CASE REPORT

Poorly Differentiated Gastric Adenocarcinoma Can Mimic Hilar Cholangiocarcinoma

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Abstract

This report describes two cases with obstructive jaundice caused by poorly differentiated gastric adenocarcinoma. Computed tomography scans showed circumferential stenosis in the hilar bile ducts. Endoscopic retrograde cholangiopancreatography showed dilatation of the bilateral hepatic ducts and stenosis of the common hepatic ducts from the bifurcation of the bilateral hepatic ducts. The first diagnoses were hilar cholangiocarcinoma and biliary drainage decreased serum bilirubin; however, both patients died of cancer within a short period of time. Autopsies revealed lymphatic vessel invasion and possible subepithelial invasion by gastric adenocarcinoma into the hilar bile ducts. A differential diagnosis should thus be required in suspected cases of hilar cholangiocarcinoma.

Key words: obstructive jaundice, gastric poorly differentiated adenocarcinoma, subepithelial lymphangitic infiltration, hilar bile duct


Introduction

Primary gastric cancer is one of the most common malignant neoplasms in East Asian countries including Japan (1). The progression of gastric cancer induces various signs and symptoms including obstructive jaundice, which is a debilitating complication that can result in recurrent sepsis. The most commonly observed site of biliary obstruction is in the vicinity of the cystic duct (2). Several causes of extrahepatic biliary duct obstruction have been found, including gallbladder stones, tumor thrombosis, metastasis to hepatoduodenal (#12a, 12b, 12p) or pancreaticoduodenal lymph nodes (LNs) (3), and direct neoplastic invasion from the primary tumor or recurrent malignancies in the stomach. There are few reports of the occurrence of the latter mechanism (4).

Primary hilar cholangiocarcinoma and gallbladder carcinoma with hilar invasion are considered to be the primary causes of severe stenosis of the common bile duct (CBD) extending to the bifurcation of the right hepatic duct (RHD) and the left hepatic duct (LHD). Kumar et al. (5) reviewed case studies between 1996 and 2012 in which malignancies including gallbladder carcinoma and benign conditions like primary sclerosing cholangitis (PSC) mimicked hilar cholangiocarcinoma. Metastatic gastric carcinoma cases were probably not included in their study because of the difficulty in making a differential diagnosis in cases of cholangiocarcinoma, especially in patients who have localized biliary stenosis in the hepatic hilar region. A correct diagnosis is more important in Western countries than in East Asian countries for patients with PSC because it is the most common disease associated with cholangiocarcinoma, which commonly induces chronic inflammation in men (6).

One report presented a Japanese man with obstructive jaundice caused by extrahepatic bile duct metastasis of signet-ring carcinoma that originated from a primary stomach tumor rather than through compression of the bile duct by lymphadenopathy (4). He had circumferential stenosis with an irregular wall in the lower bile duct and no swelling of the LNs that compressed the bile duct. These observations suggested a diagnosis of primary cholangiocarcinoma, although metastatic gastric cancer was finally diagnosed in an autopsy. Therefore, physicians need to be alert to the possibility of metastatic poorly differentiated gastric adenocarcinoma.
canceroma if they are unsure of a diagnosis of primary bile duct carcinoma.

This report describes two uncommon cases of obstructive jaundice by subepithelial lymphangitic infiltration of poorly differentiated gastric adenocarcinoma cells to the hilar bile duct, with novel findings.

Case Reports

Case 1

An 88-year-old Japanese woman was admitted to hospital in May 2007 with jaundice, eructation and nausea after meals. In addition, she had hypertension, hyperlipidemia and senile dementia, but did not have any previous malignancies. The laboratory data on admission indicated an abnormally high level of the tumor marker carbohydrate antigen 19-9 (CA19-9) and elevated hepatobiliary biomarkers including total bilirubin (T-Bil), direct bilirubin (D-Bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, γ-glutamyl transpeptidase (γ-GTP), C-reactive protein, white blood cell, hemoglobin, carcinoembryonic antigen (CEA), and tumor marker carbohydrate antigen 19-9 (CA19-9) greater than 37 U/mL were considered positive.

In both cases, contrast-enhanced abdominal computed tomography (CT) scans revealed greatly thickened CBDs (Fig. 1). In addition, endoscopic retrograde cholangiopancreatography (ERCP) showed the presence of marked dilatation of the right hepatic duct (RHD) and the left hepatic duct (LHD) and luminal narrowing in the hilar portion of both the RHD and the LHD (Fig. 2). No bile duct biopsy or biliary cytology was carried out during the ERCP. Moreover, the serum levels of T-Bil (D-Bil was superior to indirect bilirubin) and CA19-9 were highly elevated. These findings suggested that the obstructive jaundice was due to primary or metastatic bile duct carcinoma. As a result, hilar cholangiocarcinoma was initially diagnosed in both patients who underwent endoscopic biliary drainage (EBD) to alleviate their jaundice. In Case 1, we initially performed EBD for the RHD, and then percutaneous transhepatic biliary drainage (PTBD) was carried out for the LHD to alleviate the prolonged fever. In Case 2, the placement of a bare expandable metallic stent (EMS) was effective in mitigating the jaundice.

An endoscopic investigation in Case 1 identified a type 4 gastric carcinoma in the antrum of the stomach. Type 3 gastric cancer was identified in the lesser curvature of the body of the stomach in Case 2. Periodic follow-ups in Case 2 allowed for the endoscopic observation of changes that alternated between scarring and ulceration of the gastric cancer lesion over 11 years.

In both cases, the serum level of T-Bil decreased after successful biliary drainage. The general condition of Case 1 gradually improved, but then suddenly deteriorated and the patient died on day 36 of hospitalization. Case 2 developed progressive anemia, which suggested active bleeding at an unknown internal site and the patient died on day 30 of hospitalization. It was concluded that both of these patients had died of cancer; however, the detailed causes of their deaths were unknown at that time.

We performed autopsies in both of these cases in order to elucidate the causes of death. The gross appearance of the resected stomach revealed constriction of the gastric wall in both cases (Fig. 3). An examination of histology specimens revealed mainly non-solid-type poorly differentiated adenocarcinoma (por2) with signet-ring cells (sig). Malignant cells had infiltrated into the lumen of lymphatic vessels (esophagus, retroperitoneal organs, portal canal), the lumen of blood vessels (lung, pancreas) and the wall of extrabiliary bile ducts. Epithelial cells of the extrabiliary bile ducts were considered not to have originated from the undifferentiated carcinoma cells because the columnar epithelium of the extrabiliary bile ducts remained undamaged (Fig. 4). An endoscopic evaluation of the coordinate expression of cytokeratin (CK) 7 and CK20 can help in distinguishing primary from metastatic gastric carcinoma if they are unsure of a diagnosis of primary bile duct carcinoma.

Case Reports

Case 1

An 88-year-old Japanese woman first consulted us with tarry stool in 1999. An endoscopic investigation revealed gastric ulceration in the posterior wall of the lesser curvature of the gastric body. A gastric biopsy indicated a diagnosis of de novo poorly differentiated gastric adenocarcinoma with signet-ring cells. He underwent colectomy for transverse colon cancer in 1989 and transurethral resection of bladder cancer (TUR-Bt) due to urothelial cancer in 2006. Moreover, the patient also had diabetes mellitus, which was treated with glimepiride and pioglitazone. He had not undergone gastrectomy, but had been treated with anti-cancer drugs [oxifluoridine or S-1 (tegafur/gimeracil/oteracil potassium)] and anti-ulcer drugs (famotidine or sodium rabeprazole) in accordance with his refusal to undergo any more surgical treatment. Scarring and ulceration of the gastric cancer lesion had occurred alternately over 11 years and he was admitted with abdominal fullness, anorexia and jaundice in May 2011.

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Figure 1. Contrast-enhanced abdominal computed tomography (CT) revealed greatly thickened common bile ducts (CBDs) in both cases (white arrows) (A, B; axial plane). In Case 1, an axial plane contrast-enhanced CT (CE-CT) image demonstrated gastric wall thickness (white arrowhead) (C). In Case 2, an axial plane CE-CT image also showed thickening of the wall of the gastric body (D) (white arrowhead). Eventually, both cases showed gastric wall thickness, but the gastric lesions were far from the thickened CBDs.

Figure 2. Endoscopic retrograde cholangiopancreatography (ERCP) showed dilatation of the right hepatic duct (RHD) and the left hepatic duct (LHD) and luminal narrowing extending to the bifurcation of the RHD and the LHD from the CBD in both cases.

tatic sites in a number of anatomic regions. Therefore, the CK7/CK20 immunophenotypes of a large number of neoplasms have been characterized (7). To confirm the metastasis of gastric carcinoma cells, immunohistochemical staining was carried out in both the stomach and the bile duct lesions. In our study, Case 1 showed a CK7/CK20’ im-
munophenotype, whereas Case 2 had a CK7/CK20– immunophenotype at both sites (Fig. 4G and H). In contrast, both cases showed a CK7/CK20– immunophenotype in normal bile duct epithelial areas (data not shown). These findings suggest that the bile duct lesions had originated from the stomach. Moreover, both cases showed poorly differentiated adenocarcinoma with signet-ring cells, which had metastasized to a wide range of organs including the lungs and kidneys (data not shown). The middle part of the pancreas had adhered to the lesser omentum and the lesser curvature of the stomach, especially in Case 2. Moreover, foci of proliferated poorly differentiated adenocarcinoma were sequentially observed in the lower esophagus.

**Discussion**

The cause of obstructive jaundice in patients with primary gastric cancer has been widely ascribed to metastatic lymphadenopathy in the hepatoduodenal ligament (HDL) (2). A large metastatic mass in the liver can also cause hilar biliary obstruction at the confluence of the RHD and the LHD due to extrinsic compression (8). The two cases reported here showed no large mass in the liver, but did have elevated serum CA19-9 levels in common. Indeed, high levels of CA 19-9 can be caused by benign obstructive jaundice or cholangitis, but the sensitivity of a CA19-9 value >100 U/mL in diagnosing cholangiocarcinoma should be high (9). Initially, we considered primary bile duct cancer to be the cause of the obstructive jaundice in both cases. This diagnosis was made as a result of the thickened walls and severe stenosis of the common hepatic ducts (CHDs) extending to the hepatic duct bifurcations on contrast-enhanced abdominal CT and cholangiography, respectively. These features are also known to be characteristic of hilar cholangiocarcinoma, especially in affecting the bifurcation of the CHD. Hilar cholangiocarcinoma, also known as a Klatskin tumor (10), is anatomically defined as extrahepatic cholangiocarcinoma involving the hepatic duct bifurcation. However, the autopsies revealed that the observed conditions had not been caused by direct invasion, but by the distant metastasis of poorly differentiated gastric adenocarcinoma in both cases.

We conducted a comprehensive literature search using the terms “gastric carcinoma” and “obstructive jaundice” in the PubMed/MEDLINE database from 1966 to the present, and in the Japanese electronic database Japana Centra Revuo Medicina (ICHUSHI) from 1983 to 1 May, 2015. These search terms resulted in 123 and 199 hits, respectively. Our patients resemble two previously reported cases in which poorly differentiated gastric cells infiltrated into the subepithelial layers of the bile ducts.

In one case previously reported by Satake et al. (4), there was subepithelial invasion of poorly differentiated gastric adenocarcinoma cells with signet-ring cells from the stomach to the extrahepatic bile ducts. The 56-year-old man in that case showed circumferential stenosis with irregular walls in the lower bile duct by abdominal CT and ERCP, but the cytology of biliary brushing did not identify any malignancy. Our cases showed intact bile duct columnar epithelium and glands in autopsies, which did not indicate a biliary malignancy.

In an additional case previously reported by Gabata et al. (11), there was advanced gastric carcinoma that presented with obstructive jaundice caused by lymphangitis carcinomatosa of the bile duct wall originating from gastric carcinoma. In that case, a 63-year-old man presented with marked subepithelial lymphangitic infiltration, marked LN metastases and lymphangitis carcinomatosa of the bile duct wall. The authors also observed apparent infiltration into the lymphatics within the wall of the CBD via the pericholedochal lymphatic vessels in the HDL (11). Therefore, they assumed that lymphatic edema had stimulated reactive fibrosis of the bile duct wall with luminal narrowing. In contrast, our cases showed little pathological fibromatous change of the bile duct wall.

Tumor invasion around the bile duct is rarely induced alone in undifferentiated adenocarcinoma, but is often ob-
served in association with widespread retroperitoneal invasion and peritoneal dissemination (3). In our cases, the autopsies revealed the broad distribution of lymphadenopathy and suggested carcinomatous invasion into the retroperitoneum and/or lymphedema; however, epithelial cells of the extrahepatic bile ducts were considered not to have originated from the undifferentiated carcinoma cells because the columnar epithelium of the extrahepatic bile ducts remained undamaged.

Previous studies have shown that gastric cancer involving the lower third of the stomach and histopathologically well-differentiated adenocarcinoma were significantly more prevalent in elderly patients (12, 13). The frequency of advanced cancer in the elderly is higher than in young people (14), with multiple metastatic cancers being more common with age (15). Gastric cancers show a distal shift with predominantly differentiated-type carcinoma in the early stages and increased undifferentiated-type carcinomas in advanced stages, especially in patients aged 85 years or older (16).

Even though both of our patients were successfully treated to reduce their serum bilirubin level, they still died approximately one month after admission. Autopsies revealed that the cancer cells originated from poorly differen-

Figure 4. Autopsy tissue sections around the intrahepatic bile ducts revealed markedly dilated lymphatic vessels filled with poorly differentiated adenocarcinoma cells in the lamina propria [Hematoxylin and Eosin (H&E) staining; A, B]. The lymphatic vessels were filled with malignant cells (D2-40 stain; C, D). The columnar epithelium was undamaged, even though there was an invasive lesion of the bile duct wall around the lymphatic vessels. Autopsy specimens of the gastric mucosa revealed poorly to well-differentiated adenocarcinoma (H&E staining; E, F). In Case 1, immunohistochemical staining was positive for CK7 (G-1, G-3) and CK20 (G-2, G-4) in both the stomach (G-1, G-2) and the bile ducts (G-3, G-4). Meanwhile, in Case 2, immunohistochemical staining was positive for CK20 (H-2, H-4), but negative for CK7 (H-1, H-3), in both the stomach (H-1, H-2) and the bile ducts (H-3, H-4). D2-40 is an antibody against human podoplanin, a lymphatic endothelial cell marker. H&E staining: Hematoxylin and Eosin staining. A, C: low-power views (×10). B, D: intermediate-power views (×20). E, F: low-power views (×4). G-1-G-4, H-1-H-4; high-power views (×40).
tiated gastric adenocarcinomas and had metastasized to diffuse organs and tissues. There was no direct invasion, but biliary metastasis was apparent around the hilar structures. As a result, the general conditions of the patients deteriorated and they died within a short period of time.

We propose that the number of patients with severe stenosis extending to the bifurcation of the RHD and the LHD from the CBD by gastric carcinoma that mimics hilar cholangiocarcinoma might thus have been previously underestimated. Therefore, physicians in East Asian countries should be alert to the possibility of metastatic poorly differentiated gastric adenocarcinoma, especially in very elderly patients.

In conclusion, we experienced two autopsy-proven cases of severe stenosis of the hilar bile ducts extending to the hepatic duct bifurcation induced by the subepithelial lymphangitic infiltration of poorly differentiated gastric adenocarcinoma, mimicking hilar cholangiocarcinoma.

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

References


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