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SPECIAL FEATURE: REVIEW ARTICLE

Role of ultrasonography in the evaluation of autoimmune pancreatitis

# Endoscopic retrograde cholangiopancreatography and intraductal ultrasonography in the diagnosis of autoimmune pancreatitis and IgG4-related sclerosing cholangitis

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**Abstract**
Endoscopic retrograde cholangiopancreatography is used to evaluate the narrowing of the main pancreatic duct in autoimmune pancreatitis (AIP) and biliary stricture in IgG4-related sclerosing cholangitis (IgG4-SC). Intraductal ultrasonography enables detailed visualization of the thickening of the bile duct wall in IgG4-SC. Pancreatic cancer, cholangiocarcinoma, and primary sclerosing cholangitis are important mimicking conditions of AIP and IgG4-SC. Diffuse or segmental stricture without marked upstream dilatation is a typical pancreatographic finding in AIP. By contrast, a single, short stricture with marked upstream dilatation is a typical finding in pancreatic cancer. The cholangiogram of IgG4-SC is classified into four types based on biliary stricture location, and this cholangiogram classification is useful for the differential diagnosis of IgG4-SC. Endoscopic retrograde cholangiography can be used to distinguish between IgG4-SC and primary sclerosing cholangitis. A segmental/long and intrapancreatic stricture is a characteristic finding of IgG4-SC, whereas band-like strictures, a beaded or pruned-tree appearance, and diverticulum-like outpouching are characteristic of primary sclerosing cholangitis. The characteristic intraductal ultrasonographic findings of circular–symmetrical wall thickening, smooth outer and inner margins, and homogeneous internal echo at the biliary stricture site are useful for diagnosis of IgG4-SC. Thickening of the bile duct wall at non-stricture sites is also a typical intraductal ultrasonographic finding of IgG4-SC and can be used for differential diagnosis from cholangiocarcinoma. Transpapillary bile duct and duodenal papilla biopsy during endoscopic retrograde cholangiopancreatography are also useful in the diagnosis of IgG4-SC.

**Keywords** Autoimmune pancreatitis · Endoscopic retrograde cholangiopancreatography · IgG4-related disease · IgG4-related sclerosing cholangitis · Intraductal ultrasonography

## Introduction

Autoimmune pancreatitis (AIP) and IgG4-related sclerosing cholangitis (IgG4-SC) are distinct types of pancreatitis and cholangitis with unknown pathogenic mechanisms. AIP is classified into types 1 and 2 in the International Consensus Diagnostic Criteria for AIP (ICDC) [1]. Type 1 AIP is characterized by histological findings of lymphoplasmacytic sclerosing pancreatitis, and type 2 AIP is characterized by the histopathological pattern of idiopathic duct-centric pancreatitis or AIP with granulocytic epithelial lesions. Type 1 AIP and IgG4-SC are pancreatobiliary lesions of IgG4-related disease [2–7], and IgG4-SC is frequently associated with type 1 AIP. In this review, AIP indicates type 1 AIP, unless stated otherwise.

AIP shows imaging findings of a diffuse or focally enlarged pancreas and narrowing of the main pancreatic duct (MPD). IgG4-SC presents as biliary stricture and thickening of the bile duct wall. AIP and IgG4-SC respond well to steroid therapy [6, 8–10]. Pancreatic cancer is an important mimicker of AIP, as are primary sclerosing cholangitis (PSC) and cholangiocarcinoma of IgG4-SC. The differentiation of AIP and IgG4-SC from these mimicking conditions

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is important because of considerable differences in clinical outcomes and treatments.

Endoscopic retrograde cholangiopancreatography (ERCP) and ERCP-related procedures are important diagnostic modalities for the differentiation of AIP and IgG4-SC from mimicking conditions. ERCP-related procedures for the diagnosis of AIP and IgG4-SC include biliary intraductal ultrasonography (IDUS), transpapillary bile duct biopsy, and duodenal papilla biopsy. Narrowing of the MPD on ERCP is incorporated as a diagnostic item in the ICDC [1] and the Japanese clinical diagnostic criteria for AIP 2018 (JPS2018) [11]. Biliary stricture on ERCP and thickening of the bile duct wall on IDUS are also incorporated as diagnostic items in the clinical diagnostic criteria for IgG4-SC 2020 (IgG4-SC2020) [7]. Here, we review the utility of ERCP and IDUS in the diagnosis of AIP and IgG4-SC.

## Endoscopic retrograde cholangiopancreatography

1. **Procedure**

   ERCP enables visualization of the biliary and pancreatic duct systems at a higher resolution than is possible with magnetic resonance cholangiopancreatography (MRCP). Furthermore, additional procedures, such as cytology, biopsy, IDUS, and drainage of the biliary and pancreatic ducts, can be performed after ERCP. ERCP is limited by its invasiveness and the risk of adverse events, such as post-ERCP pancreatitis (PEP). However, it is useful for the diagnosis and treatment of biliary and pancreatic ductal diseases. The incidence of PEP was reported to be 4.5% in a retrospective cohort study of Nationwide Inpatient Sample data from 2011 to 2017 [12]. Diagnostic ERCP is commonly used in Japan, but rarely in Western countries. The incidence of PEP in patients with AIP, those with chronic pancreatitis, and normal controls was 1.2% (1/82), 2.9% (3/104), and 5.4% (61/1123), respectively [13]. Here, we report that the incidence of ERCP-related adverse events including PEP was low in patients with AIP. However, severe PEP is life threatening and results in substantial morbidity and occasional mortality. We should avoid unnecessary ERCP in the diagnosis of AIP and IgG4-SC, because the evaluation by MRCP is incorporated as diagnostic items in JPS2018 [11] and IgG4-SC2020 [7].
2. **Endoscopic retrograde pancreatography findings of autoimmune pancreatitis**

   The characteristic diagnostic endoscopic retrograde pancreatography (ERP) finding of AIP is distinctive narrowing of the MPD [14–18], which has been incorporated in JPS2018 [1, 11, 19]. The extent of MPD narrowing differs among AIP cases. Diffuse or segmental AIP shows narrowing of the MPD in over one-third of the entire pancreatic duct (Figure 1). By contrast, focal AIP exhibits focal narrowing of less than one-third of the MPD (Figure 2). Differentiation of focal narrowing of the MPD from pancreatic cancer is important, and ERP is useful for this purpose. The characteristic ERP findings of AIP are stricture along more than one-third the length of the MPD, multiple skipped narrowing, no upstream dilatation of the MPD above the narrowing (< 5 mm), and side branches arising from narrowed segments. By contrast, a single, short MPD stricture with upstream dilatation of the MPD is a typical ERP finding in pancreatic cancer. The sensitivity and specificity of ERP for the differential diagnosis of AIP from pancreatic cancer are 33–91% and 80–90%, respectively [14, 15, 18, 20–22]. Long (more than one-third the length of the MPD) or multiple strictures without marked upstream dilatation have been adopted as level 1 ductal imaging characteristics in the ICDC [1].

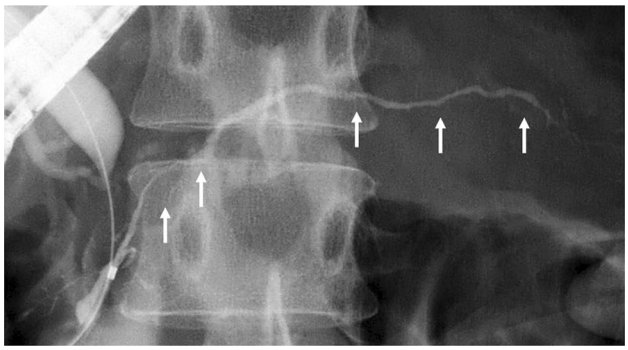

**Fig. 1** Endoscopic retrograde pancreatography showing the diffuse narrowing of the main pancreatic duct in the diffuse type of autoimmune pancreatitis. Arrows: narrowing of the main pancreatic duct

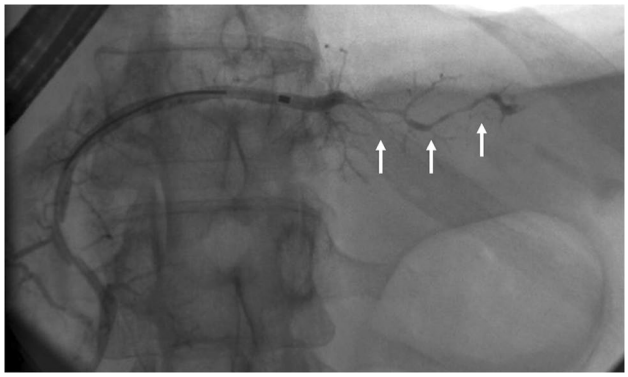

**Fig. 2** Endoscopic retrograde pancreatography showing the focal narrowing of the main pancreatic duct in the pancreatic tail in the focal type of autoimmune pancreatitis. Arrows: focal narrowing of the main pancreatic duct

MRCP can be used to evaluate narrowing of the MPD. However, its resolution is lower than that of ERP, hampering visualization of the branches of the pancreatic duct. It does enable evaluation of the area upstream of the MPD when the MPD is obstructed, which is not possible with ERP. Evaluation of the pancreatic duct using MRCP was incorporated in the JPS2018 because of the improved quality of MRCP and the utility of MRCP findings for the diagnosis of AIP [23]. MRCP will replace ERP for the evaluation of MPD narrowing in the diagnosis of AIP because of the improved resolution and lack of PEP risk.

In clinical practice, MRCP should be used for the evaluation of MPD at first because it is less invasive. It is necessary to acquire sufficient good quality images for detailed evaluation of the pancreatic duct. The detection of long or multiple strictures without marked upstream dilatation at MRCP suggests a diagnosis of AIP, and can be useful in the differential diagnosis of pancreatic cancer. When short narrowing of MPD is observed on MRCP, the differential diagnosis of pancreatic cancer is important. ERP should be considered for the evaluation of MPD if endoscopic ultrasound-fine needle aspiration cannot be performed. Additional brush cytology can be performed for the MPD stricture or cytology examination via pancreatic juice extraction using endoscopic naso-pancreatic ductal drainage after ERP.

3. **Endoscopic retrograde cholangiography findings of IgG4-SC**

Diffuse or segmental stricture of the intra- or extrahepatic bile ducts on endoscopic retrograde cholangiography (ERC) is observed in IgG4-SC. Narrowing of the intrahepatic and/or extrahepatic bile duct has been incorporated as a diagnostic item in IgG4-SC2020 [7]. ERC and percutaneous transhepatic cholangiography (PTC) are useful for the evaluation of biliary strictures. MRCP can be used to evaluate biliary strictures because of the recent improvement in image quality and its less invasive nature, and it is included in IgG4-SC2020 as a diagnostic modality for bile duct narrowing. However, MRCP is not superior to ERC or PTC for the evaluation of biliary strictures.

Stricture of the distal (intrapancreatic) bile duct is a characteristic cholangiographic finding of IgG4-SC because IgG4-SC is frequently associated with AIP. Another characteristic finding of IgG4-SC is a long stricture. By contrast, characteristic findings of PSC are band-like strictures (1–2 mm), a beaded or pruned-tree appearance, and diverticulum-like outpouching (Fig. 3). ERC can visualize these detailed differences, although these two diseases have similar cholangiographic features [24, 25]. Thus, direct cholangiographic modalities such as ERC or PTC are useful for the differentiation of IgG4-SC and PSC. Smooth biliary stricture without complete obstruction is a characteristic finding of IgG4-SC. By contrast, irregular biliary stricture and complete biliary obstruction are seen in cholangiocarcinoma or pancreatic cancer. Skipped biliary strictures are suggestive of IgG4-SC. Comparing IgG4-SC and pancreatic cancer, distal common bile duct stricture with deviation to the left is observed in pancreatic cancer [14].

Cholangiogram of IgG4-SC can be classified into four types based on the location of the biliary stricture [26] (Fig. 4). Type 1 IgG4-SC features a biliary stricture only in the lower common bile duct, and should be differentiated from pancreatic cancer, cholangiocarcinoma, and chronic pancreatitis. Type 2 IgG4-SC, in which stenosis is distributed diffusely throughout the intrahepatic and extrahepatic

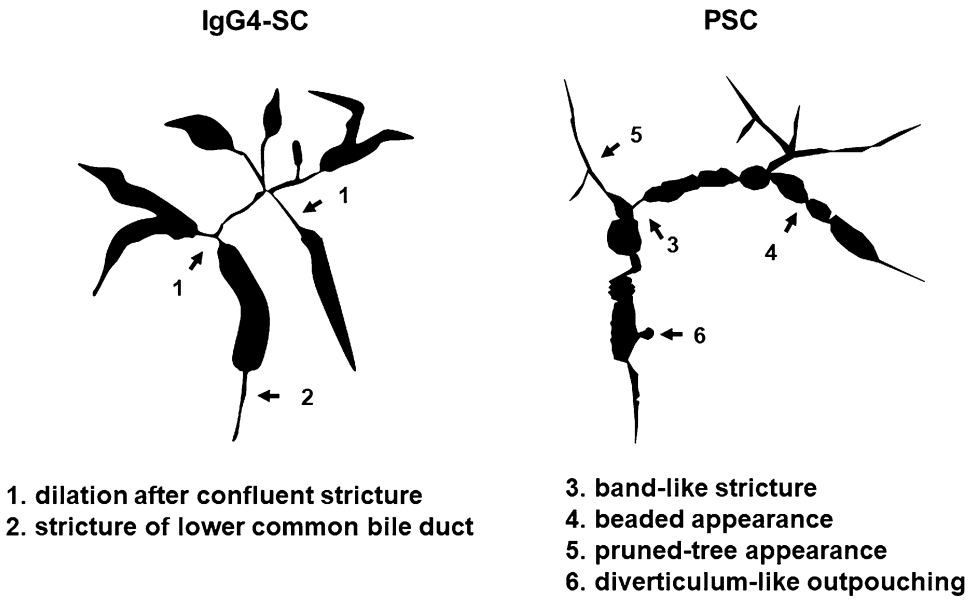


**Fig. 3** The characteristic cholangiogram features between IgG4-related sclerosing cholangitis and primary sclerosing cholangitis on endoscopic retrograde cholangiography. *IgG4-SC* IgG4-related sclerosing cholangitis; *PSC* primary sclerosing cholangitis

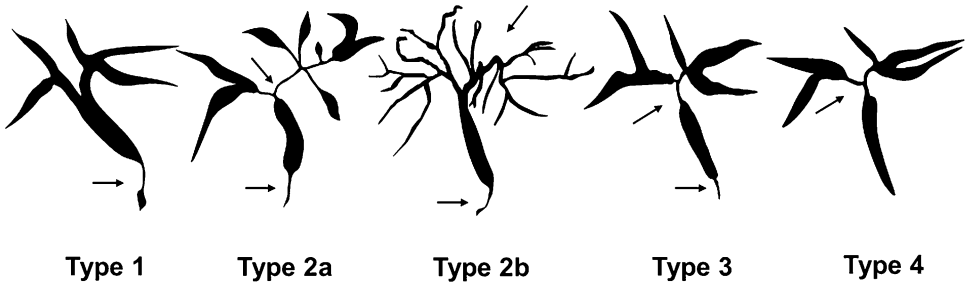


**Fig. 4** The cholangiographic classification of IgG4-related sclerosing cholangitis. Type 1: stenosis is located only in the lower common bile duct. Type 2: stenosis is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts. Type 2a: stricture of the intrahepatic bile ducts with prestenotic dilation. Type 2b: stricture of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches. Type 3: stenosis is located in both the hilar hepatic and the lower common bile ducts. Type 4: stenosis is located only in the hilar hepatic bile ducts. Arrows: stenosis of the bile ducts

bile ducts, should be differentiated from PSC. Type 2 IgG4-SC is subdivided into two subtypes: type 2a, characterized by stricture of the intrahepatic bile duct with prestenotic dilation, and type 2b, characterized by stricture of the intrahepatic bile duct without prestenotic dilation and reduced bile duct branches. Type 3 IgG4-SC is characterized by biliary stricture in the hilar hepatic and lower common bile ducts. Type 4 IgG4-SC presents with strictures of the bile duct only in hilar hepatic lesions. Types 3 and 4 IgG4-SC should be distinguished from cholangiocarcinoma, particularly that with a hilar lesion. Cholangiographic classification is useful for the differential diagnosis of IgG4-SC and is incorporated in IgG4-SC2020 [7]. In a large Japanese case series of IgG4-SC [27], type 1 was the most common type of IgG4-SC (62.9%) and IgG4-SC with AIP (69.9%), and type 4 was the most common type of IgG4-SC without AIP (30.9%).

**Fig. 5** The intraductal ultrasonography probe over the guidewire

## Intraductal ultrasonography (IDUS)

1. **Procedure**

   IDUS is a reliable procedure for evaluation of the bile duct during ERCP. It is performed using a thin-caliber ultrasonic probe that consists of a sheath catheter, transducer, and cable (Figure 5). IDUS provides high-resolution images of the bile duct wall, which typically consists of three layers and is < 0.6 mm thick [28]. IDUS should be carried out before initial biliary drainage, because mechanical inflammation can occur after biliary drainage. IDUS is useful for the differential diagnosis of indeterminate biliary strictures, superficial spread of bile duct cancer, and biliary stones.
2. **IDUS findings of IgG4-SC**

   Circular-symmetrical thickening of the bile duct wall with a smooth inner margin is a characteristic finding of IgG4-SC and is incorporated in IgG4-SC2020 [7]. Computed tomography, magnetic resonance imaging, and endoscopic ultrasound (EUS) can also be used to detect bile duct wall thickening. By providing higher-resolution images of the bile duct wall than do other modalities, EUS and IDUS facilitate the differential diagnosis of IgG4-SC. Details of the bile duct wall can be visualized more clearly with IDUS than with EUS. Thus, IDUS enables the evaluation of bile duct wall thickening in IgG4-SC.

   IDUS findings of circular–symmetrical wall thickening, smooth outer and inner margins, and a homogeneous internal echo at the biliary stricture site are useful for the diagnosis of IgG4-SC [29–33] (Figure 6). By contrast, the typical IDUS findings of PSC are circular-asymmetrical wall thickening, an irregular inner margin, an unclear outer margin, diverticulum-like outpouching, a heterogeneous internal echo, and disappearance of the three layers [34]. The different IDUS findings for IgG4-SC and PSC reflect pathological changes in the bile duct.

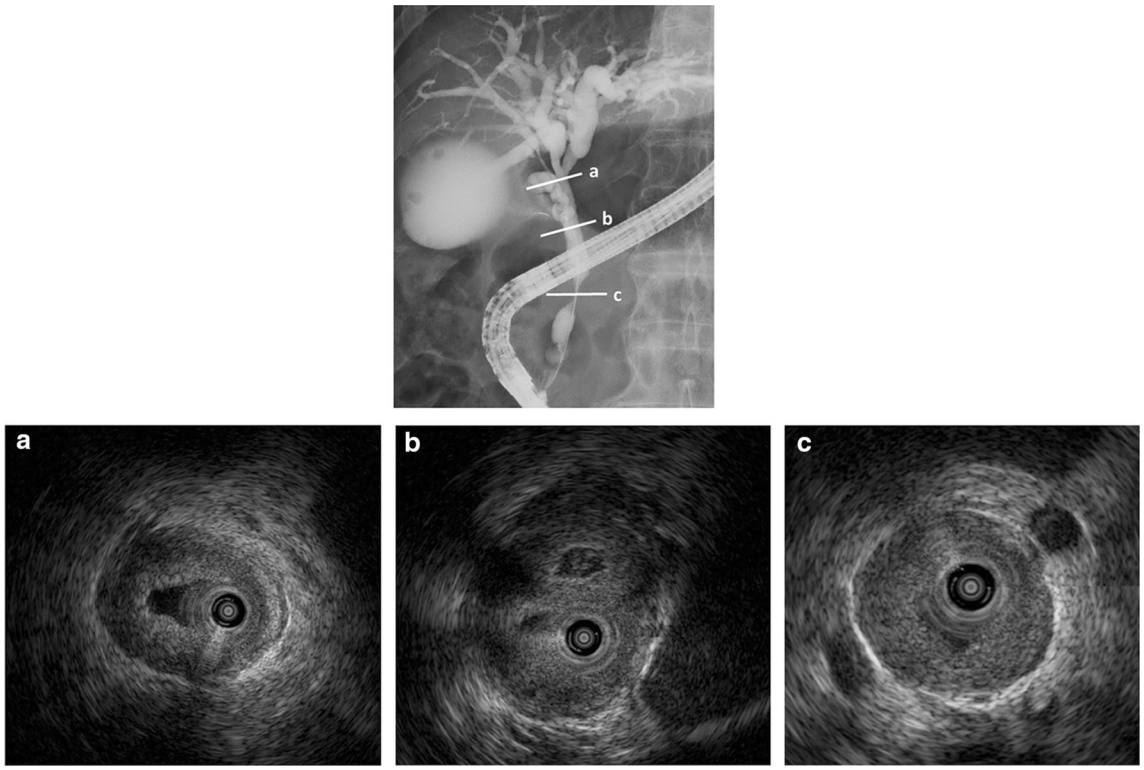


**Fig. 6** Endoscopic retrograde cholangiography showing hilar and intrapancreatic strictures in IgG4-SC. **a** Intraductal ultrasonography (IDUS) shows wall thickness in the hilar stricture. IDUS findings are circular-symmetrical wall thickening, smooth inner and outer margins, and homogeneous internal echo. **b** IDUS shows wall thickness in the middle CBD at the non-stricture site. **c** IDUS shows wall thickness in the intrapancreatic bile duct at the stricture site

Massive lymphoplasmacytic infiltration and fibrosis are observed primarily in bile duct wall stroma, and the bile duct epithelium remains intact in IgG4-SC. In contrast, the luminal side of the bile duct, including the epithelial lining, is affected more in PSC. An IDUS finding of wall thickening at the stricture site is useful for the distinction of IgG4-SC from PSC.

Thickening of the bile duct wall at non-stricture sites is also a diagnostic IDUS finding for IgG4-SC. Bile duct wall thickening spreads continuously from the intrapancreatic to the hilar bile duct in most IgG4-SC cases [29, 31, 34]. By contrast, bile duct wall thickening at non-stricture sites is not observed in cholangiocarcinoma. Thus, IDUS findings at non-stricture sites are useful for the differential diagnosis of IgG4-SC and cholangiocarcinoma [29]. In a large series of Japanese cases of IgG4-SC, wall thickening in a non-stricture area was observed significantly more frequently by IDUS than by EUS (80.9% vs. 73.8%; $p = 0.045$) [27]. The IDUS findings for IgG4-SC, PSC, and cholangiocarcinoma are summarized in Figure 7.

## Other endoscopic retrograde cholangiopancreatography-related procedures

Other ERCP-related procedures used in the diagnosis of AIP or IgG4-SC include transpapillary bile duct biopsy, duodenal papilla biopsy, and peroral cholangioscopy. Transpapillary bile duct biopsy is useful for the diagnosis of indeterminate biliary strictures. The reported sensitivity of bile duct biopsy with IgG4 immunostaining is 0–88% [29, 35–37]. This low sensitivity is attributable to the histopathological features of IgG4-SC. The bile duct epithelium is often normal, and lymphoplasmacytic infiltration and fibrosis are observed in bile duct wall stroma. Thus, a large biopsy sample containing bile duct stroma for the histopathological diagnosis of IgG4-SC is difficult to obtain. Cholangiocarcinoma is an important mimicker of IgG4-SC. The pooled sensitivity of bile duct biopsy for malignant biliary stricture was 48.1% in a systematic review and meta-analysis [38]. We reported that bile duct biopsy had a sensitivity of 82.0% for the diagnosis of cholangiocarcinoma [39]. Bile duct biopsy is important for the exclusion of cholangiocarcinoma, but it is not useful

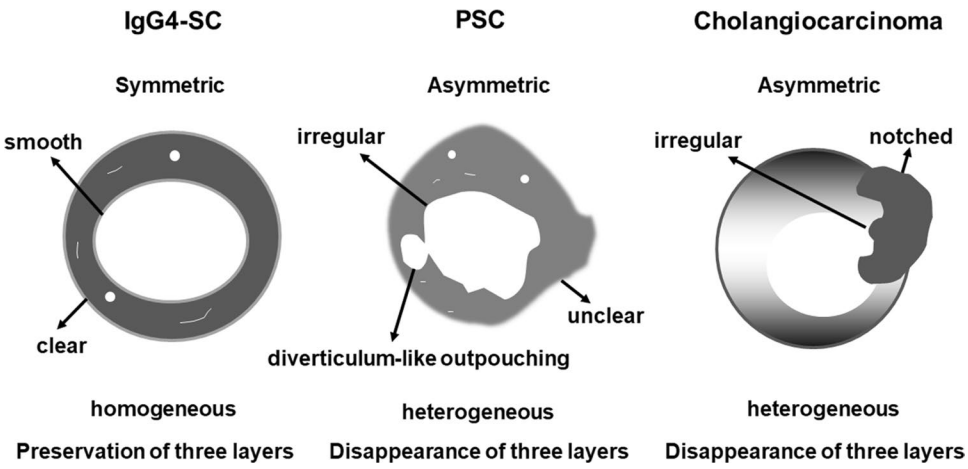


**Fig. 7** Intraductal ultrasonographic findings in the biliary stricture among IgG4-SC, primary sclerosing cholangitis, and cholangiocarcinoma. *IgG4-SC* IgG4-related sclerosing cholangitis; *PSC* primary sclerosing cholangitis

for the definitive histopathological diagnosis of IgG4-SC. Fluorescence in situ hybridization (FISH) of cytology specimens has been used in the diagnosis of biliary strictures. We reported that FISH analysis of transpapillary forceps biopsy specimens might be one option for differentiating IgG4-SC from cholangiocarcinoma [40].

Swollen duodenal papillae and abundant IgG4-positive plasma cells are duodenal papilla biopsy findings of AIP, particularly that with pancreatic head involvement. Duodenal papilla biopsy with IgG4 immunostaining aids the diagnosis of IgG4-SC [31, 41–44], and it is useful for the differential diagnosis of IgG4-SC from PSC. Duodenal papilla biopsy is listed as an option for the diagnosis of AIP in the ICDC [1]. It is simpler and easier to perform than bile duct biopsy. IgG4 immunostaining of biliary and ampullary tissue showed 51% pooled sensitivity and 97% pooled specificity for the diagnosis of AIP in a systematic review and meta-analysis [45].

Peroral cholangioscopy (POCS) is a useful modality for the differential diagnosis between benign and malignant bile duct stricture because it enables the direct endoscopic diagnosis of bile duct lesions and targeted biopsy. Characteristic POCS findings of IgG4-SC are a smooth mucosal surface, dilated and tortuous vessels without caliber alteration and disruption, and lack of easily bleeding [46, 47]. In PSC, blood vessel distribution is poor, and scarring and pseudodiverticula are seen. In cholangiocarcinoma, an irregular mucosal surface, caliber alteration and disruption of dilated vessels, and easily bleeding are observed. POCS might be a useful modality to differentiate IgG4-SC from PSC or cholangiocarcinoma, and additional histopathological examination using a POCS-guided biopsy specimen is helpful to differentiate from cholangiocarcinoma.

## Conclusions

We reviewed the utility of ERCP and IDUS for the diagnosis of AIP and IgG4-SC. ERCP is useful for the evaluation of MPD narrowing and biliary stricture. MRCP is replacing ERCP because of improvements in image quality and reduced invasiveness, and it is incorporated in JPS2018 and IgG4-SC2020. Cholangiographic classification facilitates the differential diagnosis of IgG4-SC from pancreatic cancer, PSC, and cholangiocarcinoma. ERC is useful because additional ERCP-related procedures, such as IDUS, biliary biopsy, and biliary drainage, can be performed. IDUS can be used for the differential diagnosis of IgG4-SC from PSC and cholangiocarcinoma. Bile duct biopsy is important for the differentiation of malignant biliary strictures from IgG4-SC.

## Declarations

**Conflict of interest** The authors declare that there are no conflicts of interest.

**Ethical approval** As this is a review article based on the published literature, no ethics approval was required.

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