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IgG4-related sclerosing cholangitis and autoimmune pancreatitis: Histological assessment of biopsies from Vater’s ampulla and the bile duct

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Abstract

Background and Aim: Autoimmune pancreatitis is commonly associated with immunoglobulin (Ig) G4-related sclerosing cholangitis (IgG4-SC). The discrimination between IgG4-SC and pancreatobiliary malignancies or primary sclerosing cholangitis (PSC) is now an important issue. The present study was carried out to examine the usefulness of endoscopic biopsies from Vater’s ampulla and the bile duct to diagnose IgG4-SC.

Methods: The present study included 29 IgG4-SC patients (26 with both pancreatitis and cholangitis, and 3 with cholangitis only), 6 PSC patients, and 27 pancreatobiliary carcinoma patients. All patients underwent endoscopic biopsies from Vater’s ampulla and the common bile duct. Biopsied specimens were histologically examined using immunostaining for IgG4.

Results: For the ampullary and bile duct biopsies, the IgG4-SC samples had a significantly greater number of IgG4-positive plasma cells than the PSC or pancreatobiliary carcinoma specimens. In addition, bile duct biopsies from five patients (17%) with IgG4-SC showed diffuse inflammatory cell infiltration with irregular fibrosis corresponding to the histological features of lymphoplasmacytic sclerosing pancreatocholangitis. Based on the threshold of 10 IgG4-positive plasma cells per high power field, the diagnostic rates of the ampullar and bile duct biopsies were both 52% (15/29 cases). Twenty-one patients (72%) had more than 10 IgG4-positive plasma cells in at least one biopsy. The bile duct biopsy was significantly valuable for IgG4-SC patients with swelling of the pancreatic head.

Conclusion: The present study suggested that ampullar and bile duct biopsies are useful for diagnosing IgG4-SC.

Key words
autoimmune pancreatitis, endoscopic biopsy, IgG4, IgG4-related sclerosing cholangitis, primary sclerosing cholangitis.

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Introduction

Autoimmune pancreatitis (AIP) is characterized by swelling of the pancreas, irregular stenosis of the pancreatic duct, high serum immunoglobulin (Ig) G4 concentrations and steroid sensitivity.1,2 IgG4-related diseases including AIP have characteristic pathological features, such as diffuse lymphoplasmacytic infiltration, irregular fibrosis, occasional eosinophil infiltration, obliterative phlebitis and many IgG4-positive plasma cells.3–5 AIP is commonly associated with sclerosing cholangitis, which is also called IgG4-related sclerosing cholangitis or IgG4-associated cholangitis.6,7 Much attention has focused on discriminating between AIP with cholangitis and primary sclerosing cholangitis (PSC) or pancreatobiliary malignancies, from both clinical and academic aspects.8–10 Distinguishing between these two conditions is important because their therapeutic strategies are completely different.11 In clinical situations, imaging and serological examinations, such as testing serum IgG4 levels, are carried out to discriminate these two conditions. However, in some cases, a pathological diagnosis is necessary for a definitive diagnosis.

The needle biopsy is one tool that can be used to pathologically examine the pancreas. However, interpreting the results is sometimes difficult as a result of the small specimen size and the heterogeneous distribution of inflammation in AIP.12,13 Recently, several groups reported that IgG4 immunostaining of endoscopic biopsies from Vater’s ampulla is useful for diagnosing AIP.14,15 The number of IgG4-positive plasma cells in ampullar biopsies for AIP was significantly higher than those for PSC or pancreatobiliary malignancies. Sepehr et al. also suggested that ampullary biopsies might be useful for assessing IgG4-positive plasma cells based on pathological examinations of surgically resected specimens.16 However, it seems difficult to make a definitive pathological diagnosis of AIP based only on the number of IgG4-positive cells, especially in a non-pancreatic tissue. We hypothesized that bile duct biopsies might be more useful for diagnosing AIP and more closely reflect the histopathology of...
the pancreas than ampullary biopsies because the bile duct is commonly involved in AIP.

Therefore, we carried out a clinicopathological study to examine the usefulness of endoscopic biopsies from Vater’s ampulla and the bile duct for discriminating between AIP and PSC or pancreatobiliary cancers.

Patients and methods

Patients

The present study consisted of 26 AIP patients (all associated with cholangitis), 3 patients with IgG4-related sclerosing cholangitis (without AIP), 6 PSC patients and 27 pancreatobiliary carcinoma patients. Patients with AIP or IgG4-related sclerosing cholangitis were examined in a single disease group named IgG4-related sclerosing cholangitis (IgG4-SC). All patients were diagnosed and treated at Hokkaido University Hospital from April 2006 to February 2009. After excluding four AIP patients without cholangitis, all patients diagnosed with AIP, IgG4-SC, and PSC at our institute were included in the present study. During the same period, we examined a total of 128 consecutive patients with pancreatic cancer and a total of 248 consecutive patients with bile duct cancer. Of the 128 patients with pancreatic cancer, 119 patients were excluded because of no biliary drainage (n = 5), no surgical treatment (n = 94) or biliary drainage only (n = 20). Of the 248 patients with pancreatic cancer, 230 patients were excluded because of no biliary drainage (n = 16), no surgical treatment (n = 67), biliary drainage only (n = 66) or transpapillary bile duct biopsy only (n = 81). All pancreatobiliary carcinoma patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) and ampullary and bile duct biopsies during this period were also included in the present study. The mean ages and male/female ratios were as follows: IgG4-SC, 68 years, 23/6; PSC, 44 years, 1/5; and pancreatobiliary carcinoma, 66 years, 22/5. The clinical presentations of patients with IgG4-SC included obstructive jaundice (13/29, 45%), mild abdominal pain (2/29, 7%) and bodyweight loss (1/29, 3%). Two patients (7%) were found to have elevated biliary enzymes based on a blood test. The remaining 11 patients (38%) did not have any subjective symptoms and were found to have abnormalities on a radiological examination for routine medical screening or follow-up for extra-pancreatobiliary diseases. PSC patients presented with serological liver dysfunction (4/6, 67%) and jaundice (2/6, 33%). Pancreatobiliary carcinoma patients had obstructive jaundice (21/27, 78%), elevated biliary enzymes (4/27, 15%), mild abdominal pain (1/21, 4%) and mild back pain (1/21, 4%). In accordance with the Declaration of Helsinki, written informed consent was obtained from each patient and their family members before ERCP or biopsies from Vater’s ampulla and the bile duct. As the present study comprised a retrospective review of cases, patient consent was required and the institutional review board approved the study protocols.

Diagnosis

IgG4-SC

AIP was diagnosed using the diagnostic criteria of the Japan Pancreas Society.17 All 26 patients with AIP showed diffuse or localized narrowing of the main pancreatic duct with or without swelling of the pancreas in imaging studies. All AIP patients showed bile duct involvement in these images. IgG4-SC without AIP (three patients) was diagnosed based on cholangiopancreatographic findings. The bile duct showed segmental strictures, long strictures with prestenotic dilation, and strictures of the distal common bile duct.18 No patients with IgG4-related sclerosing cholangitis showed characteristic pancreaticographic findings and swelling of the pancreas like AIP without sclerosing cholangitis. In addition, all patients, including both AIP and sclerosing cholangitis patients, had serological autoimmune abnormalities, such as hyper γ-globulinemia (8/29 cases, 28% of cases, mean 2.0 g/dL, range 1.3–6.1 g/dL), hyper IgG (18/29 cases, 62% of cases, mean 2250 mg/dL, range 1265–6160 mg/dL), hyper IgG4 (27/29 cases, 93% of cases, mean 549 mg/dL, 76–2970 mg/dL) or the presence of antinuclear antibodies (14/29 cases, 48% of cases). Two patients with normal levels of serum IgG4 showed diffuse sausage-like enlargement and delayed enhancement pattern of the pancreas with a capsule-like low-density rim and smooth margin on computed tomography (CT) and the characteristic ERCP findings described above. One of these patients had antinuclear antibodies, whereas the other had retroperitoneal fibrosis. Swelling of Vater’s ampulla was assessed using an endoscope in all patients according to previously reported criterion.18 The distribution of pancreatic swelling was also examined by CT.

PSC

PSC was diagnosed based on cholangiographic findings. The bile ducts showed multifocal stricturing and beading on ERCP. Extrahepatic and intrahepatic bile ducts were involved in all of the examined cases. All patients underwent a liver needle biopsy. All biopsies showed chronic cholangiopathic features, such as portal fibrosis, periductal fibrosis, portal inflammation, biliary epithelial damage, bile duct loss or accumulation of copper-binding protein in periportal hepatocytes. Only a few IgG4-positive plasma cells were present in portal tracts on IgG4 immunostaining. In terms of exclusion criteria, no patients had any medical history of biliary surgery, trauma or choledocholithiasis. Biliary malignancy has not been identified in any patients during the medical follow up until now. Two patients underwent liver transplantation, and explanted livers showed chronic duct destructive cholangitis consistent with PSC. The serum IgG4 concentrations were within the normal range for all six patients.

Pancreatobiliary carcinoma

The diagnosis of hepatobiliary carcinomas was made based on radiological and pathological findings. Radiologically, 18 patients had cholangiocarcinoma in their extrahepatic or hilar bile ducts, and nine patients were diagnosed with pancreatic head cancer. A pathological diagnosis was also made for all 27 patients based on surgical or biopsied specimens. All 27 patients had serum IgG4 concentrations within the normal range.

ERCP and endoscopic biopsies from Vater’s ampulla and the bile duct

All ERCP and endoscopic biopsies were carried out during the hospital stay. ERCP was carried out using a duodenoscope (JF-
A 1.7-mm-diameter cannula (PR-V416Q; Olympus Medical Systems) was inserted into the main pancreatic duct and bile ducts, cholangiopancreatograms were obtained and the location of stricture was carefully studied. After documenting the stricture, a 0.035-inch hydrophilic guidewire (stiff-type Jagwire; Boston Scientific Japan, Tokyo, Japan) was advanced to the tip of the cannula, through the stricture and into the bile duct beyond the stricture. After carrying out the ERCP, all patients underwent endoscopic biopsies using side-opening biopsy forceps (FB-45Q-1; Olympus) from Vater’s ampulla and the common bile duct in the same session. The guidewire was left in place and the biliary biopsy forceps were passed along the guidewire and into the bile duct. Bile duct biopsies were taken from the lower and intrapancreatic bile ducts or other stenotic portions in IgG4-SC patients, the extrahepatic bile duct in PSC patients and the involved bile duct in pancreatobiliary malignancy patients under fluoroscopic guidance. In all 29 IgG4-SC patients, biopsies were obtained from Vater’s ampulla and the common bile duct before corticosteroid therapy. After carrying out the bile duct biopsies, Vater’s ampulla biopsies were taken from the orifice of the common bile duct near the guidewire, but were not taken near the orifice of the pancreatic duct to avoid acute pancreatitis resulting from edema and reduced ductal flow. The procedures were finished without placing a pancreatic stent. All endoscopic procedures were carried out by the same experienced endoscopist (HK) while the patient was under conscious sedation with intravenous pethidine hydrochloride and diazepam. After the ERCP-related procedures, 50,000 units of ulinastatin were drip-infused twice (day of surgery and the next morning) over a period of 1–2 h. Antibiotics were drip-infused twice (once after the ERCP-related procedures and once the next morning) through a side tube.

**Histological examinations**

Histological examination was carried out by a pathologist (YZ) blinded to clinical information. The biopsied specimens were fixed in neutral formalin and embedded in paraffin. Sections (4 μm) were cut from each paraffin block and stained with hematoxylin–eosin or examined by immunohistochemistry. The following histological features were assessed for both biopsies: inflammatory cell infiltration (1+, mild; 2+, moderate; 3+, severe)\(^6\) (Figs 1,2), plasma cell infiltration (> 20 cells/high power field [HPF]), and eosinophil infiltration (> 20 cells/HPF). Mild inflammatory cell infiltration was defined by a small number of inflammatory cells that were scattered throughout the HPF. In severe inflammation, many diffuse inflammatory cells were observed. Samples were considered to have moderate inflammation when they showed between mild and severe inflammation. Although obliterative phlebitis is a characteristic histological feature of IgG4-SC, it was not assessed in the present study because it usually occurs in relatively large veins that were not sampled by the endoscopic biopsies.

**Immunohistochemistry**

IgG4 immunostaining was carried out with an autostainer (HX System Benchmark, Ventana Medical Systems, Tucson, AZ, USA)
following the manufacturer’s instructions. The primary antibody was an anti-IgG4 mouse monoclonal antibody (ZYMED Laboratory, San Francisco, CA, USA). Before incubating with the primary antibodies, the sections were pretreated with proteinase. IgG4-positive plasma cells were counted in the most inflamed HPF (10× eyepiece and 40× lens) in both the Vater’s ampulla and bile duct biopsies.

Statistical analysis

The degrees of inflammatory cell infiltration (mild/moderate/severe), plasma cells, eosinophils, and the numbers of IgG4-positive plasma cells on ampullary and bile duct biopsies were compared between the three groups using Tukey’s test. The numbers of IgG4-positive plasma cells in the ampullary and bile duct biopsies, and the clinical characteristics (swelling of Vater’s ampulla or the pancreatic head) of patients with IgG4-SC were also analyzed using \( \chi^2 \)-test and Fisher’s test. A value of \( P < 0.05 \) was considered statistically significant. All of the analyses were carried out using SPSS II for Windows, Version 8.0.1. J (SPSS, Chicago, IL, USA).

Results

Biopsies from Vater’s ampulla

The results of the histological examination of the ampullary biopsies are summarized in Table 1. There were no significant differences in the degrees of inflammatory cell infiltration, plasma cell infiltration (> 20 cells/HPF) and eosinophil infiltration (> 20 cells/HPF) among three disease groups. Three IgG4-SC cases had severe inflammatory cell infiltration (Fig. 1c), although they were not associated with the irregular fibrosis that is typically observed in surgical AIP or IgG4-SC specimens.

Biopsies from the common bile duct

The bile duct biopsies showed inflammatory cell infiltration, fibrosis and stromal edema to varying degrees in each case of IgG4-SC. Of the 29 IgG4-SC patients, 10 (34%) had plasma cell infiltrations greater than 20 cells/HPF, although this increase was not significantly greater than that observed in samples from PSC and pancreatobiliary carcinoma patients (Table 1). Interestingly, five of these cases (17% of all IgG4-SC patients, four with AIP and one with cholangitis only) showed lymphoplasmacytic infiltration intermixed with irregular fibrosis, which was corresponding to lymphoplasmacytic sclerosing pancreatitis and cholangitis (a pathological term of AIP/IgG4-SC) (Figs 1f, 2a). In addition, eosinophil infiltration (> 20/HPF), a characteristic feature of AIP, was only observed in patients with IgG4-SC (\( P < 0.05 \) vs pancreatobiliary malignancies) (Fig. 2b). Carcinoma tissues could be identified on the bile duct biopsy in 25 patients (93%) with pancreatobiliary malignancies.

Immunostaining of IgG4

The numbers of IgG4-positive plasma cells are shown in Table 1 and Figure 3. The number of IgG4-positive plasma cells in the ampullary biopsies from IgG4-SC patients was significantly higher than those of patients with PSC and pancreatobiliary carcinomas (\( P < 0.01 \)) (Fig. 4a). The bile duct biopsies also showed a greater number of IgG4-positive plasma cells in IgG4-SC patients. The number of IgG4-positive plasma cells in the bile duct biopsies from IgG4-SC patients was significantly higher than those of patients with PSC and pancreatobiliary carcinomas (\( P < 0.05 \) and \( P < 0.01 \), respectively). When 10 IgG4-positive cells/HPF was set as the cut-off threshold according to previous reports, the diagnostic rates of the ampullary and bile duct biopsies were both 52% (15/29 cases). Nine patients (31%) were IgG4-positive in both biopsies and 12 patients (41%) were positive in either of these biopsies. In total, 21 patients (72%) showed more than 10 IgG4-positive plasma cells in the bile duct biopsy. The diagnostic sensitivity and specificity of the biopsies were as follows: Vater’s ampulla biopsy, sensitivity 52%, specificity 89%; bile duct biopsy, sensitivity 52%, specificity 96%. All five cases showing characteristic lymphoplasmacytic sclerosing inflammation in the bile duct biopsy had more than 10 IgG4-positive plasma cells in the bile duct biopsy.
Endoscopic biopsy in IgG4-SC

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Table 1 Histological features of ampullary and bile duct biopsies

<table>
<thead>
<tr>
<th></th>
<th>IgG4-SC (n = 29)</th>
<th>PSC (n = 6)</th>
<th>PB carcinoma (n = 27)</th>
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</thead>
<tbody>
<tr>
<td>Biopsy from Vater’s ampulla</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of biopsies (mean and range)</td>
<td>1.4 (1–4)</td>
<td>1.2 (1–2)</td>
<td>1.1 (1–2)</td>
</tr>
<tr>
<td>Inflammation (mild/moderate/severe)</td>
<td>3/23/3</td>
<td>1/5/0</td>
<td>13/12/2</td>
</tr>
<tr>
<td>Plasma cells (&gt; 20/HPF)</td>
<td>7 (24%)</td>
<td>4 (67%)</td>
<td>14 (62%)</td>
</tr>
<tr>
<td>Eosinophils (&gt; 20/HPF)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IgG4-positive cells (mean and range/HPF)</td>
<td>27 (0–162)*</td>
<td>3 (0–5)</td>
<td>2 (0–20)</td>
</tr>
<tr>
<td>Biopsy from the bile duct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of biopsies (mean and range)</td>
<td>2.4 (1–7)</td>
<td>2.7 (1–7)</td>
<td>2.4 (1–12)</td>
</tr>
<tr>
<td>Inflammation (mild/moderate/severe)</td>
<td>18/9/2</td>
<td>4/1/1</td>
<td>22/5/0</td>
</tr>
<tr>
<td>Plasma cells (&gt; 20/HPF)</td>
<td>10 (34%)</td>
<td>2 (33%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Eosinophils (&gt; 20/HPF)</td>
<td>5 (17%)*</td>
<td>0</td>
<td>0</td>
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<tr>
<td>IgG4-positive cells (mean and range/HPF)</td>
<td>21 (0–157)*</td>
<td>4 (0–12)</td>
<td>1 (0–4)</td>
</tr>
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</table>

*P < 0.01 versus PSC and PB carcinoma; **P < 0.05 versus PB carcinoma; †P < 0.05 versus PSC and ‡P < 0.01 versus PB carcinoma.

Complications of ERCP and endoscopic biopsies from Vater’s ampulla and the bile duct

There were no complications related to ERCP or the biopsy, such as post-ERCP pancreatitis or cholangitis and bile duct perforation, in any of the patients.

Discussion

The results obtained from the present study can be summarized as follows: (i) out of 29 patients with IgG4-SC, 21 (72%) had more than 10 IgG4-positive plasma cells per HPF in at least either their ampullary or bile duct biopsy; (ii) compared between biopsies from Vater’s ampulla and the bile duct, the increased number of IgG4-positive plasma cells was the only histological feature that could be examined to diagnose IgG4-SC in ampullary biopsies. In contrast, eosinophil infiltration, as well as the number of IgG4-positive plasma cells, is a useful feature in bile duct biopsies; (iii) in the bile duct biopsies, 10 patients had a large number of plasma cells (> 20/HPF). Five of these patients also had lymphoplasmacytic infiltration intermixed with irregular fibrosis, which are histological features that presumably correspond to lymphoplasmacytic sclerosing pancreatitis and cholangitis; and (iv) the bile duct biopsies were especially useful for IgG4-SC patients with pancreatic head swelling.

Similar to previous reports, the present study also showed that AIP patients had a significantly higher number of IgG4-positive plasma cells in their ampullary biopsies than patients with PSC and pancreatobiliary carcinomas. Kubota et al. reported that 18 of 27 patients (67%) with AIP had more than 10 IgG4-positive plasma cells in their ampullary biopsies. Similarly, Kamisawa et al. reported that 8 of 10 patients (80%) were highly IgG4-positive (≥ 10 cells/HPF). Although the diagnostic rate of the current study was the lowest among the three endoscopic studies, 62% (41/66) of the total patients of the three studies had more than 10 IgG4-positive cells. AIP is typically diagnosed based on a combination of serological, radiological and pathological examinations. As much data have accumulated in this field, most AIP cases can be diagnosed based on serum IgG4 concentrations and characteristic radiological features. However, in some cases it is still difficult to differentiate AIP from pancreatic malignancies. For such cases, IgG4 immunostaining of ampullary biopsies might be one tool to facilitate the diagnosis of IgG4-SC or AIP.

For pathologists, it is not difficult to count the number of IgG4-positive cells in biopsied specimens, although it might be harder to interpret the number of positive cells. A pathological diagnosis is promising. However, as with all pathological studies, a high degree of experience is required to interpret the number of positive cells. A pathological diagnosis is
The number of immunoglobulin G4 (IgG4)-positive plasma cells in (a) ampullary and (b) bile duct biopsies. The number of IgG4-positive plasma cells is higher in patients with IgG4-related sclerosing cholangitis (SC) than in patients with primary sclerosing cholangitis (PSC) or pancreatobiliary (PB) carcinomas. *P < 0.01, **P < 0.05.

**Figure 4** Immunoglobulin G4 (IgG4) immunohistochemistry of a (a) Vater’s ampullary or (b) bile duct biopsy (IgG4-related sclerosing cholangitis patients). (a) Many IgG4-positive plasma cells are observed in an ampullary biopsy (magnification: x400). (b) Numerous IgG4-positive plasma cells are observed in a bile duct biopsy (magnification: x200).

**Table 2** Diagnostic rate of biopsies for IgG4-SC based on the threshold of 10 IgG4-positive cells/high power field

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<tr>
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<th>≤ 10 cells/HPF</th>
<th>&gt; 10 cell/HPF</th>
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<tr>
<td>Vater’s ampulla</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Bile duct biopsy</td>
<td>6</td>
<td>9</td>
</tr>
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</table>

HPF, high power field; IgG4-SC, immunoglobulin G4-related sclerosing cholangitis.
usually based on hematoxylin–eosin-stained specimens. Therefore, pathologists might hesitate to make a definitive pathological diagnosis of IgG4-SC or AIP based only on the number of IgG4-positive plasma cells in ampullary biopsies. For this reason, a bile duct biopsy might have an advantage compared to the standard ampullary biopsy. Five cases (17%) in the present study had a large number of plasma cells intermixed with irregular fibrosis. This sclerosing inflammation is a characteristic histological feature of IgG4-related diseases including AIP, and presumably might be biopsied from the main lesion of the pancreaticobiliary system. Indeed, the histological features of lymphoplasmacytic sclerosing pancreatitis are the most important characteristics for diagnosing AIP. In addition, all of those cases showed more than 10 IgG4-positive plasma cells per HPF in their bile duct biopsies. In those cases, a definitive diagnosis of AIP or IgG4-SC might be possible from the pathological aspect.

The ability to discriminate between IgG4-SC and PSC is currently an important issue. Similar to previous reports, the present study showed that IgG4 immunostaining of the ampullar biopsy is useful for making this distinction. Although a bile duct biopsy is also useful, it should be noted that more than 10 IgG4-positive plasma cells might rarely be observed in bile duct biopsies from PSC patients. The pathological features of IgG4-related sclerosing cholangitis and PSC are different. IgG4-cholangiopathy inflammation shows a transmural and homogeneous distribution within the bile duct wall. Erosions or intraluminal proliferation of xanthogranulomatous tissue are rare. IgG4-cholangiopathy is sometimes associated with an exuberant pseudotumorous inflammatory reaction. In contrast, inflammation is more pronounced on the luminal side with erosions or ulcerations in patients diagnosed with classical PSC. Before starting the present study, we speculated that these features might be useful for assessing bile duct biopsies. However, it was difficult to examine the distribution of inflammation on biopsied specimens because only luminal tissues were typically biopsied.

One of the limitations of the present study was the small number of PSC patients. Therefore, additional studies are necessary to conclude that bile duct biopsies are useful to discriminate between IgG4-SC and PSC. Another issue was the technical difficulty of bile duct biopsy. Biopsy samples are sometimes small or have artificial degeneration. The quality of the biopsy samples depends considerably on the experience of the endoscopists. One possible interpretation is that the diagnostic rate of pancreaticobiliary carcinoma based on a bile duct biopsy is too high in the present study. One explanation for this higher rate is that we have actively carried out this procedure for many patients who were suspected to have this malignancy and have gained technical experience.

### Conclusion

The present study showed the usefulness of Vater’s ampulla and bile duct biopsies for assessing the number of IgG4-positive plasma cells. Notably, the bile duct biopsy can show not only the number of IgG4-positive cells but also the histological features that are directly related to IgG4-SC or AIP.

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### References
