IgG4-related Sclerosing Cholangitis with No Biliary Stricture but Severe Thickening of the Bile Duct Wall

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Abstract

We herein report a case of a 56-year-old man with IgG4-related sclerosing cholangitis (IgG4-SC) with no biliary stricture, but with a severely thickened bile duct wall. Contrast-enhanced computed tomography showed diffuse swelling of the pancreas and thickening of the common bile duct (CBD) wall with delayed enhancement. Obvious diffuse wall thickening of the CBD was observed on endoscopic ultrasonography. However, endoscopic retrograde cholangiography showed no biliary stricture in the CBD that had thickened. Although IgG4-SC has been classified by a stenotic lesion on cholangiography, we should be aware of some IgG4-SC cases showing only bile duct wall thickness without any biliary stricture.

Key words: autoimmune pancreatitis, IgG4-related sclerosing cholangitis, endoscopic cholangiography, cholangiographic classification

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Introduction

The concept of IgG4-related sclerosing cholangitis (IgG4-SC) has been recognized worldwide, and IgG4-SC is the biliary manifestation of IgG4-related disease (1-6). Patients with IgG4-SC have an increased serum level of IgG4, dense infiltration of IgG4-positive plasma cells with extensive fibrosis into the bile duct wall and a good response to steroid therapy. Recently, the first clinical diagnostic criteria for IgG4-SC were proposed in Japan (7). As in the diagnostic items of the 2012 IgG4-SC diagnostic criteria, biliary tract imaging of IgG4-SC reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with thickening of the bile duct wall. IgG4-SC cholangiograms are classified into four types based on the regions of stricture as revealed by cholangiography. This cholangio-

graphic classification is very useful for making a differential diagnosis, but the presence of biliary stricture is essential in this classification system (8). However, some cases of IgG4-SC cannot be categorized into any of these four types in practice. No IgG4-SC case reports have previously shown a lack of biliary stricture with severe thickening of the bile duct wall.

We herein describe a case of IgG4-SC with no biliary stricture and severe thickening of the bile duct wall.

Case Report

A 56-year-old man was admitted to our hospital in February 2015 because of upper left abdominal pain. He had no remarkable medical history and did not drink alcohol. The family history was not relevant to the current disorder. Laboratory data showed elevated serum levels of amylase,

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IgG and IgG4, to 449 U/L (normal range, 37-125 U/L), 2,807 mg/dL (normal range, 870-1,700 mg/dL) and 1,240 mg/dL (normal range, 4.8-105 mg/dL), respectively. Serum levels of total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and γ -glutamyl transpeptidase were all within normal limits at 0.3 mg/dL (normal range, 0.3-1.2 mg/dL), 25 U/L (normal range, 13-33 U/L), 17 U/L (normal range, 6-30 U/L), 250 U/L (normal range, 100-340 U/L) and 14 U/L (normal range, 10-47 U/L), respectively. The serum level of C-reactive protein was 0.06 mg/dL (normal range, ≤ 0.3 mg/dL) and the white blood cell count was 6,200/mm³ (normal range, 3,600-9,600/mm³). Contrast-enhanced computed tomography (CT) showed diffuse swelling of the pancreatic body with a capsule-like low-density rim, and wall thickening with contrast enhancement in the region from the upper to the lower common bile duct (CBD) with delayed enhancement (Fig. 1). Magnetic resonance cholangiopancreatography (MRCP) revealed nar-

Figure 1. Contrast-enhanced computed tomography on admission revealed diffuse swelling of the pancreatic body and tail with a capsule like a low-density rim around the edge of the lesion, and wall thickening with contrast enhancement in the region from the upper to the lower common bile duct with delayed enhancement.

rowing of the main pancreatic duct (MPD) from the head to the body, but no bile duct stricture was detected (Fig. 2A). Endoscopic ultrasonography (EUS) showed obvious diffuse wall thickening of the CBD, with a maximum diameter of 4.0 mm (Fig. 3). However, endoscopic retrograde cholangiopancreatography (ERCP) revealed no stricture, but instead a slightly shaggy appearance in the upper CBD (Fig. 4A, B), and diffuse irregular narrowing of the MPD (Fig. 4C). No stenotic lesion was observed in the biliary tract despite the presence of prominent bile duct wall thickness. From a comparison between Fig. 2A (MRCP) and Fig. 4C (ERP), these pancreatography results were quite different from each other. In Fig. 4C (ERP), the contrast medium did not fill the MPD of the tail sufficiently. In addition, the resolution of the MRCP was low, as shown in Fig. 2A. These observations explain the discrepant pancreatography findings between ERP and MRCP. Transpapillary intraductal ultrasonography (IDUS) of the bile duct revealed a continuously thick wall from the intrapancreatic bile duct to the upper bile duct with a smooth circular symmetric outer margin, a smooth inner margin and a homogeneous internal echo pattern (Fig. 5). These IDUS findings are typical of IgG4-SC according to our previous report (9). We conducted a transpapillary bile duct biopsy in order to make a histopathological evaluation, and lymphoplasmacytic infiltration and abundant IgG4-positive plasma cell infiltration [>10 cells/high-power field (HPF)] were observed (Fig. 6). We therefore considered this bile duct lesion to be IgG4-SC. We found no specific histopathological findings of auto-immune pancreatitis (AIP) after EUS fine-needle aspiration of a pancreatic specimen. We finally made a diagnosis of AIP according to the 2011 Japanese diagnostic criteria and administered 30 mg of oral prednisolone (PSL).

Two weeks after starting the PSL, contrast-enhanced CT revealed an improvement in the diffuse pancreatic swelling and continually thick CBD wall. MRCP showed an improvement in the diffuse pancreatic swelling and the diffuse narrowing of the MPD. Furthermore, the biliary tract seemed to be dilated compared with the findings at admis-

Figure 2. Magnetic resonance cholangiopancreatography (MRCP) findings before and after steroid therapy. A: MRCP revealed narrowing of the main pancreatic duct (MPD) from head to body, and did not show extrahepatic bile duct stricture on admission. B: MRCP showed an improvement of diffuse narrowing of the MPD and the biliary tract seemed to be dilated in terms of its diameter after steroid therapy.

sion (Fig. 2B). No ERCP was performed after administering PSL because informed consent had not been obtained. The serum IgG and IgG4 levels decreased to 1,655 and 824 mg/dL, respectively. Thus, imaging of the pancreatic parenchyma and duct, serology categorized as level 1 and response to steroid were in line with the International Consensus Diagnostic Criteria (ICDC) (10). Therefore, we diagnosed this case as having definitive type 1 AIP according to not only the 2011 Japanese diagnostic criteria, but also the ICDC. Subsequently, the PSL dose was gradually tapered, and the patient was discharged to an outpatient clinic.

Discussion

We herein describe a case of IgG4-SC with no biliary stricture, but with a severely thickened bile duct wall. Cholangiograms of patients with IgG4-SC are classified into four types based on the region of the stricture. However, this IgG4-SC case had no biliary stricture and could not be categorized according to this cholangiographic classification. Thus, this type of IgG4-SC should also be considered when

diagnosing IgG4-SC.

A histopathological examination is the most reliable method to diagnose IgG4-SC. A histopathological diagnosis of IgG4-SC using surgical specimens is not difficult, but it is important to diagnose this condition before surgery in order to avoid any unnecessary surgical resection because steroid therapy is effective in these cases. We previously reported that the wall thickness spreads from the intrapancreatic bile duct to the upper bile duct continuously in most cases through the IDUS procedure in IgG4-SC (9). Zen et al. showed that, immunohistochemically, the infiltration of IgG4-positive plasma cells was severe within the affected areas of the bile duct in IgG4-SC (11). In a study by Kuwatani et al., there were no correlations between bile duct wall thickness and the number of IgG4-positive plasma cells. In addition, the authors obtained specimens that contained >10 IgG4-positive plasma cells/HPF in 61.1% of IgG4-SC cases (12). Furthermore, Ghazale and Kawakami et al. demonstrated positive IgG4 immunostaining (>10 IgG4-positive plasma cells/HPF) of bile duct biopsy specimens in 88% and 72% of IgG4-SC patients, respectively (13, 14). Therefore, we consider that a biliary biopsy might also be a useful procedure even from a bile duct with no biliary stricture in IgG4-SC patients. In the current patient, lymphoplasmacytic infiltration and >10 IgG4-positive plasma cells/HPF were observed by transpapillary bile duct biopsy, and these histopathological findings contributed to the IgG4-SC diagnosis. However, it is generally difficult to describe the characteristic features of IgG4-SC, such as storiform fibrosis and obliterative phlebitis, using a transpapillary bile duct biopsy. Therefore, endoscopic retrograde cholangiopancreatography (ERC) manifestations are essential to diagnose IgG4-SC.

We previously reported that IDUS is useful for the differential diagnosis of IgG4-SC (9, 15). The most characteristic IDUS finding is thickening of the bile duct wall, which appears to be normal on ERC. In the current case, ERC showed an almost normal appearance; however, IDUS of the bile duct revealed a continuously thickened wall from the intrapancreatic bile duct to the upper bile duct with a

Figure 3. Obvious diffuse wall thickening of the common bile duct, which measured up to 4.0 mm in diameter, was observed on endoscopic ultrasonography (EUS).

Figure 4. Endoscopic retrograde cholangiopancreatography (ERCP) findings before steroid therapy. A: ERC showed a slightly shaggy appearance in the upper common bile duct without biliary stricture. B: ERC showed a normal cholangiogram in the intrahepatic bile duct. C: Diffuse irregular narrowing of the main pancreatic duct was observed in the pancreatogram.

smooth circular symmetric outer margin, a smooth inner margin and a homogeneous internal echo pattern. The maximum diameter of the bile duct wall was 4.0 mm, and three layers were preserved due to EUS. The mean wall thickness of strictures in previous studies (9, 15) where the bile duct was thickest was 2.5 mm (range, 1.6-3.0 mm). Therefore, the bile duct wall in this case was considerably thicker than those reported previously.

In the present case, ERC revealed no stricture regardless of the remarkably thickened bile duct, which is a notable finding. The bile duct wall at the onset of IgG4-SC is flexible and relatively easy to expand using the pressure of contrast medium during the ERC procedure. This elasticity of the thickened bile duct wall may be the cause of the discrepancy between the EUS and ERC findings. Furthermore, the balloon pressure on the bile duct through the second part of the duodenum during the EUS procedure may have narrowed the CBD lumen (Fig. 3). This observation explains

Figure 5. Transpapillary intraductal ultrasonography (IDUS) of the bile duct revealed continuous wall thickness from the intrapancreatic bile duct to the upper bile duct with a circular symmetric smooth outer margin, a smooth inner margin and a homogeneous internal echo pattern.

the EUS and MRCP discrepancy in the CBD findings. The typical imaging finding of IgG4-SC is the narrowing of bile ducts. However, IgG4-SC cases with a thickened bile duct wall but without biliary stricture do occur, such as in the present case. We previously reported that the most characteristic IgG4-SC finding is thickening of the bile duct wall, which appears to be normal on ERC according to IDUS findings. Furthermore, EUS is not associated with complications, such as post-ERCP pancreatitis. Therefore, wall thickening of the bile duct by EUS findings is considered to be superior to a sign of narrowing of the bile duct by ERCP, and EUS is a useful and significant procedure for the diagnosis of IgG4-SC. Nakazawa et al. classified IgG4-SC into four types when making a differential diagnosis based on the cholangiographic features (8): Stricture located in the lower part of the CBD represents type 1, stricture that is diffusely distributed in the intra- and extrahepatic bile duct is type 2, stricture distributed in both the hilar hepatic region and the lower part of the CBD is type 3, and stricture of the bile duct in the hilar hepatic region is type 4. Cholangiographic findings based on this classification system often lead to misdiagnosing IgG4-SC type 1 as pancreatic carcinoma, type 2 as primary sclerosing cholangitis, and types 3 and 4 as cholangiocarcinoma. We created this classification system considering the differential diagnosis for each type. However, it was difficult to determine the differential diagnosis based on the present ERC procedure, and the findings were not applicable to any of our types. Although no reported IgG4-SC cases have previously shown almost normal ERC findings with a thick bile duct wall, such cases do sometimes arise. Some IgG4-SC cases cannot be categorized into any of the four types. Strictly speaking, we could not diagnose the current case as IgG4-SC on the basis of IgG4-SC 2012 because storiform fibrosis and obliterative phlebitis were not detected in terms of the histological appearance of the bile duct, and narrowing of the biliary tract in a cholangiogram is essential for diagnosis if we cannot obtain more than three findings in a histopathological examination. Therefore, how to classify such IgG4-SC

Figure 6. Histopathological evaluation from the transpapillary bile duct biopsy. A: Numerous lymphocytes and plasma cells in the bile duct wall (Hematoxylin and Eosin staining ×400). B: Abundant infiltration of IgG4-positive plasma cells into the bile duct wall (IgG4 staining ×400).

cases, including the present case, remains a topic for future investigation. We may have to revise our cholangiographic classification system after accumulating more IgG4-SC cases. Furthermore, we propose that the 2012 IgG4-SC diagnostic criteria should be revised to include cases that show only bile duct wall thickness without biliary stricture among the diagnostic items.

In summary, we herein described a case of IgG4-SC with a severely thickened bile duct wall without a biliary stricture. This type of IgG4-SC should be considered in the IgG4-SC diagnosis and incorporated into the cholangiographic classification system as sufficient numbers of similar cases are accumulated.

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

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