Early Bile Duct Cancer in a Background of Sclerosing Cholangitis and Autoimmune Pancreatitis

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Abstract

A 59-year-old man presented with recent onset jaundice. Initial laboratory and radiologic findings suggested autoimmune pancreatitis (AIP) with consequent obstructive jaundice. All serologic markers for AIP were, however, normal. To confirm the histologic finding of AIP and exclude the possibility of cancer at the thickened segment of common bile duct, cholangioscopic examination was performed and bile duct cancer was observed. The resected specimen showed typical features of AIP throughout the entire pancreas and early carcinomatous change on a background of abundant IgG4-positive cells in the common bile duct. Although chronic biliary inflammation and cholestasis are among bile duct cancer risk factors, the cause-and-effect relationship between sclerosing cholangitis and bile duct cancer needs to be determined by further study, as between AIP and pancreatic cancer. Importantly, histologic exclusion of malignancy is another essential step in the diagnosis of AIP and sclerosing cholangitis as malignancy may coexist in bile duct as well as in the pancreas.

Key words: Autoimmune pancreatitis, sclerosing cholangitis, common bile duct cancer

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Introduction

Autoimmune pancreatitis (AIP) is a type of chronic pancreatitis characterized by an inflammatory process that presents unique clinicopathologic features, including enlargement of pancreas and pancreatic ductal narrowing on imaging, elevated levels of IgG or IgG4, dense lymphoplasmacytic infiltration and fibrosis, and favorable response to steroid therapy (1, 2). Most patients (65-75%) present with painless jaundice (3, 4), resulting from stenosis in the intra-pancreatic portion of the common bile duct (CBD) induced by both extrinsic compression of the inflamed pancreatic head and inflammatory changes of the CBD itself (4, 5). Distal CBD strictures as well as irregular narrowing of the main pancreatic duct usually improve after steroid therapy (3). It is difficult, however, to differentiate distal CBD stricture accompanying AIP from CBD cancer, requiring biopsy or brush cytology to exclude CBD cancer before steroid therapy or persistent stricture even after steroid therapy. We report a patient with AIP, in whom early bile duct cancer overlying a background of sclerosing cholangitis was detected by cholangioscopic biopsy during diagnostic evaluation. In the literature, there is no case report of concomitant bile duct cancer in a background of sclerosing cholangitis and AIP. Although chronic biliary inflammation and cholestasis are among bile duct cancer risk factors (6), the cause-and-effect relationship between sclerosing cholangitis and bile duct cancer needs to be determined by further study, as between AIP and pancreatic cancer. Importantly, histologic exclusion of malignancy is another essential step in the diagnosis of AIP and sclerosing cholangitis as malignancy may coexist in the bile duct as well as in the pancreas.
Figure 1. a-c. Radiologic findings. (a) Enhanced CT shows diffuse enlargement of the pancreas with the peripheral hypoattenuated rim. (b) Dynamic MR with curved multiplanar reformation shows intense enhancement of the thickened common bile duct (arrow). (c) ERCP shows diffuse irregular narrowing of the main pancreatic duct.

Case Report

A 59-year-old man presented with jaundice which had developed 10 days before referral to our center. He had no previous medical problems. Physical examination revealed icteric sclerae without abdominal pain or palpable mass. Initial laboratory tests showed total bilirubin 10.7 mg/dL (normal, 0.2-1.5 mg/mL), direct bilirubin 8.1 mg/dL (0.1-0.4), aspartate aminotransferase 76 U/L (10-35), alanine aminotransferase 179 U/L (5-38), alkaline phosphatase 403 U/L (53-128), gamma-glutamyltransferase 1,574 U/L (10-73), and random plasma glucose 209 mg/dL. CT scan showed diffuse enlargement of the pancreas with the peripheral hypoattenuated halo as well as segmental wall thickening with enhancement of the CBD (Fig. 1a). MRI revealed nonvisualization of the main pancreatic duct and dense wall enhancement of the narrowed segment of the CBD (Fig. 1b). The laboratory and radiologic findings suggested autoimmune pancreatitis with consequent obstructive jaundice. Selective cannulation of the CBD under ERCP failed due to tight stricture of the distal CBD, and percutaneous transhepatic biliary drainage was performed for decompression of the biliary obstruction. A later endoscopic retrograde cholangiopancreatography (ERCP) showed diffuse narrowing of the main pancreatic duct (Fig. 1c). Further laboratory tests focused on autoimmune pancreatitis showed normal IgG and IgG4 levels and the absence of antinuclear antibody. Only the imaging findings met the diagnostic criteria of autoimmune pancreatitis proposed by both Japan Pancreas Society and Asan Medical Center (7, 8), thus preventing a definitive diagnosis. Two sets of endobiliary biopsy specimens obtained via the percutaneous transhepatic tract were too small for proper histologic examination. To confirm histologic finding of lymphoplasmacytic infiltration and exclude the possibility of bile duct cancer at the narrowed segment, cholangioscopic examination of the narrowed CBD was planned through the preexisting percutaneous tract. Cholangioscopy showed mucosal nodularity with abnormal vessels at the entrance of the narrowed CBD. Histologic results revealed atypical glandular formation suggesting bile duct cancer (Fig. 2a). Pancreatoduodenectomy was performed. Microscopic examination of the resected specimen revealed diffuse and dense infiltration of lymphoplasma cells throughout the entire pancreas, accompanying sclerosis and obliterative phlebitis (Fig. 2b). The resected specimen was immunostained using IgG4 antibodies (HP6025, The Binding Site, Birmingham, U.K., 1:100 dilution). Antibody-binding was detected using a standard labeled streptavidin-biotin system (Golden Bridge International, Inc., Life Science Division, Mukilteo, WA, USA). External positive controls were tonsillar tissue stained for IgG4, and for negative controls, the primary antibodies were omitted. Immunostaining for IgG4 showed diffuse and strong positivity (>30/HPF) in both the pancreas and bile duct (Fig. 2b and 2c). The inflammation extended into the CBD wall, with marked epithelial atypism, about 2 cm in length. The epithelial change was confined to the superficial portion and strongly stained for p53, which was consistent with early carcinomatous changes (Fig. 2d). The epithelial cells of the carcinomatous area were also strongly stained for IgG4. The patient was diagnosed with early bile duct cancer in a background of sclerosing cholangitis and autoimmune pancreatitis.
Discussion

Since Yoshida et al (9) proposed AIP as a diagnostic entity, two important clinicopathologic features have been discovered; increased serum levels of IgG4 (10) and abundant infiltration of IgG4-positive cells into the pancreas and other organs involved in AIP (11). These findings suggested that AIP is a pancreatic manifestation of systemic disease, giving rise to a new clinicopathologic entity, IgG4-related autoimmune disease (12).

There have been controversies in the diagnostic criteria for AIP. Since it is difficult to obtain a sufficient amount of pancreatic specimens, histopathologic confirmation of lymphoplasmacytic sclerosing pancreatitis (LPSP) as a criterion standard for the diagnosis of AIP lacks clinical availability (13, 14). Typical imaging findings have therefore been widely adopted as essential criteria in AIP diagnosis (8, 15). Another issue concerning diagnostic criteria for AIP is whether the response to steroid therapy should be included in the diagnostic criteria for AIP. Although inclusion of the response to steroid therapy increases the sensitivity (8), it may also increase the risk of delayed diagnosis of pancreatic cancer. Based on the new concept of IgG4-related systemic disease, IgG4 immunostaining of extrapancreatic lesions may increase the diagnostic accuracy (16). All of these issues were involved in the diagnosis of AIP in our patient, since he presented only with essential radiologic criteria, but without serologic finding. The critical issue in the diagnostic approach is whether histopathologic examination of available tissue is essential before therapeutic trial with steroid. As a stricture in the distal CBD cannot be differentiated radiologically (4), endoscopic biopsy or brush cytology should be used to exclude the possibility of malignancy. IgG4 immunostaining of endoscopic biopsy specimens shows a high sensitivity in sclerosing cholangitis accompanied in AIP (17). IgG4-positive cells, however, may also be observed in bile duct diseases other than sclerosing cholangitis as shown in the previous experiences from pancreatic diseases (14). The epithelial lining of the bile duct in this case was also strongly stained for IgG4. This may be due to reactive infiltration of IgG4-positive cells around carcinoma. Since the endobiliary biopsy specimen obtained via the percutaneous tract was too small to obtain diagnostic information, we performed a cholangioscopic evaluation to exclude bile duct cancer in our patient. Steroid trial without cholangioscopic evaluation may improve underlying cholangitis as well as AIP, but may ultimately result in delayed diagnosis of bile duct cancer. Histologic examination by any accessible methods, including endoscopic biopsy, should, therefore, be performed to exclude malignancy and to obtain supporting evidence for steroid trial. In addition, steroids should only be
given to those patients with measurable pancreatic or extra-
pancreatic lesions, in whom the response can be objectively
assessed (18).

To date, there has been only one case report of concomi-
tant AIP and pancreatic cancer (19), and two case reports of
pancreatic cancer complicating AIP years after its diagnosis
(20, 21). We could not find any case reports of patients with
pancreatic cancer complicating AIP and pancreatic cancer (19),
and two case reports of

In summary, effort should be made to obtain sufficient
evidence for the diagnosis of AIP, in order to overcome the
limitations of the current diagnostic criteria and to obtain a
rationale for steroid trial. It is important to exclude pancre-
tic or bile duct cancer in patients suspected of having AIP.

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