Primary Hepatic Adenosquamous Carcinoma Associated with Primary Sclerosing Cholangitis

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Keywords

Adenosquamous carcinoma · Primary sclerosing cholangitis · Liver tumor · Cholangiocarcinoma · Liver abscess · Ulcerative colitis

Abstract

Introduction: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disorder characterized by multiple fibrotic strictures of the bile duct. More than 40% of deaths in PSC patients are related to malignant tumors, including cholangiocarcinoma. Primary hepatic adenosquamous carcinoma (ASC) is a rare subtype of cholangiocarcinoma containing adenocarcinoma (AC) and squamous cell carcinoma (SCC) components, with a poorer prognosis than other cholangiocarcinomas. We report the first case of a hepatic ASC in a patient with PSC. **Case Report:** A 28-year-old man was referred for diagnosis and treatment of a liver abscess suspected by contrast-enhanced computed tomography (CE-CT). He had a history of ulcerative colitis and PSC. Abdominal CE-CT revealed a 60-mm-diameter ring-shaped mass with central necrosis in the left lobe. Magnetic resonance imaging demonstrated a poorly circumscribed low-signal-

intensity mass in T1-weighted imaging and a high-signal-intensity mass with a scattered low-signal-intensity area in T2-weighted imaging. Abdominal ultrasonography showed a hypoechoic component with a diffuse hyperechoic area in the tumor. Ultrasound-guided biopsy and histological examination showed tumor cells with both squamous and glandular differentiation. Left lobectomy was performed. Microscopic examination revealed 2 components, including moderately differentiated AC and well-differentiated SCC. The final diagnosis was hepatic ASC. **Conclusion:** This is the first reported case of hepatic ASC in a patient with PSC. Patients with PSC should be recognized as being at a risk of not only general cholangiocarcinoma, hepatocellular carcinoma, and metastatic liver tumor, but also ASC.

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Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disorder characterized by multiple fibrotic strictures of the intra- and extrahepatic biliary tree. Previous studies have shown that >40% of deaths in patients

Fig. 1. **a** Contrast-enhanced abdominal computed tomography. A mass 62 × 45 cm in diameter showing a low-density tumor with an irregularly enhanced rim in the left lobe. **b** Magnetic resonance imaging. T1-weighted image demonstrated a poorly circumscribed low-signal-intensity mass. **c** T2-weighted image demonstrated a high-signal-intensity mass with a scattered low-signal-intensity area in the left lobe. **d** Ultrasonography showed a hypoechoic component with a diffuse hyperechoic area in the tumor. **e** Contrast-enhanced ultrasonography showed an avascular area in the tumor.

with PSC are related to cholangiocarcinoma, gallbladder carcinoma, or colorectal carcinoma [1, 2]. Cholangiocarcinoma is the most relevant of these, with a lifetime risk in PSC patients of around 7–14% and a prognosis including a 5-year survival of <10% [2].

Primary hepatic adenosquamous carcinoma (ASC) is defined as a rare subtype of cholangiocarcinoma, accounting for 2–3% of cholangiocarcinomas [3–5]. ASC contains both adenocarcinoma (AC) and squamous cell carcinoma (SCC) components, tends to present more aggressive clinicopathologic features, and has a poorer prognosis than other cholangiocarcinomas [6, 7]. Barr and Hancock [8] first reported a case of primary hepatic

ASC in 1975, since when several cases of histologically defined primary hepatic ASC have been reported in the literature [3, 9–12]; however, none have been reported in patients with PSC. We herein report the first case of hepatic ASC in a patient with PSC.

Case Report

A 28-year-old man was referred for diagnosis and treatment of a liver abscess suspected by abdominal contrast-enhanced computed tomography (CT). The patient's chief complaints were fever and epigastric pain. He was a nonsmoker and had no history of alcohol abuse. He had a 10-year history of ulcerative colitis and a

Fig. 2. **a** AC; HE stain. **b** Immunostaining for carcinoembryonic antigen revealed cytoplasm-positive staining for AC. **c** SCC; HE stain. **d** Immunostaining for cytokeratin 5/6 revealed cytoplasm-positive staining for SCC. AC, adenocarcinoma; HE, hematoxylin and eosin; SCC, squamous cell carcinoma.

3-year history of PSC. Endoscopic biliary drainage was performed regularly to exchange the biliary stent in the left bile duct with the stenosis due to PSC.

The results of relevant laboratory studies were total bilirubin 3.4 mg/dL (normal 0.3–1.2 mg/dL), aspartate transaminase 72 IU/L (normal 13–33 IU/L), alanine transaminase 56 IU/L (normal 8–42 IU/L), alkaline phosphatase 1,554 U/L (normal 106–322 U/L), albumin 2.9 g/dL (normal 4.1–5.1 g/dL), C-reactive protein 8.07 mg/dL (normal 0–0.14 mg/dL), white blood cells 16,800/mL (normal 2,800–9,200/mL), prothrombin time international normalized ratio 1.32, indocyanine green retention rate at 15 min 26.0% (normal 0–10%), carcinoembryonic antigen 6.1 ng/mL (normal <5.0 ng/mL), carbohydrate antigen 19–9,290 U/mL (normal <37 U/mL), and SCC antigen 5.1 ng/mL (0–1.5 ng/mL). The patient tested negative for hepatitis B viral surface antigen and hepatitis C viral antibody.

Abdominal contrast-enhanced CT showed an enhanced ring-shaped mass measuring 62 × 45 mm in diameter with central necrosis in the left lobe (Fig. 1a). Magnetic resonance imaging demonstrated a poorly circumscribed low-signal-intensity mass in T1-weighted images (Fig. 1b) and a high-signal-intensity mass with a scattered low-signal intensity area in T2-weighted images (Fig. 1c). Positron emission tomography showed increased ¹⁸F-fluorodeoxyglucose uptake (maximum standardized uptake value: 9.59) in the tumor. These findings, especially the inflammatory reaction, led to suspicion of a liver abscess, but increasing tumor markers indicated a malignant liver tumor.

Abdominal ultrasonography showed a hypoechoic mass with a partial hyperechoic area (Fig. 1d), and contrast-enhanced ultrasonography showed a heterogeneous hypoechoic tumor with a partially avascular area (Fig. 1e). Ultrasonography-guided biopsy was performed, and histological examination revealed tumor cells with both squamous and glandular differentiation. The diagnosis was ASC.

Left lobectomy was performed. The cut surface of the resection specimen showed a yellowish-white solid tumor, measuring 65 × 55 × 45 mm, with partial necrosis. Microscopic examination revealed 2 components, including moderately differentiated AC (Fig. 2a) and well-differentiated SCC (Fig. 2b). The SCC component was predominant over the AC component and occupied >80% of the tumor. There was also a transitional area between the 2 components. Immunohistochemistry revealed carcinoembryonic antigen and cytokeratin 7 expression in most glandular and transitional epithelia (Fig. 2c), but no expression in the stratified squamous epithelia, whereas cytokeratin 5/6 was expressed in most of the SCC (Fig. 2d). A final diagnosis of hepatic ASC was made on the basis of the histological and immunohistochemical findings. Periductal concentric fibrosis of the bile ducts (onion skin-like appearance) suggested the presence of PSC (Fig. 3).

Recurrence was detected in the liver by follow-up examination 1 month postoperatively, and the patient died of ASC recurrence 2 months after surgery.

Discussion

PSC is a chronic inflammatory liver disease of unknown etiology, primarily targeting cholangiocytes at any portion of the biliary tree. Liver transplantation is currently the only effective treatment. PSC shows a close association with inflammatory bowel disease, mainly ulcerative colitis. As in many chronic inflammatory conditions, PSC may be complicated by cancer development, which accounts for >40% of deaths in patients with PSC

Fig. 3. Periductal concentric fibrosis of the bile ducts was present (onion skin-like appearance).

[1, 2, 13]. Cholangiocarcinoma, gallbladder carcinoma, and colorectal carcinoma have been variably associated with PSC, with prevalences of up to 13–14% [14].

ASC is a rare subtype of cholangiocarcinoma with more aggressive clinical and pathological features than other cholangiocarcinomas, and the prognosis of patients with hepatic ASC is extremely poor. Kobayashi et al. [6] reported a mean survival time for patients with hepatic ASC of 8.7 months, and the overall 1-, 2-, and 3-year survival rates after surgery were 38.5, 16.2, and 10.8%, respectively. Uenishi et al. [15] reported a 1-year survival rate for intrahepatic cholangiocarcinoma of 68%, indicating that the prognosis of patients with primary hepatic ASC was poorer than that of patients with the common type of hepatic cholangiocarcinoma.

Chronic inflammation of the biliary tree is thought to be caused by PSC, congenital biliary abnormalities, and hepatolithiasis. The pathogenesis of ASC is still unclear, but it may be caused by continuous irritation of the bile ducts by chronic inflammation or associated with congenital cysts of the biliary tract [16]. Barr and Hancock [8] and Hamaya et al. [17] found no normal epithelium in the tumors they observed, which contained only AC, AC metaplasia, and SCC components, leading them to suggest that ASC may arise from squamous metaplasia of AC cells. In the present case, recurrent acute inflammation due to PSC and/or retrograde cholangitis due to placement of the biliary stent initially led to chronic inflammation, which may then have been responsible for metaplastic changes in the biliary epithelium. The AC component was, therefore, located near the intrahepatic bile duct and was surrounded by the SCC component, with a transitional area between the 2 components.

Liver tumors in patients with PSC include cholangiocarcinoma, hepatocellular carcinoma, metastatic liver tu-

mor, and liver abscess [18, 19]. Imaging of the tumor as a low-density lesion surrounded by a highly enhanced rim on CT may resemble the findings for cholangiocarcinoma, metastatic liver disease, and liver abscess. ASC is a rare subtype of cholangiocarcinoma, and an accurate pre-biopsy diagnosis by radiological imaging was difficult in this case. However, echo-guided ultrasound biopsy was useful for diagnosis, and echo-enhanced tissue sampling enabled biopsy of the optimal part of the tumor, avoiding the necrotic area.

In conclusion, this is the first report describing resection of a hepatic ASC in a patient with PSC. Patients with PSC should be recognized as being at risk of hepatic ASC, in addition to general cholangiocarcinoma, hepatocellular carcinoma, and metastatic liver tumor.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report.

Disclosure Statement

The authors declare that they have no competing interests.

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Author Contributions

K.Y. drafted the manuscript. A.N., S.O., K.K., K.M., and T.M. worked on clinical data acquisition. H.I. contributed to the treatment of the patient. M.T., I.M., Y.T., and M.K. revised the manuscript critically for important intellectual content. T.C. performed the pathological analysis. All authors read and approved the final manuscript.

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