—Case Reports—

A Case of IgG4-related Sclerosing Cholangitis with a Normal Serum IgG4 Level: Report of a Case

Satoshi Mizutani[1,2], Hideyuki Suzuki[1,2], Hiroshi Yoshida[1,3],
Yasuo Arima[1], Yasuhiko Kitayama[4] and Eiji Uchida[1]

[1]Surgery for Organ Function and Biological Regulation, Graduate School of Medicine, Nippon Medical School
[2]Institute of Gastroenterology, Nippon Medical School Musashi Kosugi Hospital
[3]Department of Surgery, Nippon Medical School Tama Nagayama Hospital
[4]Department of Pathology, Nippon Medical School Musashi Kosugi Hospital

Abstract

Although hilar cholangioma is the most common cause of stricture of the hilar bile duct, several diseases can contribute to stenosis. Here, we report on a patient with immunoglobulin (Ig) G4-related sclerosing cholangitis (IgG4-SC) of the hilar bile duct arising from obstructive jaundice. The patient had undergone laparoscopic cholecystectomy for the removal of gallstones. The differential diagnosis for icterus included hilar cholangiocarcinoma, primary sclerosing cholangitis, IgG4 sclerosing cholangitis, ischemic bile duct stenosis, a complication of cholecystitis, amputation neuroma, and iatrogenic stenosis. Numerous examinations were performed, but a definite diagnosis remained elusive. Because cholangiocarcinoma could not be ruled out, we proposed surgical resection. The patient subsequently underwent extended right liver lobectomy and intrahepatic cholangiojejunostomy. Pathological examination revealed numerous inflammatory cell infiltrates resembling IgG4-positive antibody plasma cells in the stromal layer of the stenotic bile duct walls. Hypertrophy of the nerve fiber fascicles was not observed. The serum IgG4 level of the patient was within the normal range. Few reports of IgG4-SC with a normal serum IgG4 level have been published. When this condition presents as it did in the present case, establishing a definite diagnosis can be difficult.
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Key words: IgG4-related sclerosing cholangitis, IgG4-related sclerosing disease, autoimmune pancreatitis, hilar cholangiocarcinoma

Introduction

Hilar cholangiocarcinoma is the most common cause of stricture of the hilar bile duct, but several diseases can lead to bile duct stenosis. Therefore, definitive diagnoses can be difficult to make solely on the basis of characteristic findings[1]. In patients with immunoglobulin (Ig) G4-related sclerosing disease, serum IgG4 levels are frequently and significantly elevated[2–4] but can be normal[5]. Here, we report a case in which a definitive diagnosis was
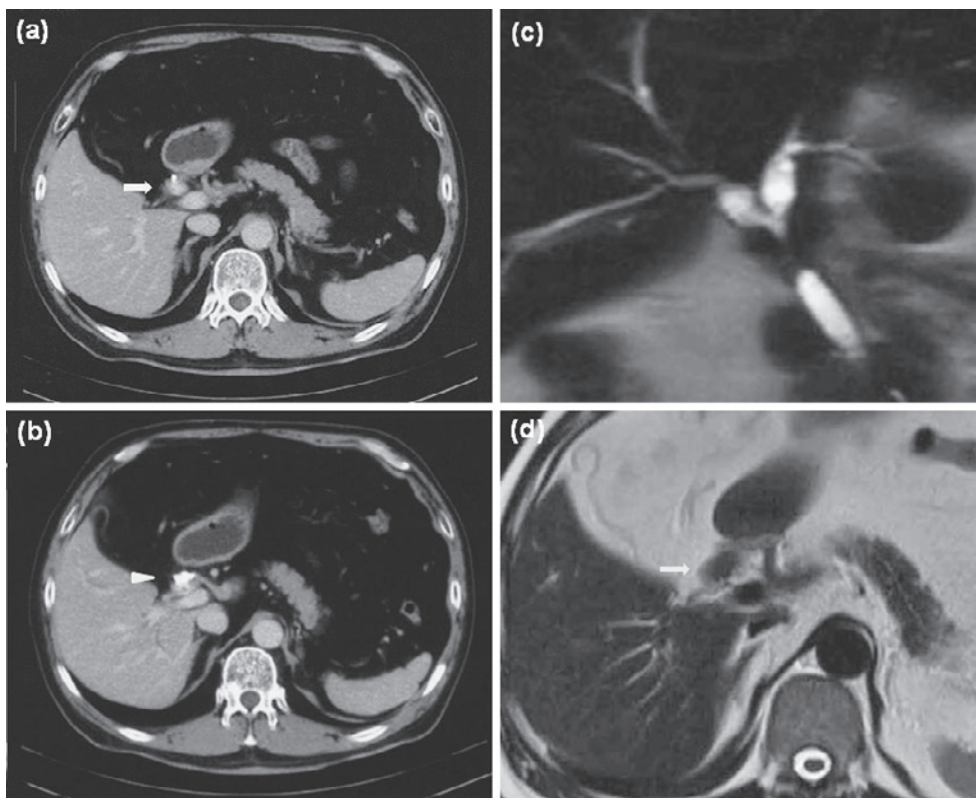
Fig. 1　Contrast-enhanced CT images of the bile duct (a) show wall thickening with enhancement during the later phase (**arrow**). Diffuse or localized enlargement of the pancreas was not apparent. Clips (**arrowhead**) were present proximal to the narrowed bile duct (b). Magnetic resonance cholangiopancreatograph showing hilar bile duct stenosis (c). The **arrow** indicates the edge of the wall thickening without stenosis within 1 mm of the edge of the stricture (d).

difficult to make on the basis of diagnostic imaging findings.

Case Report

A 59-year-old man presented to our hospital with obstructive jaundice. The patient's past medical history was notable only for laparoscopic cholecystectomy to remove gallstones performed 4 years earlier. Laboratory findings were as follows: white blood cell count, 8,420 /μL; C-reactive protein, 0.75 mg/dL; aspartate aminotransferase, 236 IU/L; alanine aminotransferase, 473 IU / L; alkaline phosphatase, 998 IU/L; γ glutamyl transferase, 1,093 IU/L; total bilirubin, 7.0 mg/dL; direct bilirubin, 5.45 mg / dL; fasting blood sugar, 88 mg / dL; carcinoembryonic antigen, 1.9 ng/mL; carbohydrate antigen 19-9, 5 U/mL; Duke pancreatic monoclonal antigen type 2, 27 U/mL; Span1, 1.0 U/mL; IgG4, 110

mg/dL (normal, <135 mg/dL); IgG, 1,535 mg/dL (normal, 870−1,700 mg / dL); IgG4 / IgG, 7.2%; perinuclear antineutrophilic cytoplasmic antibody (−); anti-mitochondrial antibody (−); antinuclear antibody (−); and anti-smooth muscle antibody (−). Ultrasonography of the abdomen demonstrated only intrahepatic bile duct dilatation. Contrast-enhanced computed tomography of the abdomen showed a thickened wall in an area with a diameter of 2.5 cm, and an enhanced central focus on the hilar bile duct was visible during a later phase. Surgical clips that had been used to close the cystic duct and artery were observed near the region of the primary disease (**Fig. 1a, b**). Magnetic resonance cholangiopancreatography and magnetic resonance imaging (MRI) showed a sharp-beaked stenosis in the hilar bile duct, and wall thickening (low-intensity mass) was observed only within this area (**Fig. 1c, d**). A bile duct stricture similar to that observed with
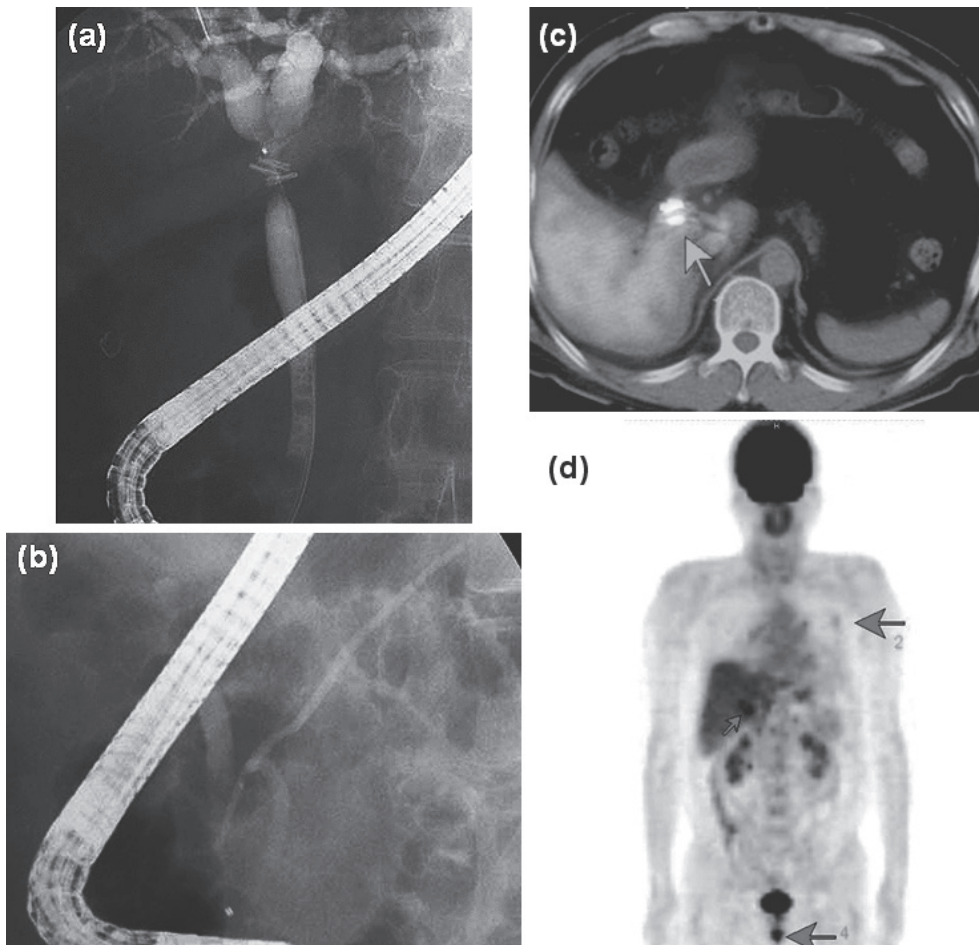
Fig. 2   Only hilar stenosis was observed in the intrahepatic and extrahepatic bile ducts that were visualized with endoscopic retrograde cholangiography (a). No suggestion of diffuse or segmental narrowing of the main pancreatic duct was visible (b). The **arrow** indicates an area with an elevated SUV that corresponds to the bile duct stenosis (c). No other areas of elevated SUV were observed, except for areas with physiological accumulation (d).

MRI was also demonstrated with endoscopic retrograde cholangiopancreaticography. Exfoliative cytologic examination of the bile duct revealed atypical inflammatory cells with loss of nuclear polarity. The main pancreatic duct was normal (**Fig. 2a, b**). Positron emission tomography/CT showed an elevated standardized uptake value (SUV) (SUV_{max} = 6.1) in an area corresponding to the hilar bile duct. No uptake was observed in any other organ, such as the pancreas, salivary glands, or retroperitoneum (**Fig. 2c, d**). Abdominal arterial angiography showed the presence of normal hepatic arteries.

Because a malignant tumor could not be ruled out, we recommended surgical resection. The patient underwent extended right liver lobectomy and intrahepatic cholangiojejunostomy 21 days after

right portal embolization (**Fig. 3**). He had no complications during his postoperative course and was discharged 20 days after the operation.

Pathological examination revealed inflammation extending from the bile duct wall to the periductal fat tissue. In the bile duct wall, only inflammatory cell infiltrates of lymphocytes and fibrosis were observed. In contrast, considerable inflammatory cell infiltrates, such as IgG4-positive plasma cells (>50 per high-power field), were observed in the periductal fat tissue. Storiform fibrosis and obliterative phlebitis were also present in this tissue. Hypertrophy of the nerve fiber fascicles was not observed (**Fig. 4**). There were no histological signs of carcinoma. Retrospectively, IgG4 expression was not detected in the gallbladder at the time of the
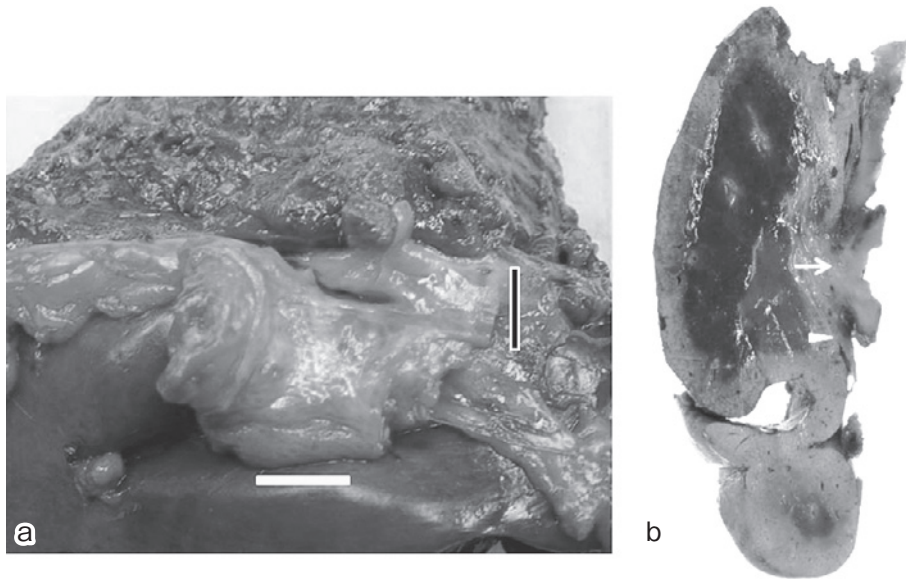
Fig. 3 Macroscopic findings of the cut end of the middle common bile duct **(white bar)** and the left hepatic duct **(black bar)**, which were flexible and not involved in the stricture (a). The thickened hilar bile duct **(arrow)** was compressing the right portal vein in the cut specimen (b).
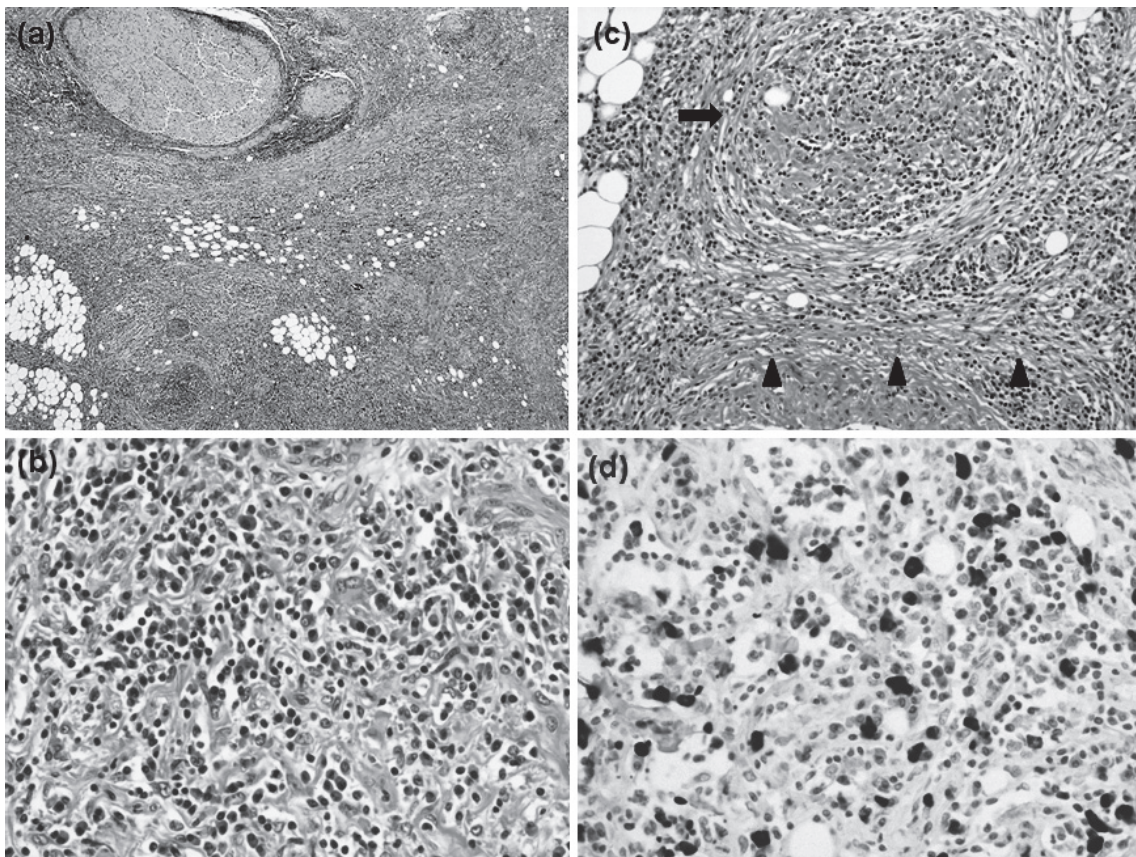

Fig. 4 Histopathological examination shows transmural fibrosis and lymphoplasmacytic infiltration in the periductal fat tissue. Hypertrophy of the nerve fiber fascicles was not observed **(a**: magnification×2, **b**: magnification×20, hematoxylin and eosin staining). Storiform fibrosis **(arrowhead)** and obliterative phlebitis **(arrow)** were prominent in the lesion **(c**: magnification×10, hematoxylin and eosin). Immunostaining of the specimen for IgG4 **(d**: magnification×20) indicates abundant IgG4-positive plasma cells (>50 per high-power field).

previous surgery.

Discussion

The major diseases contributing to stricture of the hilar bile duct include hilar cholanigocarcinoma, primary sclerosing cholangitis (PSC), IgG4-SC, ischemic bile duct stenosis, complications of cholecystitis, amputation neuroma, and iatrogenic stenosis. Although the diagnosis is clear in most patients, a preoperative diagnosis is difficult to establish in other patients. Recently, IgG4-related sclerosing disease has been suggested to be a systemic disease characterized by extensive IgG4-positive plasma cells and T-lymphocyte infiltrates in various organs (e.g., pancreas, bile duct, gallbladder, salivary gland, retroperitoneum, kidney, lung, and prostate). The histopathological features include fibrosis with obliterative phlebitis[2–4]. IgG4-SC is frequently associated with autoimmune pancreatitis (74% to 90% of cases)[1,6,7]. Nakazawa et al have described the characteristic cholangiographic features discriminating IgG4 SC without autoimmune pancreatitis from PSC[8]. They classified IgG4-SC into 4 categories depending on the location of the stenosis[8]. The present case was classified as type 4, with only hilar bile duct stenosis. The serum IgG4 level is elevated in about 80% of cases of IgG4-related sclerosing disease[9,10]. However, serial changes in elevated serum IgG4 levels are determined by the disease activity of the IgG4-related sclerosing disease[10]. Inoue et al have reported that even if the serum IgG4 level is not elevated, an IgG4/IgG ratio greater than 8% could be used to distinguish IgG4-related SC from PSC[5].

There were several reasons why a definitive preoperative diagnosis could not be established in the present case. First, the serum IgG4 level differed from the IgG4 expression level in the lesion[5,11,12]. Cholangiography did not reveal the typical features of an IgG4-SC[8]. Furthermore, if the lesion had been a typical IgG4-SC, the wall thickening would have extended beyond the bile duct stenosis[8]. Clinical manifestations of IgG4-related sclerosing disease, other than the sclerosing cholangitis, were not apparent[7–9]. Furthermore, in a positron emission tomography/CT study, an elevated SUV (SUV_{max}= 6.1), compatible with findings for a malignant tumor, was observed. In addition, an amputation neuroma could not be ruled out in light of the patient's previous laparoscopic cholecystectomy. If we had determined that the stenosis was likely to have been caused by IgG4-SC, administration of steroids would have been taken into account before the surgery. Our ability to distinguish IgG4-SC from cholangiocarcinoma remains inadequate, even if IgG4 expression is observed in the biopsy specimen[11–13]. Recently, the use of cholangioscopy for the discrimination of IgG4-SC has been attempted[14].

Because malignant tumors are frequently suspected under these conditions, the possibility of IgG4-SC should be considered when using new imaging modalities so that unnecessary surgery can be avoided.

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