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CASE REPORT

Two cases of immunoglobulin G4-related sclerosing cholangitis in which transabdominal ultrasonography was useful in diagnosis and follow-up observation

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Abstract Immunoglobulin G4-related disease (IgG4-RD) represents a group of disorders that share features of inflammation, plasma cell infiltrates, and fibrosis. Sclerosing cholangitis is a disorder involving inflammation, scarring, and destruction of the bile ducts. IgG4-related sclerosing cholangitis (IgG4-SC) has been proposed as a bile duct lesion associated with IgG4-RD. This disease entity can be distinguished from other types of sclerosing cholangitis and classified into four types based upon the region of strictures revealed by cholangiography. Here, we present two cases in which the finding of bile duct wall thickening visualized with transabdominal ultrasonography was useful in the diagnosis of patients with IgG4-SC. At present, transabdominal ultrasonography is not included in the diagnostic algorithm for IgG4-SC. We are certain that detailed observation of the bile duct wall with transabdominal ultrasonography can make a significant contribution to the diagnosis of IgG4-SC. Furthermore, we propose that transabdominal ultrasonography may be useful in following clinical improvement in cases where a steroid trial is the best option for treatment. Both cases emphasize the practicality of transabdominal ultrasonography in the diagnosis and follow-up observation of IgG4-SC.

Keywords Sclerosing cholangitis · Immunoglobulin · IgG4 · Transabdominal ultrasonography · IgG4-related disease · IgG4-related sclerosing cholangitis

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Introduction

IgG4-related sclerosing cholangitis (IgG4-SC) has been proposed as a bile duct lesion associated with IgG4-related disease (IgG4-RD). It is a disease that presents with local fibrosis at the site of the lesion and bile duct stenosis due to marked infiltration with IgG4-positive plasma cells. Nakazawa et al. reported that IgG4-SC can be classified into four types based on the region of strictures revealed by cholangiography [1]. These types include type 1, in which stenosis is located only in the lower part of the common bile duct; type 2, in which stenosis is diffusely distributed throughout the intra- and extrahepatic bile ducts; type 3, in which stenosis is detected in both the hilar hepatic region and the lower part of the common bile duct; and type 4, in which strictures of the bile duct are detected only in the hilar hepatic region. IgG-SC is often related to autoimmune pancreatitis (AIP); and while there are reports describing findings of bile duct wall thickening with endoscopic ultrasonography [2], we have found no reports describing the usefulness of transabdominal ultrasonography.

We report two cases in which the finding of bile duct wall thickening visible on transabdominal ultrasonography was useful in the diagnosis and follow-up observation of patients with IgG4-SC.

Case 1

A 71-year-old man was admitted to our hospital with jaundice. His medical history included hearing difficulty of unknown cause. There was nothing else noteworthy in his medical or family history. Elevations were seen in his total bilirubin at 22.5 mg/dL and hepatobiliary enzymes with aspartate aminotransferase (AST) 77 IU/L and alanine

aminotransferase (ALT) 90 IU/L. His total IgG level was elevated at 2391 mg/dL and his IgG4 level was 1080 mg/dL. Of the measured tumor markers, a slight elevation was seen in his CA19-9 at 44 U/mL. Amylase was within the normal range.

A transabdominal ultrasound image is shown in Fig. 1. Although no obvious dilation was seen in the right intrahepatic bile duct, the bile duct wall was thickened with mixed hypoechoic and hyperechoic areas, and parts of the border were indistinct (Fig. 1a). Mild dilation was seen in the left intrahepatic bile duct (Fig. 1b). The hilar bile duct wall was thickened, and tapered stenosis was present in the hepatic direction. The bile duct wall was visualized as a three-layer structure of hyperechoic, hypoechoic, and hyperechoic layers (Fig. 1c). No neoplastic-appearing lesions were observed intra- or extrahepatically. There were no abnormal findings in the gallbladder or pancreas.

Magnetic resonance cholangiopancreatography (MRCP) is shown in Fig. 2. Stenosis of the hilar and middle bile duct was seen. Irregular stenosis was seen in the right intrahepatic bile duct, and mild dilation was seen in the left intrahepatic bile duct. No stenosis or dilation was seen in the main pancreatic duct. An abdominal contrast computed tomography (CT) scan was obtained, but no neoplastic lesions were seen. On the MRCP presented, part of the main pancreatic duct appeared to be irregular, but we concluded that there was no complicating pancreatitis from an overall consideration of other slices, abdominal CT, and

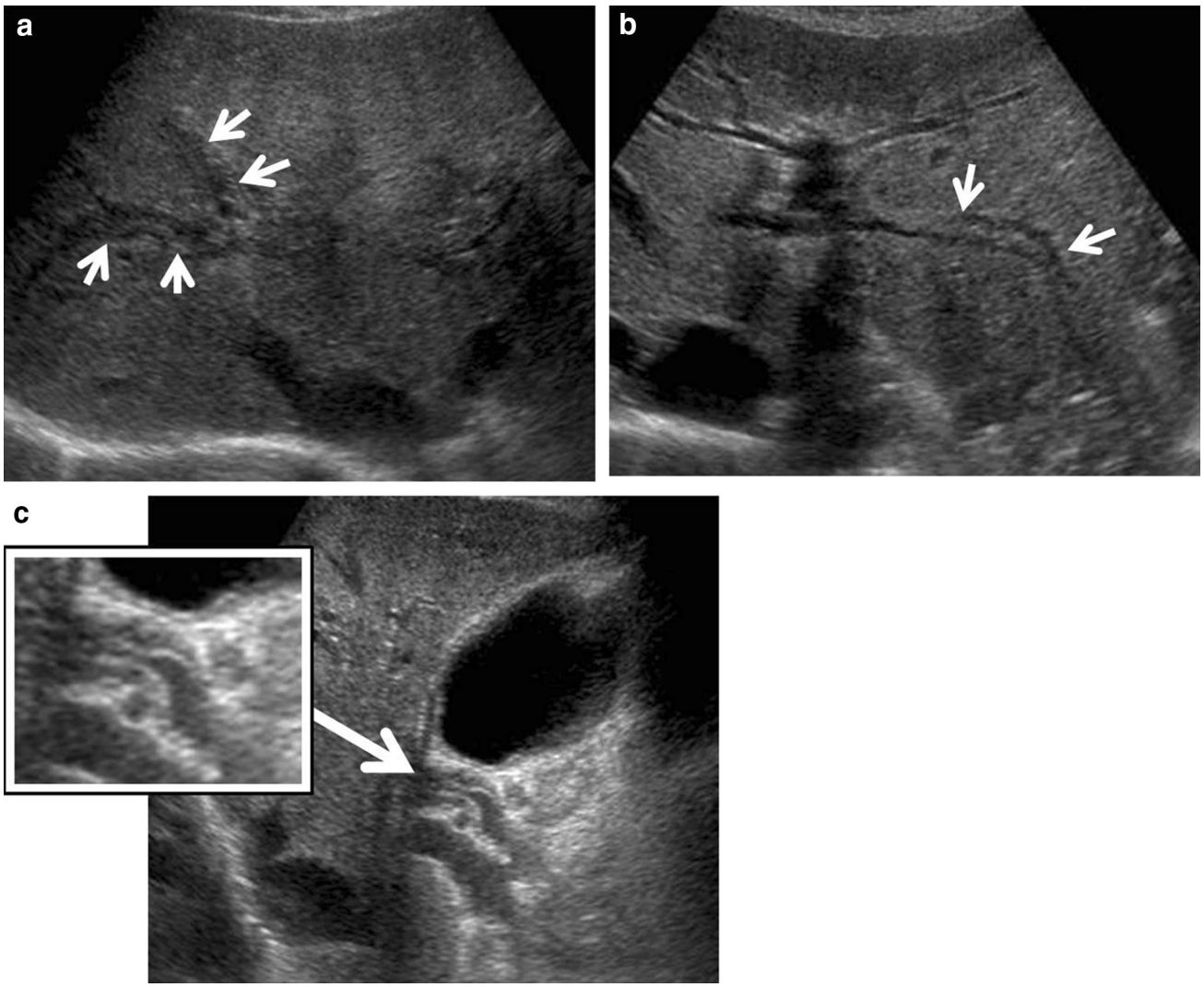

Fig. 1 Pre-treatment transabdominal ultrasound image (case 1). The right intrahepatic bile duct wall is thickened with mixed hypoechoic and hyperechoic areas, and parts of the border are indistinct (*arrow*), but no obvious dilation of the bile duct is seen (**a**). The left intrahepatic bile duct is mildly dilated in the segment indicated by the *arrow* (**b**). The hilar bile duct wall is thickened and shows tapered stenosis in the hepatic direction. The structure of the thickened bile duct wall consists of three layers that are hyperechoic, hypoechoic, and hyperechoic (**c**)

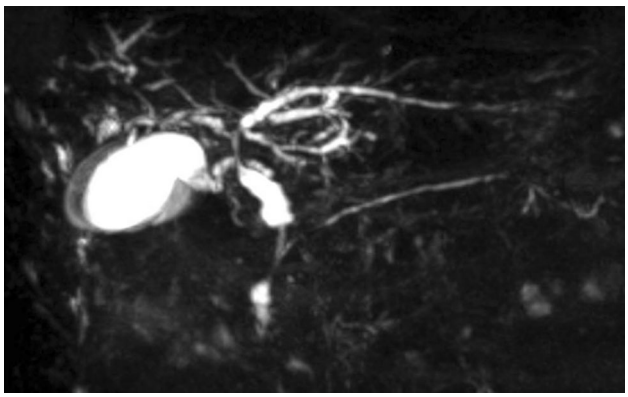

Fig. 2 Pre-treatment magnetic resonance cholangiopancreatography (case 1). Stenosis is seen in the hilar and middle bile ducts. Irregular stenosis is seen in the right intrahepatic bile duct, while mild dilation is seen in the left intrahepatic bile duct. No stenosis or dilation is seen in the main pancreatic duct

transabdominal ultrasonography. Based on the above, type 2 IgG4-SC was suspected. A liver biopsy was performed, and a definitive diagnosis of IgG4-SC was made histologically (Fig. 3). No complicating AIP was found.

After the diagnosis, treatment was initiated with oral prednisolone (PSL) 0.6 mg/kg/day (35 mg). Following the start of treatment, his hepatobiliary enzymes, total bilirubin, total IgG, and IgG4 soon returned to normal. A transabdominal ultrasound image from 2 months after initiation of treatment is shown in Fig. 4. The previous findings in the intrahepatic bile duct and hilar bile duct wall had improved. MRCP was performed around the same time (Fig. 5), and although slight narrowing was seen in the central portion of the bile duct, hilar bile duct findings were improved, similar to findings on transabdominal ultrasonography.

Case 2

A 72-year-old man was admitted to our hospital with jaundice. He had a history of treatment for a urinary calculus. There was nothing else noteworthy in his medical or family history. Elevations were seen in his total bilirubin at 6.6 mg/dL and hepatobiliary enzymes with AST 88 IU/L and ALT 71 IU/L. His total IgG level was elevated at 2039 mg/dL and his IgG4 level was 508 mg/dL. Pancreatic enzymes and tumor markers were within the normal range.

A transabdominal ultrasound image is shown in Fig. 6. The extrahepatic bile duct wall was thickened, and there was tapered stenosis toward the lower bile duct. The bile duct wall consisted of a three-layer structure of hyperechoic, hypoechoic, and hyperechoic layers. Although dilation was seen in the intrahepatic bile duct, there was neither thickening in the bile duct wall nor any edematous change noted. The pancreas was poorly observed because of intestinal gas.

In Fig. 7, an MRCP image is shown. Tapered stenosis was seen in the middle bile duct, and dilation of the intrahepatic bile duct and hilar bile duct was seen. There was narrowing of the main pancreatic duct in the pancreatic head and mild dilation of the pancreatic duct in the body and tail regions. On an abdominal contrast CT scan, there was thickening of the central bile duct wall and enlargement of the pancreatic head region, but no neoplastic-appearing lesions were seen (Fig. 8).

Type 1 IgG4-SC complicated by AIP was suspected based upon the above findings. A transpapillary bile duct biopsy was performed, and a bile duct stent was placed. We ruled out a neoplastic lesion in the obtained tissue, but a definitive diagnosis of IgG4-SC could not be made because of an insufficient number of plasma cells in the tissue.

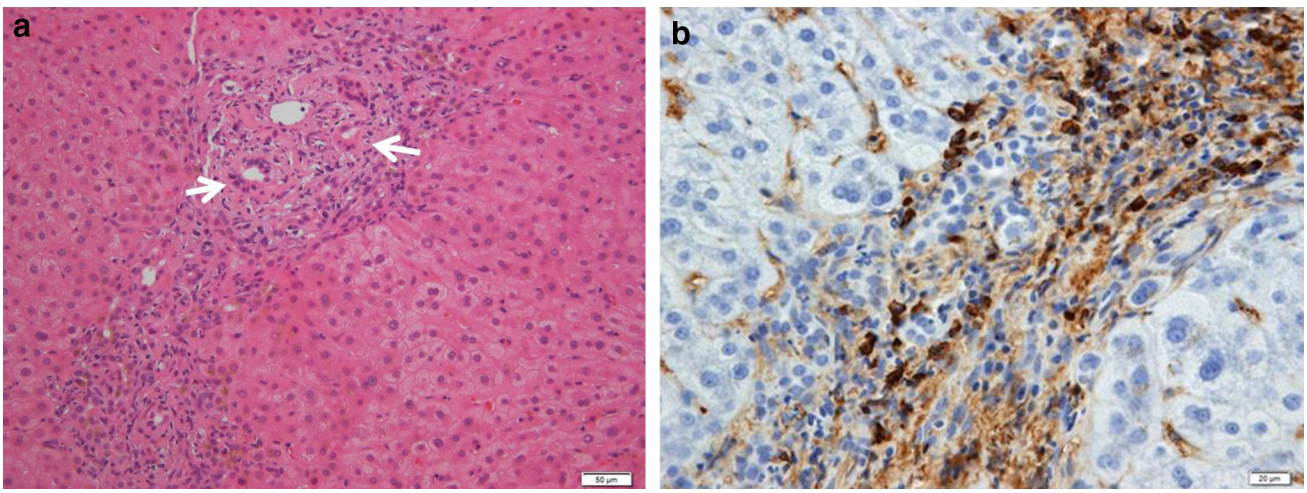

Fig. 3 Histopathology of liver biopsy (case 1). With H&E stain, lymphocytic and plasmacytic infiltration is seen around the bile duct wall (*arrows*) (**a**). With strongly magnified immunohistological staining, ten or more IgG-4-positive plasma cells are seen (**b**)

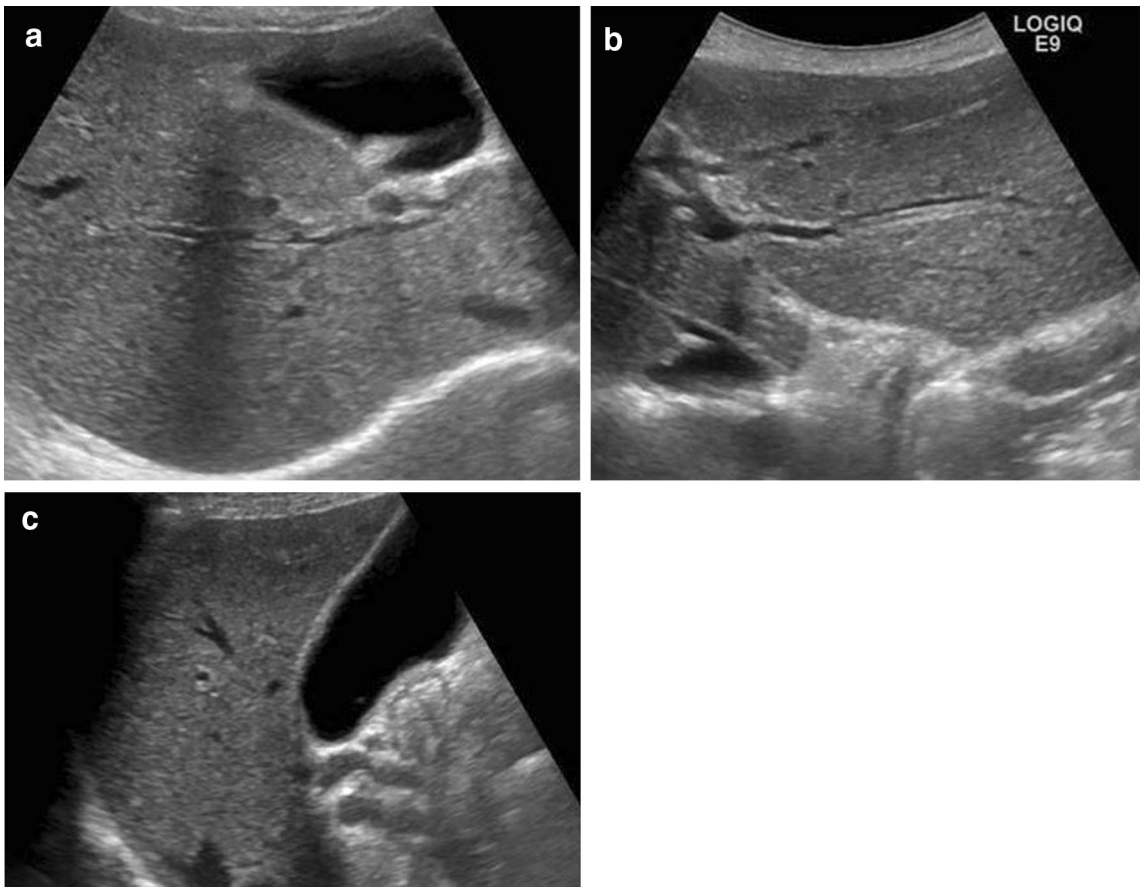

Fig. 4 Transabdominal ultrasound image 2 months after the start of treatment (case 1). The thickness with mixed hypoechoic and hyperechoic areas of the right intrahepatic bile duct (**a**), dilation of the left intrahepatic bile duct (**b**), and tapered stenosis and thickening of the wall of the hilar bile duct (**c**) are all improved

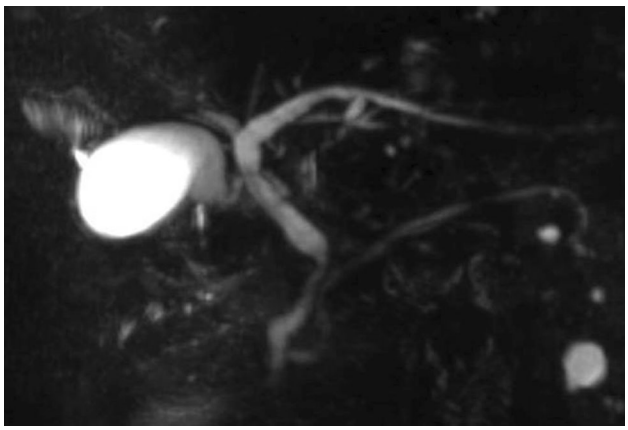

Fig. 5 Magnetic resonance cholangiopancreatography 2 months after the start of treatment (case 1). Slight narrowing is seen in the middle bile duct, but improvements are seen in hilar bile duct stenosis and right and left intrahepatic bile duct findings

Hepatobiliary enzymes quickly returned to normal with placement of the bile duct stent, but no improvement was seen in total IgG and IgG4 levels. Since a neoplastic-

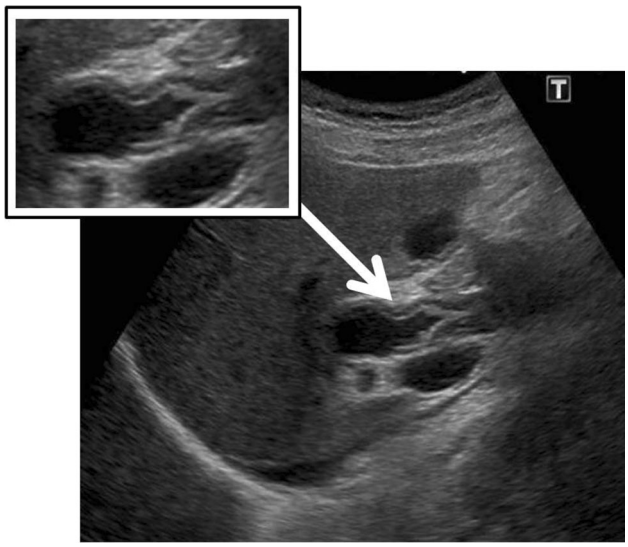

Fig. 6 Pre-treatment transabdominal ultrasound image (case 2). The extrahepatic bile duct wall is thickened, and tapered stenosis is seen toward the lower bile duct. The bile duct wall structure consists of three layers that are hyperechoic, hypoechoic, and hyperechoic

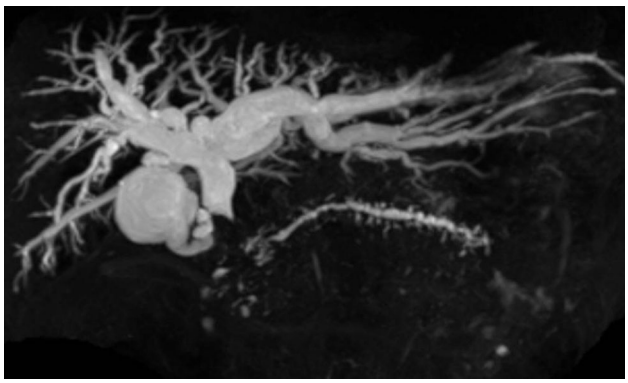

Fig. 7 Pre-treatment magnetic resonance cholangiopancreatography (case 2). Tapered stenosis in the middle bile duct and dilation of the intrahepatic bile duct and hilar bile duct are seen. There is narrowing of the main pancreatic duct in the pancreatic head and mild dilation of the pancreatic duct in the body and tail regions

appearing lesion was judged to be negative pathologically, treatment was started with PSL 0.6 mg/kg/day (30 mg) as a steroid trial. After this, the patient's total IgG and IgG4 quickly normalized, and a final diagnosis of IgG4-SC was made. Findings on transabdominal ultrasonography (Fig. 9) and MRCP (Fig. 10) 1 month after treatment demonstrated the stenosis of the extrahepatic bile duct had improved. On MRCP, narrowing of the pancreatic duct had also improved.

Discussion

The concept of IgG4-SC has been recognized worldwide, and the clinical diagnostic criteria for IgG4-SC were first proposed recently in Japan [3]. Association with AIP and

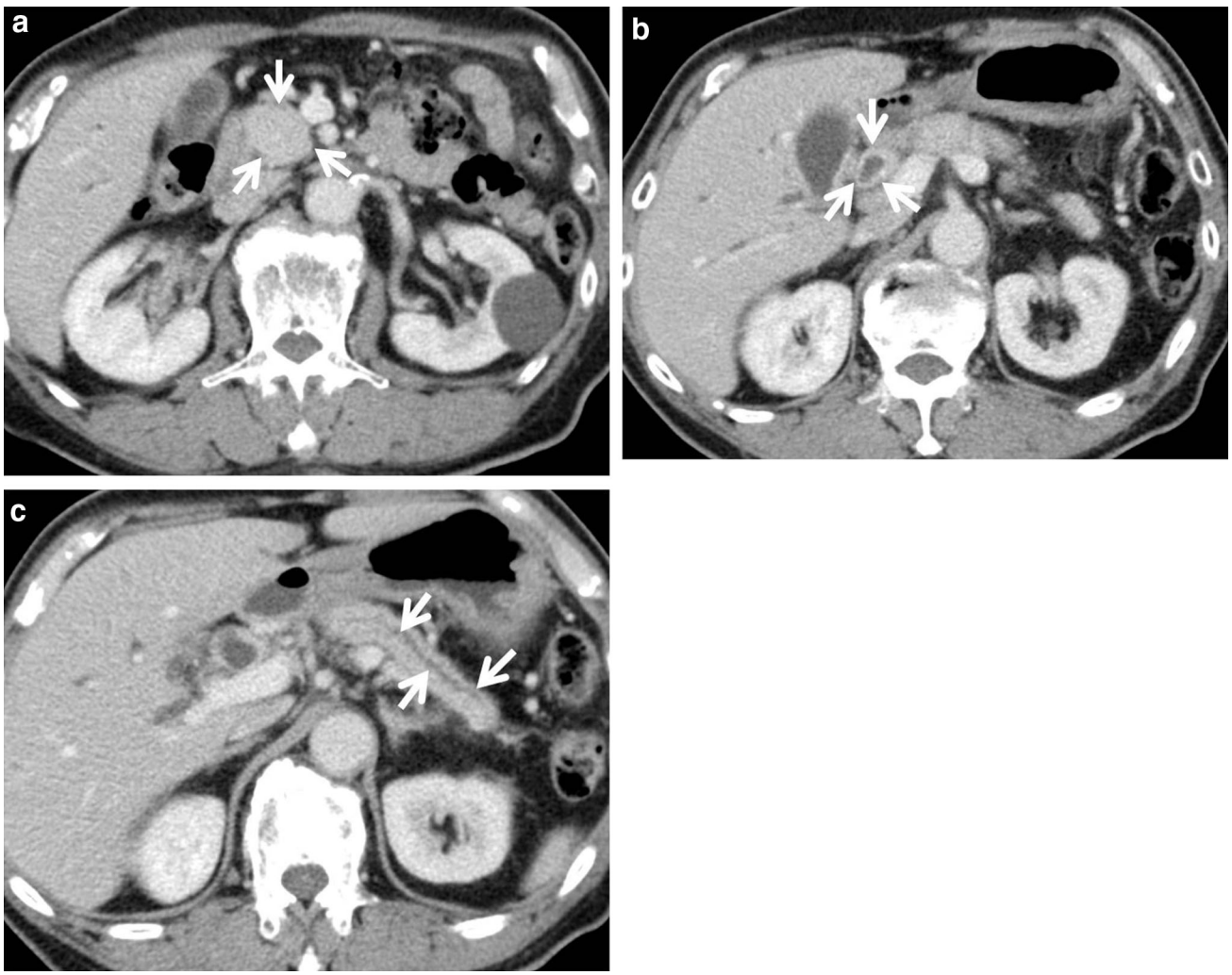

Fig. 8 Abdominal contrast computed tomography scan (case 2). There is enlargement of the pancreatic head region (*arrows*) (**a**), thickening of the central bile duct wall (*arrows*) (**b**), and mild dilation of the pancreatic duct in the body and tail regions (*arrows*) (**c**), but no neoplastic-appearing lesions are seen

Fig. 9 Transabdominal ultrasound image 1 month after the start of treatment (case 2). Improvements are seen in the tapered stenosis and thickened wall of the hilar bile duct

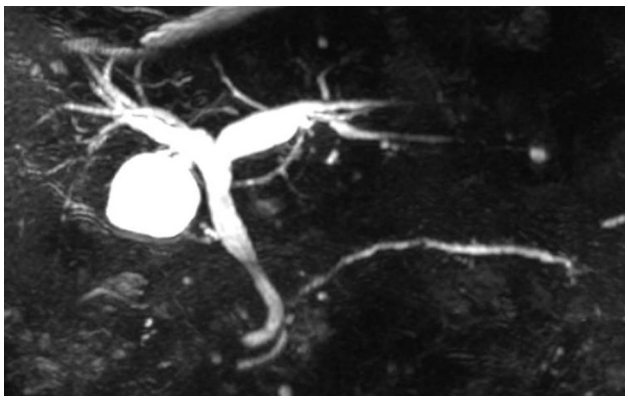

Fig. 10 Magnetic resonance cholangiopancreatography 2 months after the start of treatment (case 2). There are improvements in the stenosis of the middle bile duct and dilation of the intrahepatic and hilar bile ducts. There is also improvement in the narrowing of the main pancreatic duct

other organ involvement, such as sclerosing sialadenitis or retroperitoneal fibrosis, are useful findings in the diagnosis of IgG4-SC [4].

Cholangiographic findings cannot clearly distinguish sclerosing cholangitis from other disease entities. Specifically, type 1 may be misdiagnosed as pancreatic carcinoma, type 2 as primary sclerosing cholangitis (PSC), and types 3 and 4 may be confused with cholangiocellular carcinoma (CC) [5].

To further clarify the diagnosis, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is useful in excluding pancreatic cancer in the diagnosis of type 1, and liver biopsy is useful for distinguishing type 2 [6]. With types 3 and 4, confirmation of IgG4-positive plasma cells by transpapillary bile duct wall biopsy is useful [7], but limitations exist with regard to diagnostic transpapillary bile duct biopsy for both IgG4-SC and CC [8, 9]. For these reasons, intraductal ultrasonography (IDUS) is reported to be the most useful of the previous methods in the differential diagnosis [10, 11].

The characteristics of IgG4-SC bile duct walls on IDUS include a smooth inner margin and preservation of a three-layer structure. Conversely, the findings of an irregular inner margin, diverticulum-like outpouching, and disappearance of the three layers are specific IDUS findings for PSC [12]. The bile duct wall in patients with IgG4-SC is circular-symmetric in appearance, and a homogenous internal echo in the stricture is seen. The characteristics of the bile duct wall in CC, on the other hand, include circular-asymmetry, papillary changes of the inner margin, notch-like changes of the outer margin, and non-uniformity of the internal echo [6].

The use of transabdominal ultrasound for diagnosis of sclerosing cholangitis was reported by Carroll et al. [13]. They stated the importance of focusing on the thickening of the bile duct wall but reported nothing about the internal echo or layered structure of the wall. This was likely due to limitations in image resolution with diagnostic ultrasound equipment in the early 1980s. In the two cases reported here, it was possible to delineate the three-layer structure of the bile duct wall with transabdominal ultrasonography. This structure is thought to be important among the IDUS findings seen in the affected areas of the hilar and central bile ducts. In addition, both cases of bile duct stenosis were tapered, and the circular-symmetric findings that are emphasized on IDUS (cross-sectional findings of the bile duct) are thought to be observed from the lengthwise direction of the bile duct on transabdominal visualization. Furthermore, because we focused on the changes in the intrahepatic bile duct in case 1, we were able to suspect type 2 IgG-SC. Based on this evidence, a liver biopsy was selected, and a definitive diagnosis was obtained.

At present, transabdominal ultrasonography is not included in the diagnostic algorithm for IgG4-SC [10, 11]. In the diagnosis of obstructive jaundice, however, transabdominal ultrasonography should be done before MRCP or IDUS [14]. In this report, we discuss the use of transabdominal ultrasonography for diagnosis of IgG4-SC. By carefully scanning the bile duct wall in the hilar region, we can adequately distinguish types 2, 3, and 4; and with imaging conditions such as those in the cases presented here, it is also possible to distinguish type 1. Transabdominal ultrasonography is simple and noninvasive, and thus does not place a burden on the patient, even when performed frequently. While a consensus has not been reached regarding the evidence of improvement in bile duct wall findings after the start of steroid treatment for IgG4-SC, transabdominal ultrasonography may be of help in following the clinical course in cases where a steroid trial is

the best option for treatment, such as in case 2. However, we must remember that there are also several disadvantages to transabdominal ultrasonography. For example, the observable area becomes smaller in cases where the abdominal wall is thick, as in obesity, or where there is much gas in the gastrointestinal tract.

The most important point in diagnosing IgG4-SC is to keep in mind the existence of IgG4-SC when examining patients with obstructive jaundice [15]. We are certain that detailed observation of the bile duct wall with transabdominal ultrasonography can make a significant contribution to the diagnosis of IgG4-SC. Furthermore, we propose that transabdominal ultrasonography may be useful in following the clinical course in cases where a steroid trial is the best option for treatment.

Compliance with ethical standards

Conflict of interest Ikuhiro Kobori, Toshikuni Suda, Akihiro Nakamoto, Hiroki Saito, Osamu Okawa, Rion Sudo, Yoshinori Gyotoku, Yasumi Katayama, and Masaya Tamano declare that they have no conflicts of interest.

Human rights statements and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients included in the study. Additional informed consent was obtained from all patients for whom identifying information is included in this article.

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