INTERNAL MEDICINE

□ CASE REPORT □

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

Oh Hyoung-Chul[1], Kim Jae Gyu[1], Kim Jeong Wook[1], Lee Kwang Sun[1], Kim Mi Kyung[2], Chi Kyong Choun[3], Kim Yong Seok[3] and Kim Ki Hyun[4]

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

(Inter Med 47: 2025-2028, 2008)
(DOI: 10.2169/internalmedicine.47.1347)

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 intrapancreatic 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.

[1]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea, [2]Department of Pathology, Chung-Ang University College of Medicine, Seoul, Korea, [3]Department of General Surgery, Chung-Ang University College of Medicine, Seoul, Korea and [4]Department of Radiology, Chung-Ang University College of Medicine, Seoul, Korea
Received for publication May 26, 2008; Accepted for publication August 31, 2008
Correspondence to Dr. Kim Jae Gyu, jgkimd@cau.ac.kr

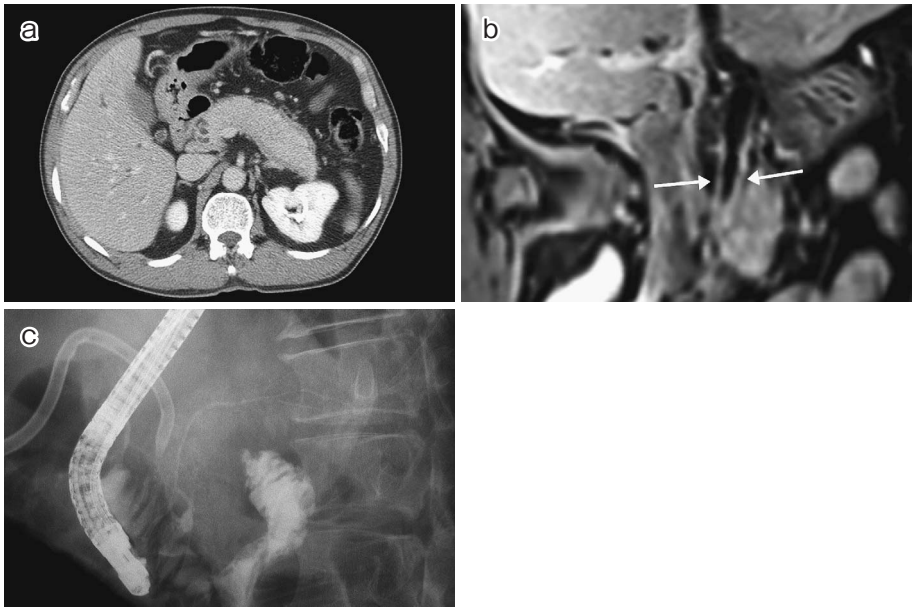

Figure 1. **a-c. Radiologic findings. (a) Enhanced CT shows diffuse enlargement of the pancreas with the peripheral hypoattenuated rim. (b) Dynamic MR with curved multiplanar reformation shows intense enhancement of the thickened common bile duct (arrow). (c) ERCP shows diffuse irregular narrowing of 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). Pancreaticoduodenectomy 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.

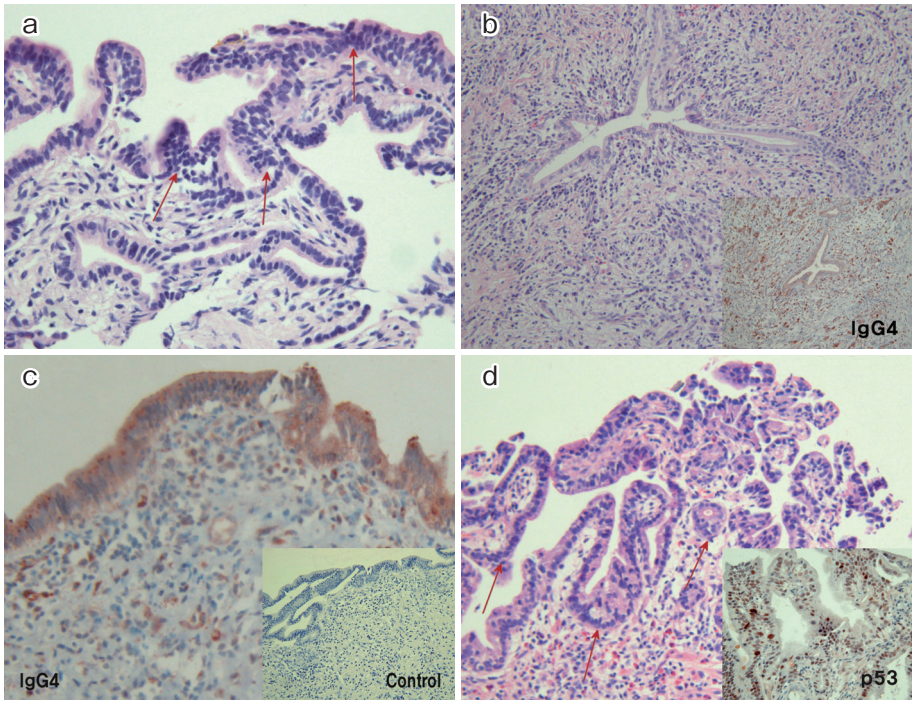

Figure 2. **a-d. Histologic findings. (a) Cholangioscopic biopsy shows abnormal glandular formation (arrows) suggesting bile duct cancer. (b) Microscopic view of the resected pancreas shows lymphoplasmacytic slcerosing pancreatitis and high density of IgG4- positive cells on IgG4 immunostaining (box in the right corner). (c) Immunostaining for IgG4 of the resected bile duct showed high density of IgG4-positive cells, contrasting with negative staining control (box in the right corner). (d) High power microscopic view of carcinomatous change in the bile duct (arrows), which is also strongly positive for p53 immunostaining (box in the right corner).**

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 extrapancreatic lesions, in whom the response can be objectively assessed (18).

To date, there has been only one case report of concomitant 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 concomitant bile duct cancer plus sclerosing cholangitis and AIP. The risk of pancreatic cancer is significantly higher in patients with chronic pancreatitis. Although the natural course of AIP remains uncertain, repeated inflammation may enhance the development of pancreatic cancer. However, pancreatic cancer may also develop independently of AIP in an elderly man patient, as both conditions, pancreatic cancer and AIP, share the prevalent demographic features of old age and man (20). Likewise, among the bile duct cancer risk factors are chronic biliary inflammation and cholestasis (6), both of which may contribute to malignant transformation of cholangiocytes even in sclerosing cholangitis. Since our patient had a short duration of overt AIP, is elderly, and lives in a country with a high prevalence of bile duct cancer, the possibility of a cause-and-effect relationship between sclerosing cholangitis and bile duct cancer may be low. On the other hand, early bile duct cancer present superficially in a background of sclerosing cholangitis and AIP may suggest their relationship.

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 pancreatic or bile duct cancer in patients suspected of having AIP.

Acknowledgement

This research was supported by the Chung-Ang University Research Grant in 2008.

References

1. Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Autoimmune pancreatitis. N Engl J Med **355**: 2670-2676, 2006.
2. Otsuki M. Autoimmune pancreatitis: a message from Japan. J Gastroenterol **42** Suppl 18 : 1-5, 2007.
3. Horiuchi A, Kawa S, Hamano H, Hayama M, Ota H, Kiyosawa K. ERCP features in 27 patients with autoimmune pancreatitis. Gastrointest Endosc **55**: 494-499, 2002.
4. Kim KP, Kim MH, Song MH, Lee SS, Seo DW, Lee SK. Autoimmune chronic pancreatitis. Am J Gastroenterol **99**: 1605-1616, 2004.
5. Kloppel G, Luttges J, Lohr M, Zamboni G, Longnecker D. Autoimmune pancreatitis: pathological, clinical, and immunological features. Pancreas **27**: 14-19, 2003.
6. Lazaridis KN, Gores GJ. Cholangiocarcinoma. Gastroenterology **128**: 1655-1667, 2005.
7. Okazaki K, Kawa S, Kamisawa T, et al. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. J Gastroenterol **41**: 626-631, 2006.
8. Kim KP, Kim MH, Kim JC, Lee SS, Seo DW, Lee SK. Diagnostic criteria for autoimmune chronic pancreatitis revisited. World J Gastroenterol **12**: 2487-2496, 2006.
9. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci **40**: 1561-1568, 1995.
10. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med **344**: 732-738, 2001.
11. Kamisawa T. IgG4-positive plasma cells specifically infiltrate various organs in autoimmune pancreatitis. Pancreas **29**: 167-168, 2004.
12. Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol **38**: 982-984, 2003.
13. Zamboni G, Luttges J, Capelli P, et al. Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: a study on 53 resection specimens and 9 biopsy specimens. Virchows Arch **445**: 552-563, 2004.
14. Bang SJ, Kim MH, Kim do H, et al. Is pancreatic core biopsy sufficient to diagnose autoimmune chronic pancreatitis? Pancreas **36**: 84-89, 2008.
15. Japan Pancreas. Society. Diagnostic criteria for autoimmune pancreatitis by the Japan Pancreas Society. J Jpn Pancreas Soc **17**: 585-587, 2002.
16. Kamisawa T. Diagnostic criteria for autoimmune pancreatitis. J Clin Gastroenterol **42**: 404-407, 2008.
17. Ghazale A, Chari ST, Zhang L, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology **134**: 706-715, 2008.
18. Chari ST, Smyrk TC, Levy MJ, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol **4**: 1010-1016; quiz 1934, 2006.
19. Inoue H, Miyatani H, Sawada Y, Yoshida Y. A case of pancreas cancer with autoimmune pancreatitis. Pancreas **33**: 208-209, 2006.
20. Ghazale A, Chari S. Is autoimmune pancreatitis a risk factor for pancreatic cancer? Pancreas **35**: 376, 2007.
21. Fukui T, Mitsuyama T, Takaoka M, Uchida K, Matsushita M, Okazaki K. Pancreatic cancer associated with autoimmune pancreatitis in remission. Intern Med **47**: 151-155, 2008.