric cancer, liver metastasis, lymphangiosis carcinomatosa

(Intern Med 64: 1321-1326, 2025)
(DOI: 10.2169/internalmedicine.4357-24)

Introduction

Lymphangiosis carcinomatosa of the liver is a rare metastatic manifestation characterized by diffuse lymphangitic spread of tumor cells in portal areas without mass formation (1). Tumor cells usually spread from the hepatic hilum to the peripheral liver through the lymphatics at the portal areas; however, changes in the extrahepatic bile duct have not been well elucidated. Lymphangiosis carcinomatosa of the liver was observed in 4% of 250 autopsied cases with liver metastasis, and gastric cancer was observed in 8 cases (2). The gross findings of the autopsies were linear tumors radiating along the portal areas from the hepatic hilum to the peripheral liver (2). Microscopically, the linear lesions were composed of large amounts of tumor emboli that filled the dilated lymphatics, which compressed or obliterated the portal vein, biliary duct, and hepatic artery (2, 3). The diagnosis of lymphangiosis carcinomatosa before death is challenging because of its rarity, rapid progression, and lack of characteristic imaging findings. To demonstrate the effectiveness of endoscopic examination, we herein report the case of a patient with gastric cancer and lymphangiosis carcinomatosa of the liver and extrahepatic bile duct who presented with elevated serum protein induced by vitamin K absence or antagonist-II (PIVKA-II), and who was diagnosed using biopsy samples.

Case Report

A 78-year-old man was referred to our department because of anemia. He was prescribed medications for atrial fibrillation, chronic heart failure, hypertension, and diabetes mellitus (DM). With the exception of the patient's hemoglobin level (9.9 g/dL), his laboratory data were almost normal. Esophagogastroduodenoscopy revealed a type 3 tumor in the posterior wall of the lower gastric body (Fig. 1a). The background gastric mucosa showed complete atrophy and increased mucus production, suggesting a *Helicobacter pylori* infection. A pathological analysis revealed poorly differenti-

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Received: July 2, 2024; Accepted: August 1, 2024; Advance Publication by J-STAGE: September 18, 2024
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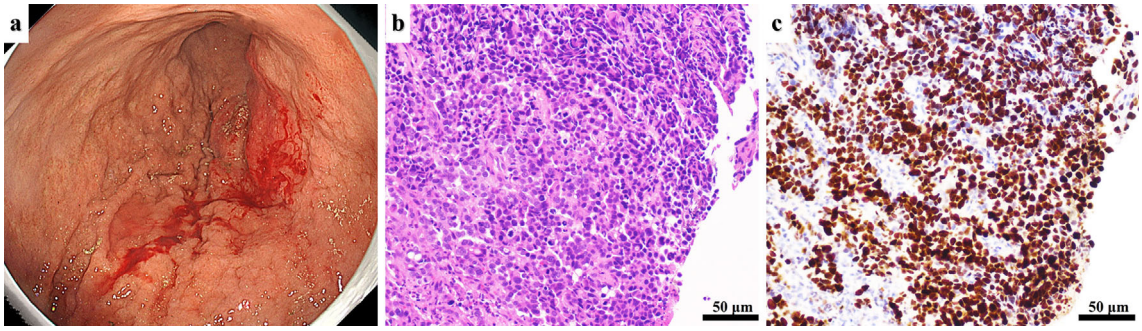

Figure 1. Endoscopic and pathological findings of the primary gastric cancer. Esophagogastroduodenoscopy shows a type 3 tumor at the posterior wall of the lower gastric body (a). A pathological analysis reveals a poorly differentiated adenocarcinoma (b). The tumor cells showed a markedly high Ki-67 labeling index (80-90%) (c).

ated adenocarcinoma. The immunohistochemistry score for human epidermal growth factor receptor 2 was 1+, and a markedly high Ki-67 labeling index (80-90%) was observed in the tumor cells (Fig. 1b, c). Contrast-enhanced computed tomography (CECT) revealed enlarged regional and para-aortic lymph nodes and intraperitoneal nodules, indicating peritoneal dissemination of the tumor. No abnormal imaging findings in the liver or biliary tract were observed. We proposed the induction of systemic chemotherapy because of the advanced stage of gastric cancer; however, the patient requested a second opinion. As the second opinion was similar to ours, the patient was admitted to our hospital for systemic chemotherapy 2 months after the initial diagnosis. On admission the patient complained of general fatigue and jaundice. Hematological tests revealed nearly normal levels. The patient's biochemical data were as follows: serum albumin, 3.1 g/dL; total bilirubin, 4.6 mg/dL; aspartate aminotransferase, 252 U/L; alanine aminotransferase, 393 U/L; alkaline phosphatase, 944 U/L; and gamma glutamyl transpeptidase, 754 U/L. The prothrombin activity decreased by 49%. Hepatitis virus markers were negative. The following tumor markers were elevated: carbohydrate antigen 19-9, 441.7 U/mL; PIVKA-II, 47,700 mAU/mL; carcinoembryonic antigen, 2.9 ng/mL; and alpha fetoprotein, 2.4 ng/mL. Immunological markers, including antinuclear antibodies, antimitochondrial antibodies, immunoglobulin G4, and myeloperoxidase antineutrophil cytoplasmic antibodies, were within the normal levels. Ultrasonography revealed a homogenous texture of the hepatic parenchyma and a diffuse ill-defined hyperechoic area around the vessels and bile duct. No hepatic masses were observed (Fig. 2a). A second CECT scan revealed progressive ascites, and a periportal collar sign and narrowed intrahepatic portal vein were newly detected (Fig. 2b, c). No findings were suggestive of tumor emboli in the hepatic artery or portal vein. The walls of the extrahepatic bile duct, including the gallbladder, thickened owing to the contrast effects (Fig. 2d, e). Enlarged lymph nodes were detected in the hepatic hilum, para-aortic area, and around the superior mesenteric artery (Fig. 2f). Magnetic resonance imaging revealed diffuse thickening of the extrahepatic bile ducts, consistent with the CT findings. Diffusion-weighted imaging revealed hyperintense changes in both the extrahepatic bile duct and the periportal area of the liver (Fig. 2g, h). The gastric tumor had increased in size, although it was not adjacent to the bile duct. Endoscopic ultrasonography (EUS) demonstrated diffuse and marked homogeneous thickening of the extrahepatic bile duct, including the gallbladder and illegible lumen, without an apparent obstructive lesion (Fig. 3a-c). Subsequently, EUS-guided fine-needle biopsy (EUS-FNB) of segment 3 of the liver was performed using a 22-gauge needle (Trident, Century Medical, Tokyo, Japan) (Fig. 3d). Endoscopic retrograde cholangiography (ERC) revealed an overall narrowing with smooth surfaces and mild caliber variation of the intra- and extrahepatic bile ducts (Fig. 3e). As no apparent bile duct obstruction was observed, we did not place a biliary stent and performed a transpapillary biopsy of the extrahepatic bile duct.

The hepatic pathology showed solid and funicular proliferation of tumor cells in the portal areas but not in the liver parenchyma or sinusoids (Fig. 4a, b). In the portal areas, tumor cells proliferated with an ill-defined glandular structure and cytoplasmic vacuolization, and compressed the bile duct with reactive epithelial atypia, suggesting peripheral bile duct injury (Fig. 4c). The portal and hepatic arteries were obscured. A biopsy of the extrahepatic bile duct confirmed that the tumor cells had proliferated in the submucosal layer, with edematous changes and reactive epithelial atypia in the bile duct (Fig. 4d). The tumor cells were suggestive of poorly differentiated adenocarcinoma. The cells were partially positive for alcian blue, positive for keratin 7 (K7), and negative for K20 and hepatocyte paraffin 1, presenting the same pattern as primary gastric cancer (Fig. 4e). Based on the characteristic tumor cell infiltration in the portal areas and immunohistochemical analysis, the patient was diagnosed with lymphangiosis cacrinomatosa of the liver and extrahepatic bile duct due to gastric cancer. We initiated administration of ursodeoxycholic acid (600 mg/day) on hospital day 9. Despite the treatment, the patient's general condition and jaundice worsened. A CT scan performed 17 days

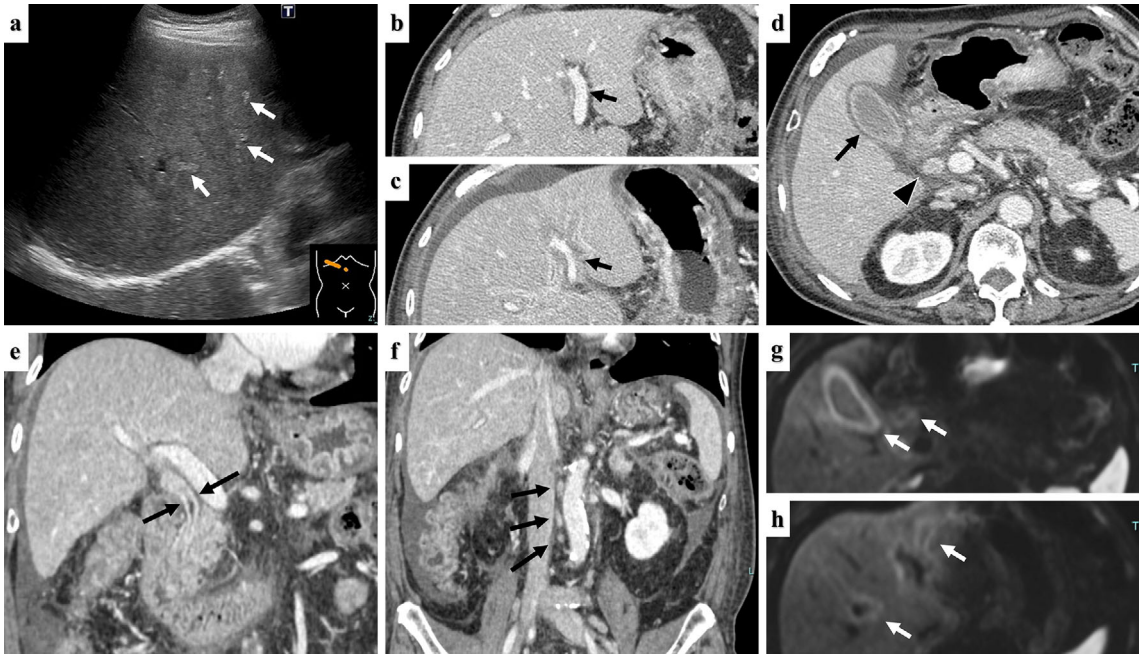

Figure 2. **Radiological findings of the present case. Ultrasonography showed a homogenous texture of the hepatic parenchyma and a diffuse, ill-defined hyperechoic area (arrows) around the vessels and bile duct without hepatic masses (a). Contrast-enhanced computed tomography at the initial diagnosis showed a normal left branch of the portal vein (arrow) (b), and a narrow portal vein with a periportal collar sign (arrow) and ascites after 2 months (c). The walls of the extrahepatic bile duct (arrowhead), including the gallbladder (arrow), were thickened with a contrast effect (d). Bile duct thickening was consecutively observed next to the major papilla (arrows) (e). Enlargement of the para-aortic lymph nodes was observed (arrows) (f). Magnetic resonance imaging revealed hyperintense changes in the extrahepatic bile duct and gallbladder (arrows) (g), and the periportal area of the liver (arrows) (h) on diffusion-weighted imaging.**

after hospitalization revealed liver atrophy and increased ascites without bile duct obstruction. The patient was comatose on day 20 of hospitalization. We abandoned the treatment and transitioned to palliative care. The patient died of liver failure on the 28th day of hospitalization.

Discussion

In the present case, the patient presented with severe jaundice, elevated biliary enzyme levels, and a periportal collar sign with a diffuse contrast effect of the extrahepatic bile duct. Because obstruction or dilatation of the bile duct was not observed, we considered cancer-related cholestatic diseases, including sclerosing cholangitis (SC) and diffuse bile duct metastasis.

Initially, we assumed that the patient had SC. In comparison to typical SC, our endoscopic findings showed: (1) marked widening of the extrahepatic bile duct wall on EUS and (2) overall narrowing with smooth surfaces and mild caliber variation of the bile duct on ERC. As no apparent obstructive site was observed on EUS, and diffuse injury of the intra- and extrahepatic bile ducts was suspected, we subsequently performed EUS-FNB of the liver. Ascites located on the surface of the liver complicates percutaneous liver biopsy. Therefore, a transjugular or laparoscopic liver biopsy may be useful in such cases (4). Hepatic tissue was acquired by an EUS-FNB due to the lower volume of ascites between the stomach and segment 3 of the liver and because the scope angle enabled space elimination. The utility and safety of an EUS-FNB of the liver in patients with ascites have been reported (5, 6). To obtain adequate and optimal liver tissue for an EUS-FNB, a 19-gauge FNB needle has recently been recommended (7). However, we selected a 22-gauge FNB needle, considering the risk of hemorrhage due to the patient's low prothrombin activity and ascites.

Gastric cancer can cause intraductal metastasis to the bile duct, leading to obstructive jaundice (8, 9), and patients may require biliary drainage or bile duct reconstruction. The prognosis of patients who undergo surgical treatment for localized biliary obstruction is usually favorable (9). In the present case, tumor cells infiltrated the portal areas, compressed the bile duct, and infiltrated diffusely into the submucosal layer of the extrahepatic bile duct. Lymphadenopathy in patients with extrahepatic bile duct cancer is usually observed (1) along the common hepatic artery predominantly over the retro-pancreatic area, (2) around the superior mesenteric artery, (3) around the head of the pancreas, and (4) in the para-aortic area (10). In the present case, lympha-

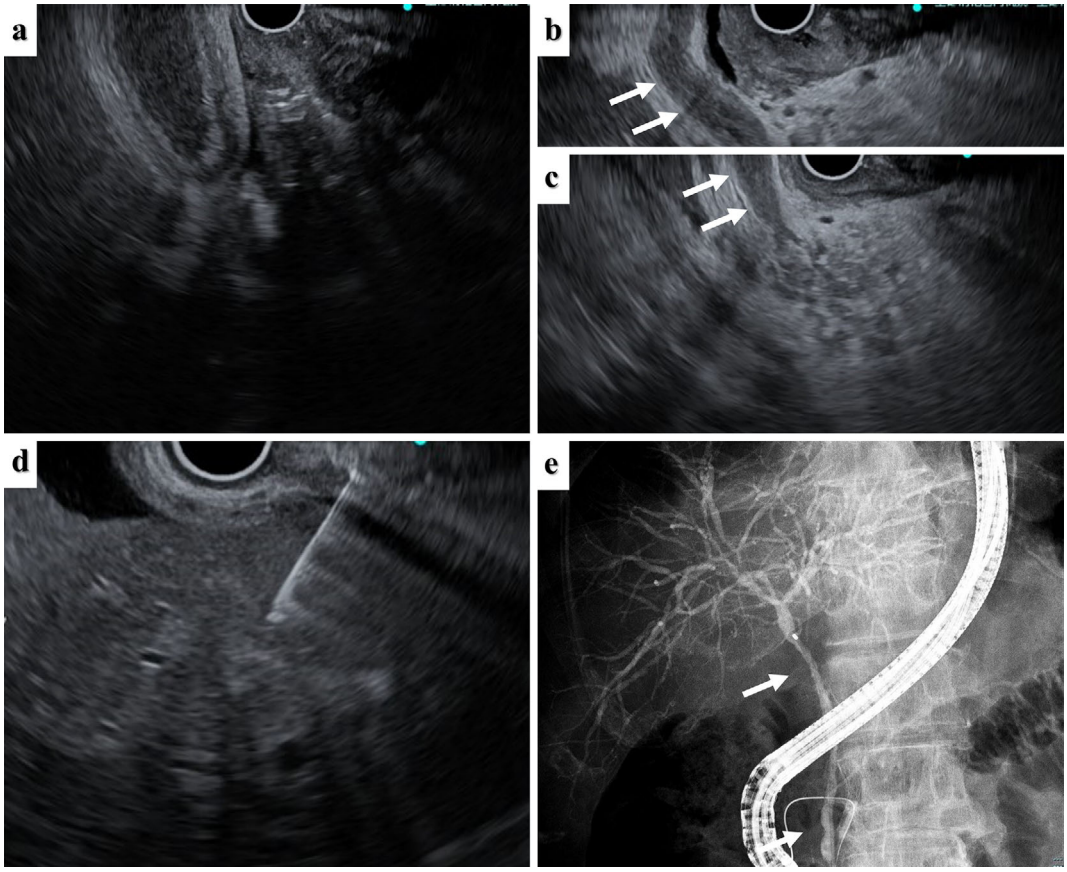

Figure 3. **Endoscopic findings in the present case. Endoscopic ultrasonography (EUS) demonstrated diffuse marked homogeneous thickening of the gallbladder wall (a). The perihilar extrahepatic bile duct (arrows) (b) and distal bile duct (arrows) (c) also showed diffuse marked homogenous thickening with an indistinct lumen. An EUS-guided fine-needle biopsy of segment 3 of the liver (d). Endoscopic retrograde cholangiography showed a narrow, smooth-surfaced bile duct with mild caliber variation in both the intra- and extrahepatic regions (arrows) (e).**

denopathy was observed in the hepatic hilum, around the superior mesenteric artery and in the para-aortic area. Tumor cells might have spread retrogradely from these lymph nodes to the submucosal layer of the extrahepatic bile duct and subsequently from the hepatic hilum to the peripheral liver along the portal area. The presence of lymph vessels in the submucosal layer of the extrahepatic bile duct has been pathologically proven and identified as a pathway for the spread of tumor cells (11). Moreover, intrahepatic lymph vessels in the portal areas can be interconnected with the submucosal lymph vessels of the extrahepatic bile duct. As the metastatic routes have not been fully elucidated, further research in these cases is required.

We have summarized the reports of lymphangiosis carcinomatosa of the liver in Table (12-14). Few reports have described a successful diagnosis of the disease before death because of its poor prognosis. Liver failure or related syndromes were the major cause of death. Gastric cancer is the primary condition and often has a poorly differentiated histology (2). This could be because poorly differentiated cancer cells have weak adhesiveness and cohesiveness, enabling their dissemination into the peripheral lymphatics (2). Furthermore, lymphangiosis carcinomatosa of the liver occurs in patients with progressive lymph node metastasis. The Ki-67 labeling index of the tumor cells was remarkably high in the present case (80-90%). The overexpression of Ki-67 is significantly correlated with lymph node metastasis and the prognosis of gastric cancer, indicating high tumor cell proliferative activity (15). Although Ki-67 staining of tumor cells was not performed in previous cases, lymphangiosis carcinomatosa of the liver may occur in patients with gastric cancer and the marked overexpression of Ki-67. When encountering patients with poorly differentiated gastric cancer presenting with severe jaundice and multiple lymph node metastases without a liver mass or bile obstruction, lymphangiosis carcinomatosa should be considered. Systemic chemotherapy may be a fundamental treatment option for this disease. There is a report of a patient who survived for 14 months with systemic chemotherapy (14); therefore, the early recognition of the disease at the onset of slight jaundice and liver dysfunction is crucial.

In the present case, a marked elevation in the patient's serum PIVKA-II concentration was observed. Although obstructive jaundice induces this phenomenon, tumor cells may produce high concentrations of PIVKA-II. PIVKA-II-producing gastric cancer tends to metastasize to the liver

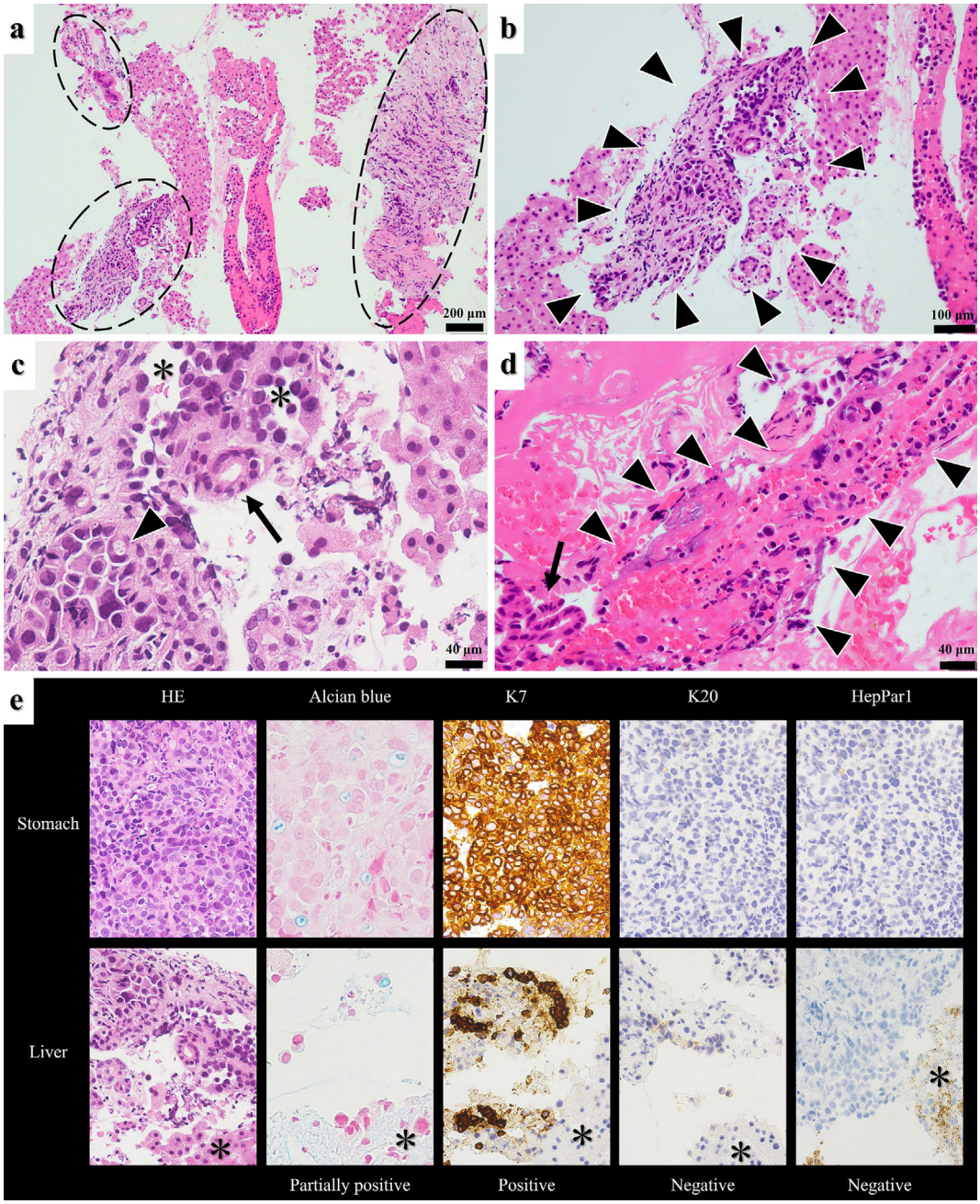

Figure 4. **Pathological findings in the present case. Hematoxylin and Eosin (H&E) staining of the liver showed the involvement of certain portal areas (dotted circles) (a). Solid and funicular proliferation of the tumor cells was observed in the portal areas (arrowheads) but not in the liver parenchyma or sinusoids (b). Within the portal areas, tumor cells proliferated with an ill-defined glandular structure (*) and exhibited cytoplasmic vacuolization (arrowhead), compressing the bile duct with reactive epithelial atypia (arrow), suggesting peripheral bile duct injury (c). A biopsy of the extrahepatic bile duct confirmed the proliferation of tumor cells in the submucosal layer with edematous changes (arrowheads) and reactive epithelial atypia of the bile duct (arrow) (d). The tumor cells adjacent to the normal liver (*) showed similarities to the cells of the stomach in H&E staining. They were partially positive for Alcian blue, positive for keratin 7 (K7), negative for K20, and negative for hepatocyte paraffin 1 (HepPar1), presenting a pattern similar to that of primary gastric cancer (e).**

with mass formation and lymphovascular invasion, and its prognosis is poor in comparison to non-PIVKA-II-producing gastric cancer (16). We could not perform PIVKA-II immunohistochemical staining of the tumor cells; however, marked elevation of the serum PIVKA-II concentration may be an indicator of lymphangiosis carcinomatosa in the liver.

Tumor infiltration in the lymphatics could not be detected, irrespective of D2-40 staining, in both the liver and extrahepatic bile duct. Most lymphangiosis carcinomatosa of the liver is diagnosed using hepatic hilar samples from autop-

Table. **Case Series of Liver Lymphangiosis Carcinomatosa.**

Reference	Age/Sex	Primary disease Histological type	Lymph node metastasis	Hepatobiliary image findings	Pathological diagnosis	Treatment Prognosis/cause
[12]	64/F	Gallbladder AC	Periportal juxtapancreatic	Periportal collar homogenous opacification of hepatic parenchyma focal thickness of the gallbladder neck	Liver biopsy and autopsy	BSC 32 days/hepatorenal failure
[13]	38/F	Gastric AC Scirrhous	Localized (unknown)	None	Autopsy	None 36 hours/pulmonary hypertension
[14]	68/M	Gastric AC Mucinous	Regional para-aortic	Periportal collar periportal branching calcification	None	Chemotherapy 14 months/liver failure
Our case	78/M	Gastric AC Poorly	Hepatic hilar SMA para-aortic	Periportal collar homogenous opacification of hepatic parenchyma narrowed portal vein diffuse thickness of the extrahepatic bile ducts	Liver and bile duct biopsy	BSC 28 days/liver failure

AC: adenocarcinoma, BSC: best supportive care, SMA: superior mesenteric artery

sies, which show thrombi of carcinoma cells within dilated lymphatics (2). Although the lymphatic structure may be difficult to recognize in the peripheral liver samples acquired as in the present case, localized carcinoma cell infiltration around the portal areas is characteristic of lymphangiosis carcinomatosa.

In conclusion, gastric cancer can lead to lymphangiotic carcinomatosa in the liver and extrahepatic bile ducts. This condition should be considered when patients with malignancies present with severe jaundice and multiple lymph node metastases. A liver biopsy guided by the serum PIVKA-II level should be performed even in the absence of liver masses. Both EUS and EUS-FNB are effective diagnostic tools for identifying lymphangiosis-related carcinomatosa.

The authors state that they have no Conflict of Interest (COI).

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