Imaging: ERCP

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Introduction

Further insights into autoimmune pancreatitis (AIP) have been revealed by many researchers since a report by Yoshida et al. in 1995 [1]. Bile duct stricture accompanied by AIP has been considered as IgG4-related sclerosing cholangitis (IgG4-SC) based on several reports [2, 3]. Recently, IgG4-SC is regarded as a manifestation of a systemic IgG4-related disease (IgG4-RD) [4]. The diagnosis of IgG4-SC is based on the clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012 [5]. The clinical symptoms of IgG4-SC are similar to those of AIP. IgG4-SC is often observed in patients aged 60 years or older; it is more common in males, is associated with elevated levels of serum IgG4, and responds well to steroids. A progressive course, such as that observed in cases of primary sclerosing cholangitis (PSC), is rare, and the short-term prognosis is extremely favorable. However, the long-term prognosis for IgG4-SC remains unclear. Accurate diagnosis of IgG4-SC is essential for proper management of this disease. We present bile duct images using endoscopic retrograde cholangiopancreatography (ERCP) in cases of IgG4-SC.

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Histopathological Features of IgG4-SC and PSC

To diagnose IgG4-SC on the basis of bile duct images, understanding of the histopathological features of the disease is essential. In cases of IgG4-SC, extensive thickening of the bile duct walls is noted, in addition to lymphocyte and IgG4-positive plasma cell infiltration, fibrosis, and obliterative phlebitis [6]. At times it can be difficult to distinguish between IgG4-SC and PSC.

On the other hand, PSC is a non-specific and chronic bile duct inflammation and fibrosis, characterized by narrowing, occlusion, or dilation of the bile duct. PSC can progress to cholestatic hepatocirrhosis. In addition, onion skin-like periductal fibrosis can be observed around the interlobular ductules, along with vanishing bile duct syndrome [7]. Bile duct findings on ERCP are reflected by these histopathological features.

Establishment of the Clinical Diagnostic Criteria of IgG4-Related Sclerosing Cholangitis 2012

Recently, IgG4-RD has been considered as a systemic disease. Comprehensive diagnostic criteria for IgG4-RD have been proposed for diagnosing several conditions [4]. According to these criteria, cases that do not fulfill the criteria for IgG4-RD must be diagnosed under the diagnostic

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criteria for each individual organ. For biliary manifestations of IgG4-RD, a research group from the Ministry of Health, Labour and Welfare and the Japan Biliary Association established the IgG4-SC diagnostic criteria [5]. According to these criteria, the diagnosis is made on the basis of the following factors: bile duct imaging findings, elevated serum IgG4 levels, IgG4-RD complications, concerning organs other than the bile ducts, and histological bile duct findings. Response to steroids was set as an optional factor similar to AIP. Therefore, comprehensive diagnosis on the basis of the clinical diagnostic criteria for IgG4-SC is important in addition to bile duct findings.

Bile Duct Images in Cases of IgG4-SC

Nakazawa et al. classified IgG4-SC into four categories (Fig. 10.1). Type 1 displays strictures in the lower part of the common bile duct that should be differentiated from the constrictions caused by pancreatic cancer or bile duct cancer. Type 2 displays strictures diffusely distributed not only in the

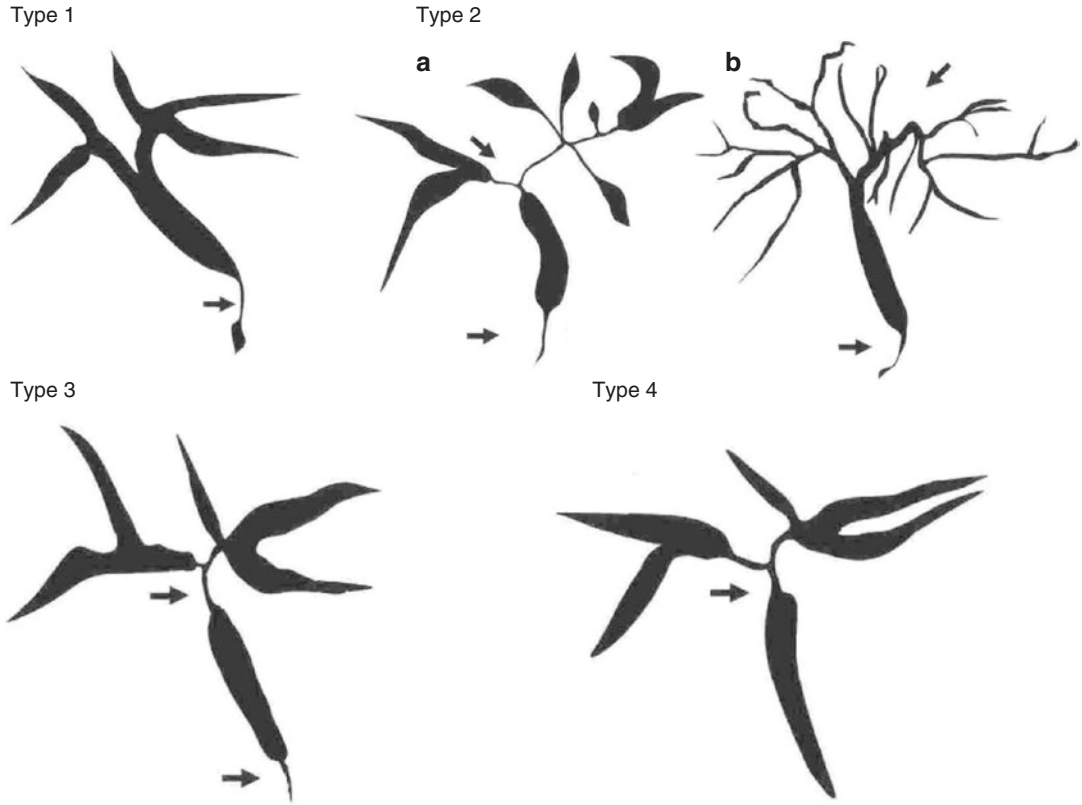

Fig. 10.1 Bile ducts affected by IgG4-related sclerosing cholangitis [8]. Type 1: Strictures only in the lower part of the common bile duct. This condition needs to be differentiated from pancreatic cancer. Type 2: Strictures are diffusely distributed in the lower part of the common bile duct and the intrahepatic bile ducts. This condition needs to be differentiated from primary sclerosing cholangitis. Type 2a is characterized by narrowing of the intrahepatic bile ducts with prestenotic dilation, and Type 2b is characterized by narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches. Type 3: Strictures are displayed in the lower part of the common bile duct and the hepatic portal region. This condition needs to be differentiated from bile duct cancer. Type 4: Strictures are displayed only in the bile ducts of the hepatic portal region. This condition needs to be differentiated from bile duct cancer

lower part of the common bile duct but also in the intrahepatic bile ducts. These types can be further divided into two subtypes, both of which should be differentiated from PSC. Type 3 shows strictures in the perihilar and the lower part of the bile duct. Type 4 displays strictures only in the bile ducts of the perihilar region and should be differentiated from bile duct cancer. The differential diagnosis in each type of bile duct stricture should be performed by careful examination.

Distinguishing Between IgG4-SC and PSC

Characteristics of the bile duct strictures are different between PSC and IgG4-SC [8, 9]. Bile duct findings for PSC and IgG4-SC are shown in Fig. 10.2. The findings of bile duct images of PSC exhibit short band-like strictures (1–2 mm), a beaded appearance with short strictures and dilations alternately appearing, a pruned-tree appearance with reduced intrahepatic branching, and diverticulum-like outpouching. In contrast, bile duct findings of IgG4-SC are characterized by longer segmental strictures (3 mm or longer), long strictures with prestenotic dilatation (10 mm or longer), and strictures in the lower part of the common bile duct. It is important to accurately diagnose these bile duct findings. Strictures that occur with PSC are extremely stiff, and often a guidewire is not able to pass through the duct, despite contrast medium being able to flow to the liver side. In contrast, bile duct strictures of IgG4-SC are softer, and it is generally easier to pass a guidewire and to insert a bile duct stent. It is also important to consider this bile duct "hardness," observed during ERCP, for the diagnosis.

Distinguishing Between IgG4-SC and Bile Duct Cancer

In addition to PSC, bile duct cancer should be differentiated from IgG4-SC. According to the Nakazawa et al. classification scheme, Types 1

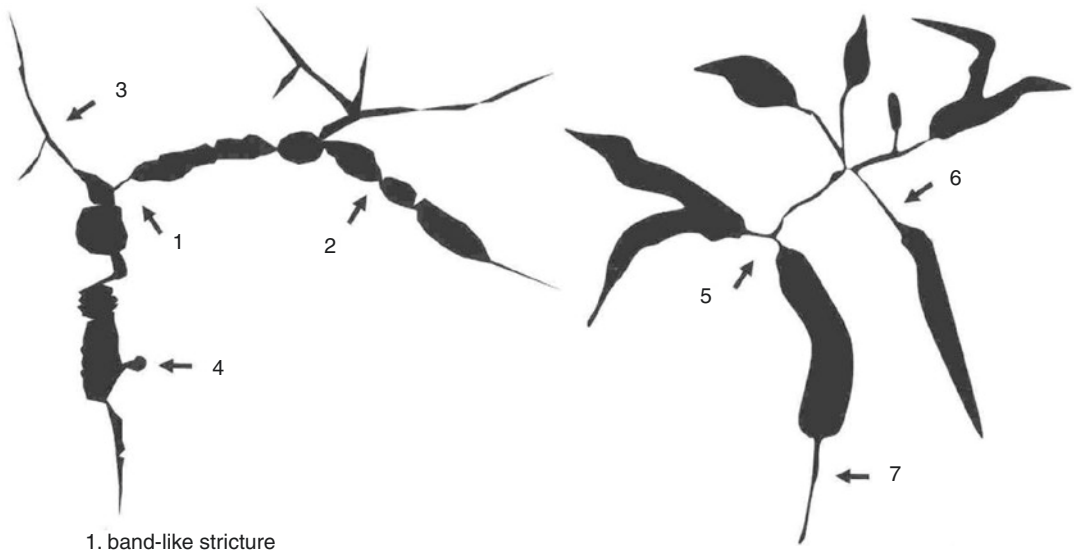

Fig. 10.2 Bile duct imaging characteristics in primary sclerosing cholangitis (PSC) and IgG4-related sclerosing cholangitis (IgG4-SC) [9]. 1–4 are specific to PSC, whereas 5–7 are characteristic of IgG4-SC

and 3 require differentiation from lower bile duct cancer, whereas Types 3 and 4 require differentiation from perihilar cholangiocarcinoma [4, 8]. Because most cases are very difficult to diagnose only on the basis of bile duct findings, it is important to consider factors that suggest the presence of IgG4-RD complications involving other organs, such as the pancreas, and whether or not the salivary glands are enlarged. The levels of serum IgG4 are also useful for differentiating between IgG4-SC and bile duct cancer. Ghazale et al. reported that elevated serum IgG4 levels were observed in 74% of 53 cases of IgG4-SC [3]. Nakazawa et al. also reported elevated IgG4 levels in 41 of the 47 cases they observed [10], suggesting that these findings are highly sensitive and specific. However, Ohara et al. reported an IgG4-SC cutoff level of 207 mg/dl for differentiating between IgG4-SC and bile duct cancer [11], indicating that the bile duct cancer with serum IgG4 ≥ 135 mg/dl may be misdiagnosed as IgG4-SC. Intraductal ultrasonography (IDUS) is useful for diagnosing IgG4-SC. Naitoh et al. reported the use of IDUS for differentiating IgG4-SC from bile duct cancer [12]. The bile duct wall thickening evidenced by IDUS in IgG4-SC and bile duct cancer is symmetrical and asymmetrical, respectively [12]. Kuwatani et al. reported that both IDUS and serum IgG4 should be used for diagnosing IgG4-SC and bile duct cancer [13]. It is important to diagnose on the basis of bile duct pathology; consequently, IgG4 immunostaining should be used in addition to hematoxylin and eosin staining for diagnosing IgG4-SC. Ghazale et al. reported the diagnostic yield of transpapillary bile duct biopsy to be 88% (14 of 16 cases) [3]. Kawakami et al. reported a high diagnostic performance of 52% (15 of 29 cases) [14]. However, the small sample volumes obtained from transpapillary bile duct biopsies make it difficult to identify obstructive phlebitis or storiform fibrosis. Naitoh et al. reported that only 18% of cases (3 of 17) could be accurately diagnosed with IgG4-SC after transpapillary bile duct biopsy [12], indicating that it is difficult to make an accurate diagnosis based solely on such a biopsy. Because there have been reports on the usefulness of liver biopsies [15–17] and the value of computed tomography (CT) scanning in differentiating IgG4-SC from bile duct cancer [18], it is important to use several modalities when diagnosing IgG4-SC.

Cases

Case 1 (Figs. 10.3 and 10.4)

The patient was a 66-year-old female, admitted to our hospital for examination of jaundice. An abdominal CT showed diffuse pancreatic swelling and bile duct dilatation. Her serum IgG4 level was 842 mg/dl. The findings of ERCP revealed a stricture in the lower part of the common bile duct. IDUS images showed symmetrical bile duct wall thickening. The patient was diagnosed with AIP complicated with IgG4-SC. Prednisolone (30 mg/day) was administered, and pancreatic swelling and the stricture in the lower part of the common bile duct improved after 1 month of treatment.

Case 2 (Figs. 10.5 and 10.6)

The patient was a 67-year-old male, referred to our hospital for examination of elevated levels of hepatobiliary enzymes and dilatation of the hilar bile duct. An abdominal CT showed swelling in the pancreatic tail and a stricture in the bile ducts in the perihilar portion. Serum IgG4 was high at 740 mg/dl and ERCP showed a perihilar bile duct stricture. IDUS images of the stricture showed symmetrical bile duct wall thickening and the histological findings of the bile duct were negative for malignancy. The patient was diagnosed as having AIP complicated with IgG4-SC. Treatment

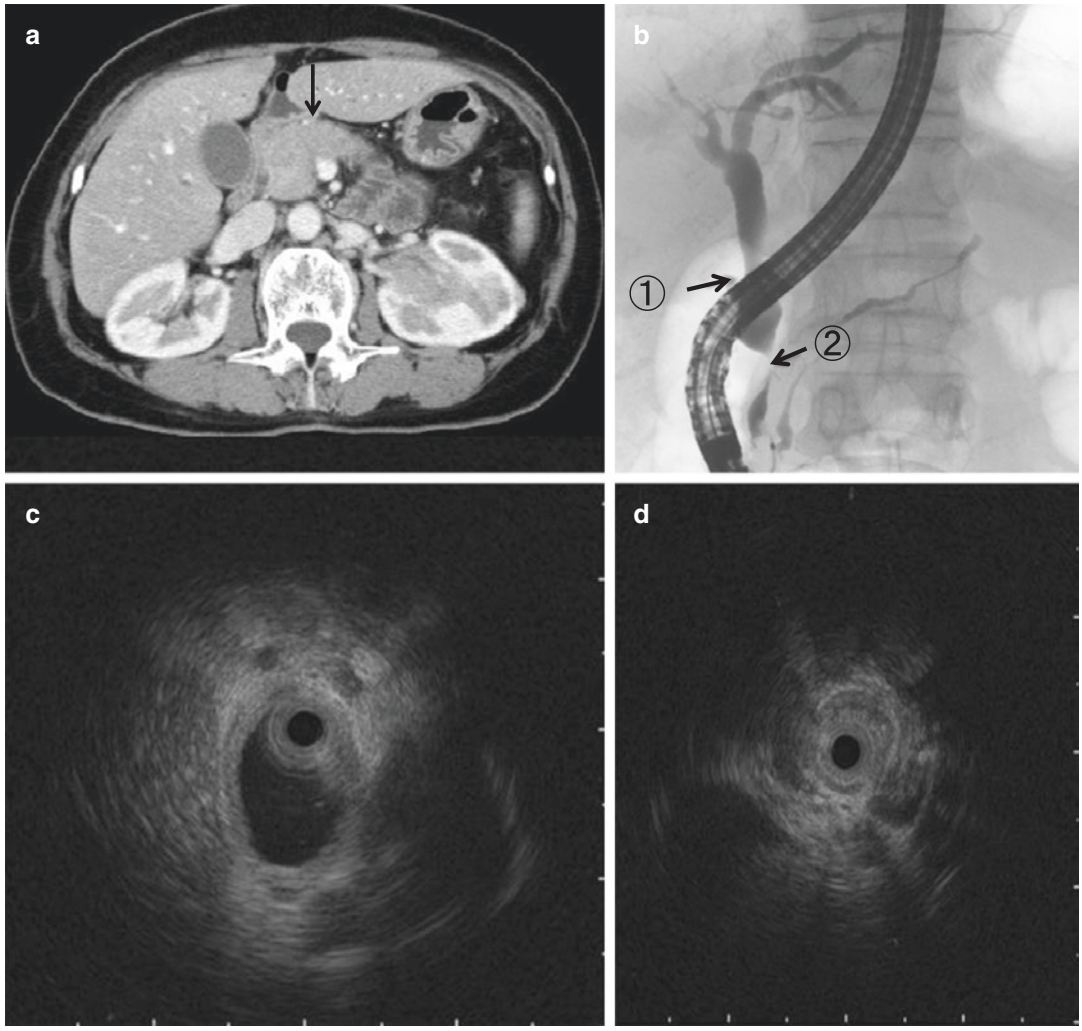

Fig. 10.3 IgG4-related sclerosing cholangitis with a stricture in the lower part of the common bile duct (case 1, pretreatment). (**a**) Abdominal computed tomography image showing pancreatic swelling (arrow). (**b**) Endoscopic retrograde cholangiopancreatography image showing a stricture in the lower part of the common bile duct (arrow 2). (**c**) Intraductal ultrasonography (IDUS) image (**b**, arrow 1) showing wall thickening outside a stricture. (**d**) IDUS image (**b**, arrow 2) showing asymmetrical wall thickening in a stricture

involved prednisolone (40 mg/day). The swelling in the pancreatic tail and perihilar bile duct stricture improved after 1 month.

We presented bile duct findings of IgG4-SC. Clinical diagnostic criteria for IgG4-SC enable better understanding of these diseases. There are many difficult cases to diagnose, such as cases of IgG4-negative IgG4-SC, IgG4-SC without AIP, or bile duct cancer with high serum IgG4 levels. We should diagnose these cases using bile duct findings, along with other modalities.

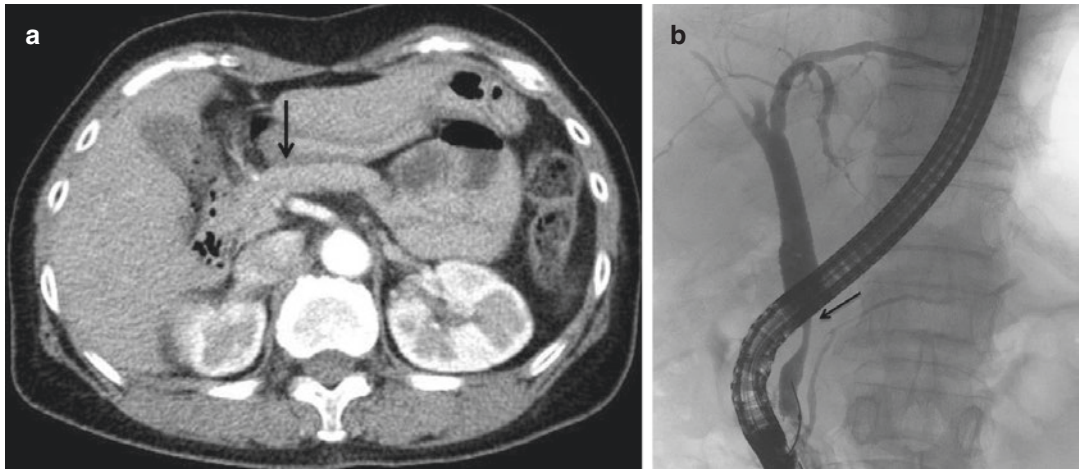

Fig. 10.4 IgG4-related sclerosing cholangitis with a stricture in the lower part of the common bile duct (case 1, posttreatment). (**a**) Abdominal computed tomography image showing an improvement in the pancreatic swelling (arrow). (**b**) Endoscopic retrograde cholangiopancreatography image showing an improvement in the stricture in the lower part of the common bile duct (arrow)

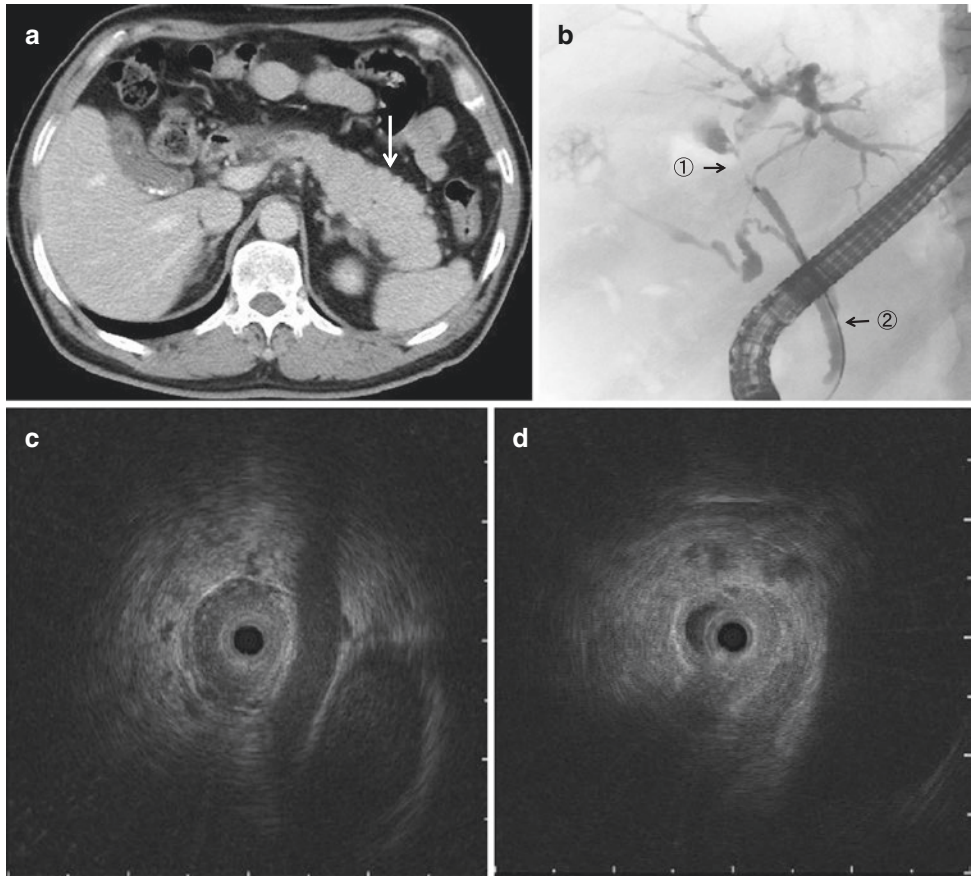

Fig. 10.5 IgG4-related sclerosing cholangitis with a stricture in a bile duct in the hepatic portal region (case 2, pretreatment). (**a**) Abdominal computed tomography image showing swelling in the pancreatic tail (arrow). (**b**) Endoscopic retrograde cholangiopancreatography image showing a stricture in a bile duct in the hepatic portal region (arrow 1). (**c**) Intraductal ultrasonography (IDUS) images (**b**, arrow 1) showing symmetrical wall thickening in the stricture. (**d**) IDUS images (**b**, arrow 2) showing asymmetrical wall thickening outside the stricture

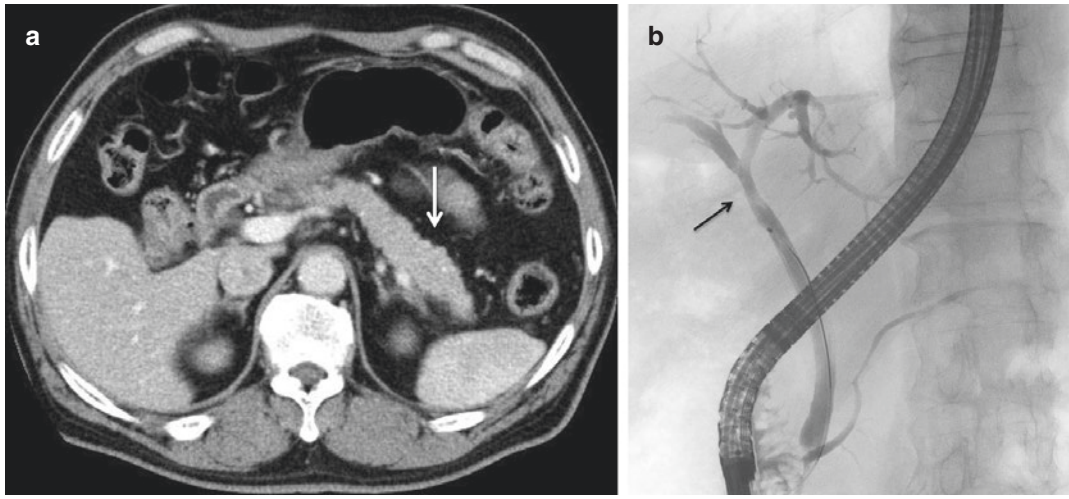

Fig. 10.6 IgG4-related sclerosing cholangitis with a stricture in a bile duct in the hepatic portal region (case 2, posttreatment). (**a**) Abdominal computed tomography image showing an improvement in the swelling in the pancreatic tail (arrow). (**b**) Endoscopic retrograde cholangiopancreatography image showing improvement in the stricture in the hepatic portal region (arrow)

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