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CASE REPORT

Diagnostic usefulness of precise examinations with intraductal ultrasonography, peroral cholangioscopy and laparoscopy of immunoglobulin G4-related sclerosing cholangitis

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Herein, a case of immunoglobulin G4 (IgG4)-related sclerosing cholangitis is reported. IgG4 was diagnosed based on observations from peroral cholangioscopy and laparoscopy, and these methods are proposed for definitive and precise diagnosis of this disease. A 76-year-old male patient with inguinal Paget's disease had intrahepatic bile duct dilatations detected with computed tomography at his periodic check-up. Magnetic resonance cholangiography showed stenosis of the upper common bile duct and poststenotic dilatation of left intrahepatic bile ducts. The portal tract and bilateral intrahepatic bile ducts were surrounded by a low-density area, facing a tumor-like lesion at segment 2. Cytological examinations of the stenotic and dilated lesions revealed no cellular atypia. Histological examination of the tumor showed normal liver tissue with infiltration of lymphocytes, indicating an inflammatory pseudotumor. Peroral cholangioscopy excluded the possibility of biliary cancer and indicated that the stenotic legion was of submucosal, not mucosal, origin. Laparoscopic observations showed discoloration with wide yellowish-white lobular markings and wide depressed lesions at segments 2 and 7. Liver histology showed mild cholangitis with infiltration of IgG4-positive plasma cells around the bile ducts. Serum IgG4 levels were elevated. From these findings, the patient was diagnosed with IgG4-related sclerosing cholangitis. After treatment with prednisolone, blood liver enzymes and IgG4 rapidly normalized, bile duct dilatations improved, and the hepatic pseudotumor disappeared. The cholangitis did not recur. In this case, biliary cancer was ruled out by observation with peroral cholangioscopy, and the spread of cholangitis in the liver periphery was verified with laparoscopy; this information could not be obtained with other modalities.

Key words: immunoglobulin G4 (IgG4)-related sclerosing cholangitis, intraductal ultrasonography, laparoscopy, peroral chlangioscopy.

INTRODUCTION

Immunoglobulin G4 (IgG4)-related disease has been recognized as a systemic lymphoproliferative syndrome characterized by hyper-IgG4-γ-globulinemia in affected organs. IgG4-related sclerosing cholangitis is an IgG4-related disease that frequently occurs in the lower common bile duct in conjunction with autoimmune pancreatitis.[1] There are several reports of IgG4-related sclerosing cholangitis occurring without coexisting pancreatitis, but the frequency is thought to be as low as 10%.[1–3] A definitive diagnosis for IgG4-related sclerosing cholangitis is difficult to make because of the possibility of biliary cancer. Diagnostic criteria for IgG4-related sclerosing cholangitis have been proposed using cholangiography.[3] However, the severity of disease progression in the liver is not equivalent to that in the bile duct, and a comprehensive analysis to determine the affected regions in the liver is difficult to achieve with information from a liver biopsy and cholangiography. Here, we report a case of IgG4-related sclerosing cholangitis, in which the possibility of biliary cancer was excluded based on the results of precise examinations with intraductal ultrasonography (IDUS) and peroral cholangioscopy (POCS). The patient's liver was also evaluated by laparoscopic examination, showing the diagnostic usefulness of laparoscopy for determining the affected regions and disease severity of IgG4-related sclerosing cholangitis.

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CASE REPORT

A 76-year-old man with inguinal Paget's disease was referred to our department for further examination because abdominal computed tomography (CT) revealed intrahepatic bile duct dilatations at his periodic check-up. Imaging examinations with abdominal magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography showed

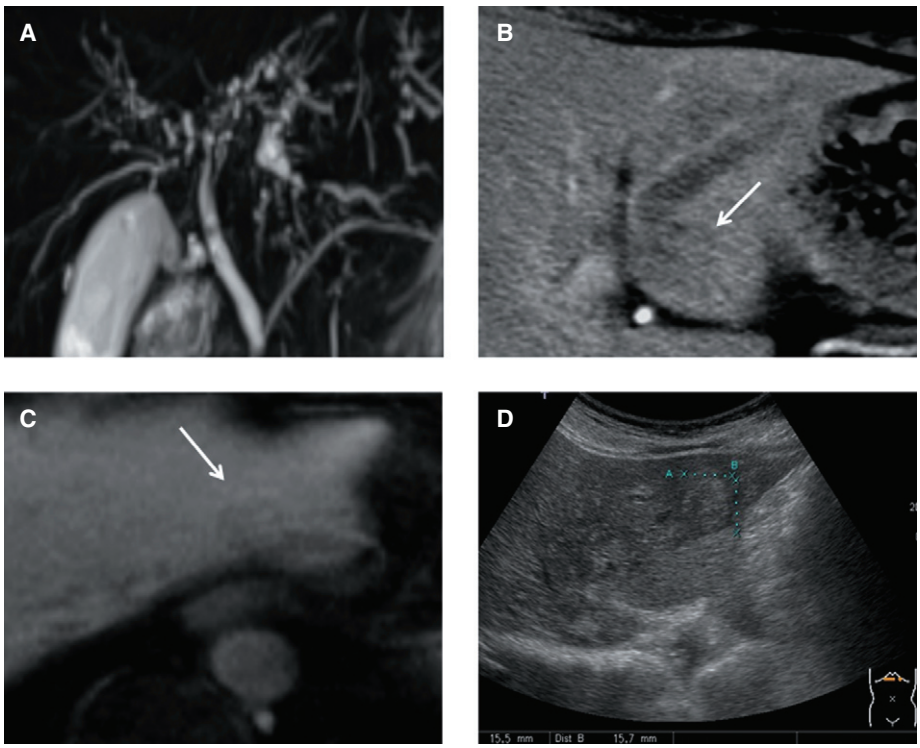

Fig. 1. Imaging studies of the liver of a patient with immunoglobulin G4-related sclerosing cholangitis. (a) Magnetic resonance cholangiopancreatography showed stenosis of the upper common bile duct and poststenotic dilatation of the left intrahepatic bile ducts. (b) Dynamic computed tomography showed low-density areas with delayed enhancement surrounding the portal tract and bilateral intrahepatic bile ducts, and a tumor-like lesion (diameter 1.5) cm was detected in a low-density area in early phase at segment 2 in an axial view (white arrow). (c) This tumor was also observed with a gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic magnetic resonance image as a low intensity area in early phase in an axial view (white arrow), and without clear detection of tumor-like lesion in plain T_1 or T_2 imaging. (d) Abdominal ultrasonography (axial view) showed that the tumor was round and had a low echoic tumor with high echoic margin.

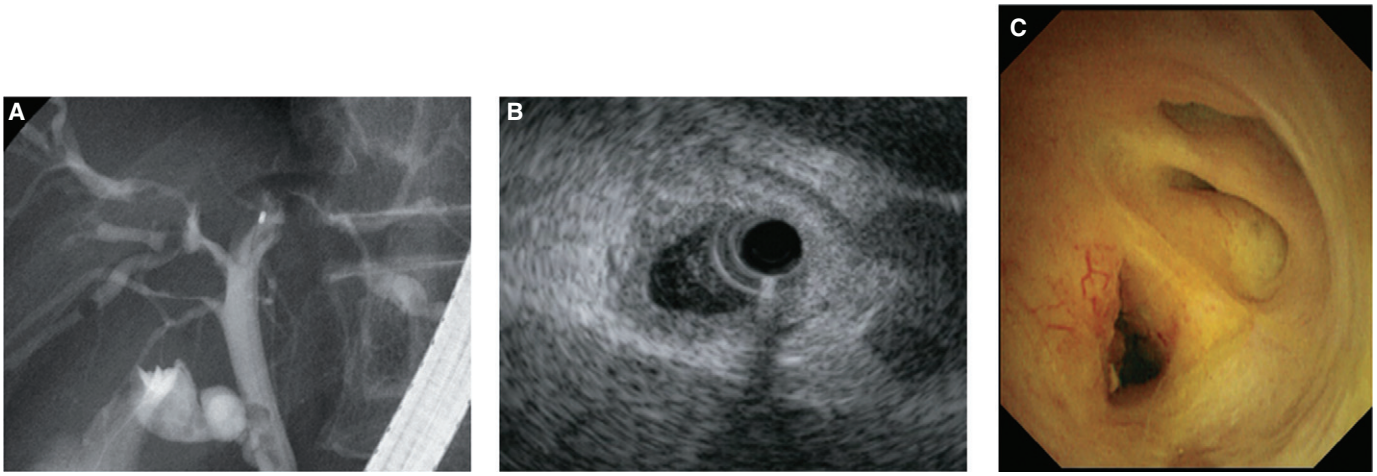

Fig. 2. Endoscopic examinations of the bile ducts of a patient with immunoglobulin G4-related sclerosing cholangitis. (a) Narrowed intrahepatic bile ducts were observed in the hepatic hilum on endoscopic retrograde cholangiography . (b) The walls of narrowed bile ducts were diffusely and circumferentially thickened to3.2 mm through the stenosis based on intraductal ultrasonography. (c) The mucosa of the lower site of the stenosis was smooth with proliferation of blood vessels based on peroral cholangioscopy.

stenosis of the upper common bile duct and poststenotic dilatation of the left intrahepatic bile ducts (Fig. 1a). No abnormalities were detected in the pancreas. Dynamic CT showed low-density areas with delayed enhancement surrounding the portal tract and bilateral intrahepatic bile ducts, and a small tumor, 1.5 cm in diameter, was detected in a low-density area at segment 2 in the early phase (Fig. 1b). This tumor was also observed with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid MRI as low intensity in early phase area, without clear detection of a tumor-like lesion in plain T_1 or T_2 imaging (Fig. 1c). The histological examination of the tumor with ultrasound-guided biopsy showed normal liver tissue with infiltration of lymphocytes and plasma cells, indicating an inflammatory pseudotumor. Abdominal ultrasonography showed that this tumor was round and had a low echoic tumor with high echoic margin. (Fig. 1d)

To exclude the possibility of biliary cancer, the patient was further examined with IDUS and POCS. As shown in Figure 2a, narrowed intrahepatic bile ducts were observed in the hepatic hilum on endoscopic retrograde cholangiography. The walls of narrowed bile ducts were diffusely and circumferentially thickened to 3.2 mm through the stenosis based on IDUS (Fig 2b), and the mucosa of the lower site of the

Table 1. Patient characteristics

Peripheral blood		Biochemistry		Immunological test	
WBC	4.91 ×10³/μL	TP	7.1 g/dL	IgA	70.5 mg/dL
Ne	70.5%	Alb	3.8 g/dL	IgM	30.7 mg/dL
Ly	15.2%	T-bil	2.61 g/dL	IgG	1636 mg/dL
Eos	4.8%	D-bil	1.23 g/dL	IgG4	819 mg/dL
RBC	3.43 ×10⁶/μL	AST	104 IU/L	ANA	<5.0
Hb	13.0 g/dL	ALT	116 IU/L	RF	<1.5 IU/mL
Plt	230 ×10³/μL	ALP	805 IU/L	AMA M2	<5.0
Tumor marker		γGTP	483 IU/L	PR3-ANCA	1.6 U/mL
CEA	4.79 ng/mL	AMY	91 IU/L	MPO-ANCA	1.6 U/ml
CA19-9	31.1 U/mL	CRP	1.43 mg/dL	–	–

Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA M2, antimitochondrial M2 antibody; AMY, amylase; ANA, anti-nuclear antigen; AST, aspartate aminotransferase; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; D-bil, direct bilirubin; Eos, eosinophil; γGTP, γ-glutamyl transpeptidase; Hb, hemoglobin; IgA, immunoglobulin A; IgG, immunoglobulin G; IgG4, immunoglobulin G4; IgM, immunoglobulin M; Ly, lymphocyte; MPO-ANCA, myeloperoxidase antineutrophil cytoplasmic antibody Ne, neutrophil; Plt, platelet count; PR3-ANCA, proteinase 3 antineutrophil cytoplasmic antibody; RBC, red blood cell; RF, rheumatoid factor; T-bil, total bilirubin; TP, total protein; WBC, white blood cell.

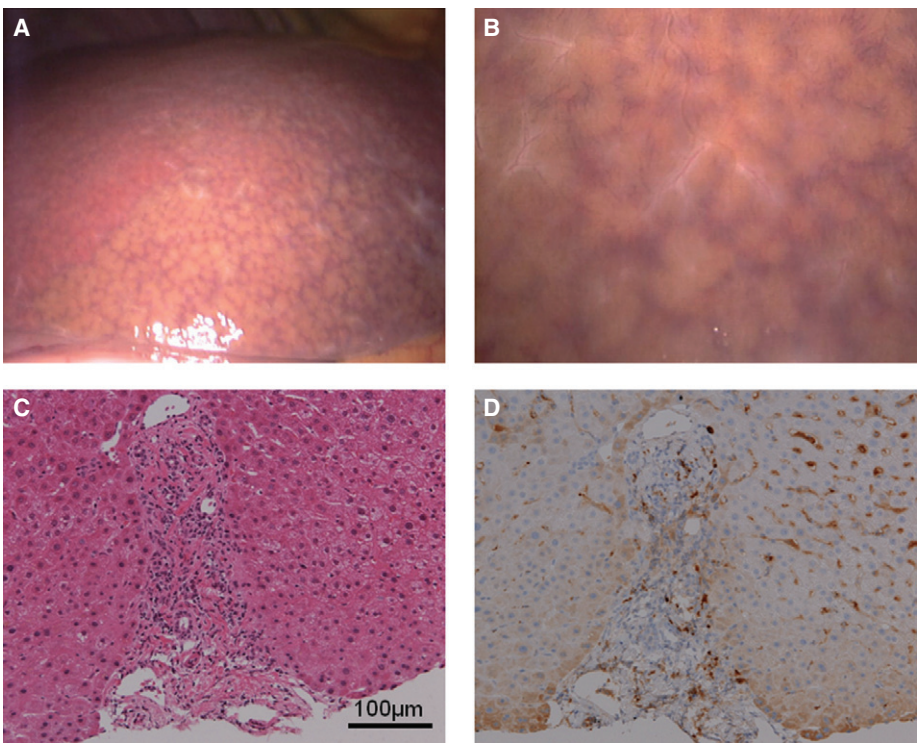

Fig. 3. Laparoscopic examinations and liver histology of a patient with immunoglobulin G4 (IgG4)-related sclerosing cholangitis. (a,b) The liver surface was dark brown in color with wide yellowish-white lobular markings, similar to the laparoscopic characteristics of primary biliary cirrhosis or primary sclerosing cholangitis. (c) Histology of the tissue obtained from segment 5 showed mild cholangitis with conventional hematoxylin and eosin staining, (d) with infiltration of IgG4-positive plasma cells around the bile ducts with IgG4-immunohistochemical staining .

stenosis was smooth with proliferation of blood vessels based on POCS (Fig 2c). Cytological examination of the stenotic and dilated lesions showed no cellular atypia. Therefore, biliary malignancies were not considered. Regarding IgG4-related cholangitis, the patient's IgG4 serum level was elevated to 819 mg/dL (Table 1), and the histochemical study of the inflammatory pseudotumor with anti-IgG1, and anti-IgG4 antibodies showed that more than 10 infiltrated lymphocytes in the high-power field were IgG4 positive. From these results, the patient was diagnosed of IgG4-related sclerosing cholangitis.

To further evaluate liver damage due to IgG4-related sclerosing cholangitis, a laparoscopic examination was also performed. The liver surface was dark brown in color with wide yellowish-white lobular markings, similar to the laparoscopic characteristics observed in primary biliary cirrhosis or primary sclerosing cholangitis (Fig. 3a,b). Wide depressed lesions were observed at segments 2 and 7, indicating severe liver damage at these sites. A liver biopsy sample was obtained from a peripheral lesion in segment 5, which showed wide yellowish-white markings on laparoscopy. The peripheral bile duct 5 was not dilated on endoscopic retrograde cholangiography, although the right intrahepatic bile duct was stenotic in the hilum. Histology showed mild cholangitis with infiltration of IgG4-positive plasma cells around the bile ducts without infiltration of IgG1 (Fig. 3c,d).

The patient was administered 30 mg prednisolone daily, and his blood liver enzymes rapidly normalized. Serum IgG4 levels decreased to 566 mg/dL 12 ays after the start of treatment and were 519 mg/dL 4 months later. The bile duct dilatations improved soon after, and the pseudotumor in the liver disappeared. Recurrence or progression of the cholangitis was not observed thereafter.

DISCUSSION

In cases of IgG4-related sclerosing cholangitis, steroids should be the first and standard treatment, and most patients respond well to this. However, it has been reported that all the patients with IgG4-related diseases do not respond to steroid.[4] Therefore, precise information about the severity of disease progression should be required. There have been several studies showing the imaging findings and pathological features of IgG4-related sclerosing cholangitis,[5,6] and diagnostic criteria for this disease have been proposed using cholangiography.[3] However, diagnoses using cholangiography seem inadequate for assessing disease progression in the liver because the severity of disease progression in the liver is not equivalent to that in the bile duct. Histopathological examination performed by ultrasonography-guided liver biopsy carries a risk of sampling errors. Therefore, a comprehensive assessment of disease severity in the whole liver is difficult to obtain using cholangiography and ultrasonography-guided liver biopsy alone. Indeed, in the present case, patchy distribution of hepatic peripheral lesions, except for an inflammatory pseudotumor, was difficult to detect with CT, MRI, or cholangiography. Only laparoscopic imaging was able to reveal the severity of disease progression in the whole liver, although there have been several reports about pseudotumor in the liver complicated with IgG4-related syndrome.[7,8] To our knowledge, this is the first report to propose the usefulness of laparoscopy as an additional examination for evaluating the severity of disease progression of IgG4-related sclerosing cholangitis.

Laparoscopy allows a survey view of the liver surface, and its clinical value has been reported in the diagnosis of viral hepatitis,[9] primary biliary cirrhosis,[10,11] and primary sclerosing cholangitis.[12] In the present case, wide depressed lesions at segments 2 and 7, indicating severe liver damage, were clearly observed with laparoscopy but not with other imaging modalities. Laparoscopy-guided liver biopsy can recognize patchy distribution of liver damage and select adequate sites for liver biopsy, which can reduce the risk of sampling errors and offer definitive and precise diagnosis of the severity of the liver disease. Furthermore, wide yellowish-white lobular markings in the liver suggested chronic liver injury due to cholangitis in the peripheral bile ducts, a similar profile to those from previous studies of primary biliary cirrhosis or primary sclerosing cholangitis.[10–12] Further accumulation of laparoscopic findings of IgG4-related sclerosing cholangitis is necessary to clarify the specific findings of this disease.

Based on the MRI, dynamic CT, and magnetic resonance cholangiopancreatography results, the possibility of biliary cancer was initially considered, although the brush cytologies of the stenotic bile ducts did not show cell atypia. The POCS observation clearly showed that the stenosis of the bile ducts at the hepatic hilum did not result from a mucosal disease such as biliary cancer. Therefore, the present case supports the idea that POCS is very helpful for differential diagnosis when biliary cancer is suspected, because brush cytology cannot always provide accurate diagnosis of this disease.[13]

In conclusion, a case of IgG4-related sclerosing cholangitis, in which the possibility of biliary cancer was excluded by the results of precise examinations with IDUS and POCS, was reported. Additionally, the liver was evaluated with laparoscopy, which demonstrated the diagnostic usefulness of laparoscopy for assessing the severity of disease progression of IgG4-related sclerosing cholangitis.

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