Surg Today (2013) 43:1175–1179
DOI 10.1007/s00595-012-0448-6

CASE REPORT

IgG4-related intrahepatic sclerosing cholangitis resulting in sepsis caused by secondary suppurative inflammation: report of a case

Motonobu Saito · Tatsuo Shimura · Yuko Hashimoto · Teruhide Ishigame · Rei Yashima · Yoshihisa Koyama · Seiichi Takenoshita

Received: 15 November 2011 / Accepted: 26 April 2012 / Published online: 18 December 2012

Abstract We report a case of pre-disseminated intravascular coagulation caused by secondary suppurative inflammation in a patient with immunoglobulin (Ig) G4-related sclerosing cholangitis. The patient was a 78-year-old man in whom a localized stenosis of the intrahepatic bile duct was found without any other bile duct stricture or symptoms. He underwent surgical resection 6 months later for acute severe cholangitis and sepsis caused by bile duct obstruction. The resected specimen contained an abscess and nodulary mass in the liver. Immunohistochemical analysis revealed IgG4-positive plasma cell infiltration, whereby we diagnosed IgG4-related sclerosing cholangitis. As IgG4-related sclerosing cholangitis limited to within the intrahepatic portion is extremely rare, we present this case with a review of the literature.

Keywords IgG4-related sclerosing cholangitis · Intrahepatic bile duct stenosis · Suppurative inflammation

Introduction

Immunoglobulin (Ig) G4-related sclerosing cholangitis is a bile duct lesion associated with IgG4-related sclerosing disease, characterized by the infiltration of IgG4-positive plasma cells and T lymphocytes into various organs, with elevated levels of serum IgG4. As the stenosis usually occurs in the distal portion of the common bile duct, bile duct stenosis limited to the intrahepatic portion is often misdiagnosed as a malignant tumor [1–4]. Furthermore, sepsis or disseminated intravascular coagulation (DIC) caused by severe cholangitis is extremely rare in IgG4-related sclerosing cholangitis. We report a case of intrahepatic IgG4-related sclerosing cholangitis associated with severe suppurative inflammation.

M. Saito (✉) · T. Shimura · T. Ishigame · R. Yashima · Y. Koyama · S. Takenoshita
Department of Organ Regulatory Surgery, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima 960-1295, Japan
e-mail: bobibobu@yahoo.co.jp

Y. Hashimoto
Department of Pathology, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima 960-1295, Japan

Case report

A 78-year-old man was admitted to a local hospital complaining of epigastric pain. Laboratory data showed no significant abnormalities; however, computed tomography (CT) revealed an atrophic parenchyma and dilated intrahepatic bile duct in the left lobe of the liver without any obvious intrahepatic masses (Fig. 1a). The surrounding organs, including the pancreas, mediastinal lymph nodes, and retroperitoneal organs, appeared normal. He was transferred to our hospital for further investigations and treatment. Endoscopic retrograde cholangiopancreatography (ERCP) revealed a localized stenosis of the intrahepatic bile duct and a cystic lesion, 20 mm in diameter, connecting with the bile duct in the left lateral segment (Fig. 1b). Stenosis was not found in any other portion of the bile duct. Magnetic resonance imaging (MRI) showed no abnormality of the pancreatic duct (Fig. 1c). As the bile duct stenosis in the intrahepatic portion was the only remarkable finding, the possibility of IgG4-related sclerosing cholangitis was not considered at this point, and for this reason we did not measure the serum IgG4 level. Brush cytology specimens obtained at the stenotic portion of the

bile duct and bile juice cytology during ERCP could not confirm definitive malignant features (class I–III). Because he did not have any clinical symptoms, he was discharged to be carefully followed up at the outpatient clinic of the local hospital.

Soon after the 6-month follow-up, he was readmitted to the local hospital with severe abdominal pain, high fever (>38 °C), and leukocytosis (>12,000/mm^3). Sepsis resulting from severe acute cholangitis was diagnosed. Because the blood test results confirmed pre-DIC (DIC score 6, platelet count 6.0 × 10^4/mm^3, FDP 16 μg/ml, fibrinogen 140 mg/dl), intravenous antibiotics and gabexate mesilate were started immediately. After showing signs of clinical improvement, he was transferred to our hospital for further treatment. As bile duct obstruction was found only in the same portion of the intrahepatic bile duct, an endoscopic nasobiliary drainage (ENBD) tube was inserted (Fig. 1d). Brush cytology of the stenotic bile duct revealed no malignancy (class I–III), although the CA19-9 level was elevated, at 1,580 U/ml (normal <37 U/ml). As the cholangitis was apparently caused by the bile duct obstruction and as the possibility of intrahepatic cholangiocarcinoma could not be ruled out, we performed left hepatic lobotomy after the patient gave his informed consent.

Intraoperative examination revealed an atrophied left lobe of the liver with an uneven, granular surface, adhered to the stomach. Furthermore, the dilated bile duct in the left lobe was filled with pus, suggesting that the obstruction had led to suppurative change in the cystic lesion (Fig. 2a, b). Intraoperative frozen section examination revealed no malignancy in the stump of the resected bile duct. Pathological examination revealed no malignancy but fibroinflammatory pseudotumor-like features such as numerous neutrophils and plasma cells infiltrating around the bile duct with phlebitis (Fig. 2c, d). Immunohistochemical analysis revealed many IgG4-positive plasma cells infiltrating diffusely in the fibrously thickened bile duct wall (IgG4/IgG cell ratio of 33.8 %; Fig. 2e). These findings were compatible with IgG4-related sclerosing cholangitis.

When last seen 8 months after the operation, the patient was doing well without any signs or symptoms of further disorder.

Discussion

There is accumulating evidence that IgG4-related sclerosing disease affects various organs, but most commonly the

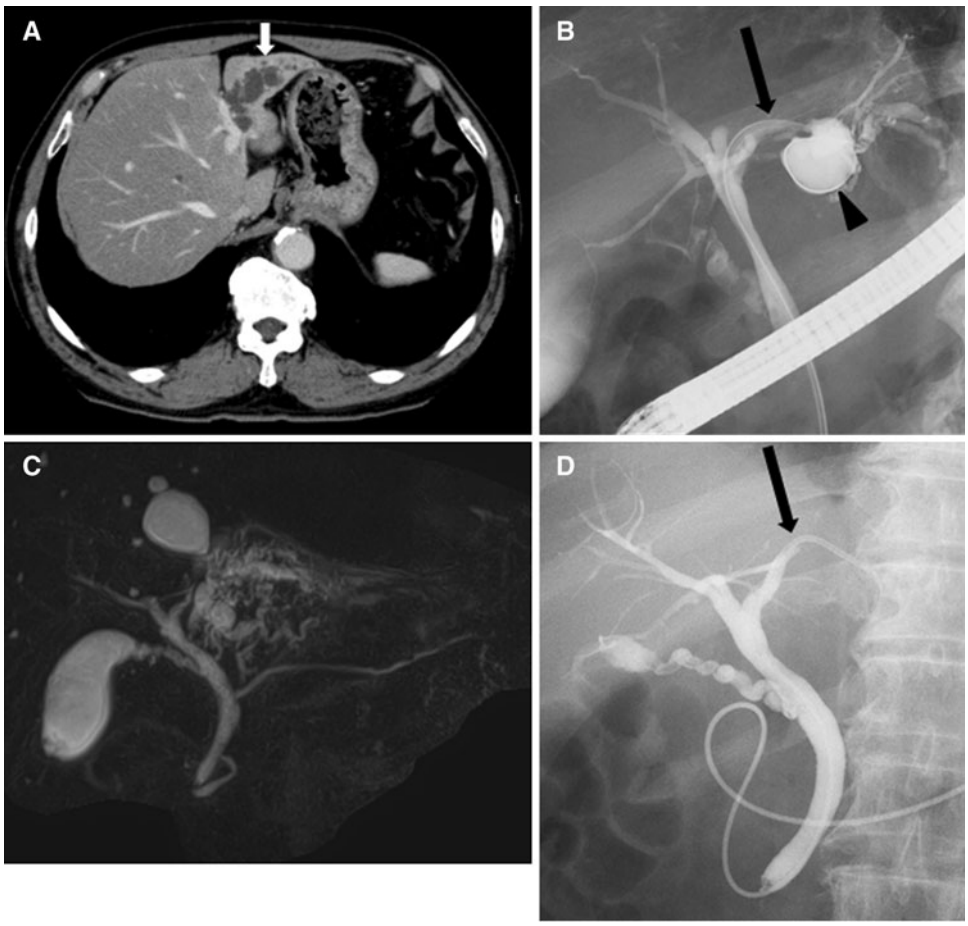

Fig. 1 **a** Computed tomography showed atrophy of the left lobe of the liver and dilated intrahepatic bile ducts without any obvious intrahepatic mass (*white arrow*). **b** Endoscopic retrograde cholangiopancreatography (ERCP) revealed localized stenosis of the intrahepatic bile duct (*arrow*) and pre-stenotic dilatation forming a cyst (*arrow head*). **c** Magnetic resonance imaging showed no abnormality of the pancreatic duct. **d** ERCP revealed intrahepatic bile duct obstruction (*arrow*). An endoscopic nasobiliary drainage tube was inserted into the peripheral bile duct though the stricture

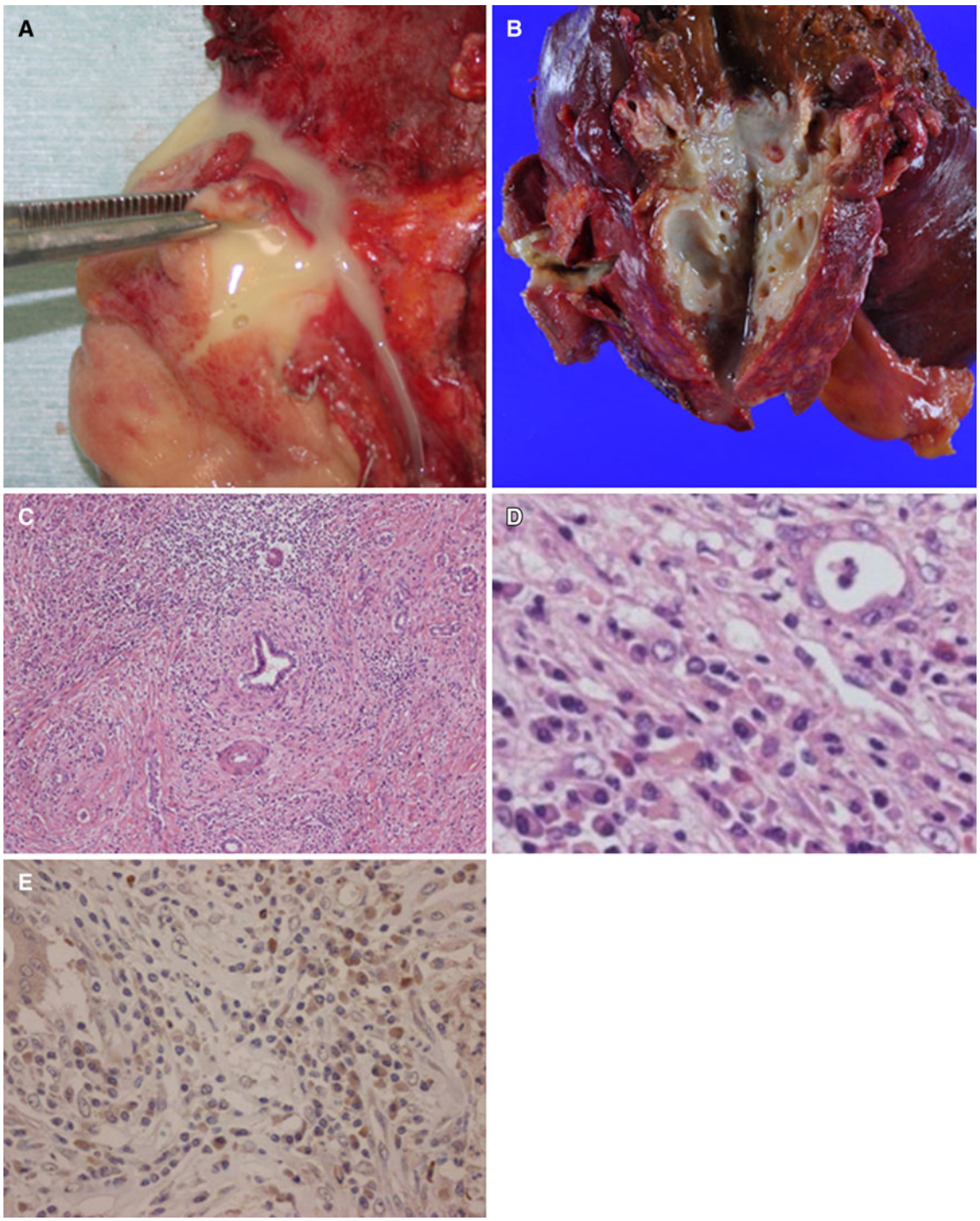

Fig. 2 **a**, **b** Gross appearance of the resected specimen. **a** The left lateral segment of the liver was strongly adhered to the stomach, forming a mass filled with pus. **b** An irregular, nodular mass was found in the left lateral segment of the liver. **c**, **d** Histopathological examination revealed numerous neutrophils and plasma cells infiltrating around the bile duct (H&E stain, **c** ×4, **d** ×40). **e** Plasma cells were stained strongly positive for IgG4 (×20)

pancreas and the bile duct [5, 6]. According to the novel concept of the disease, IgG4-related sclerosing cholangitis is the biliary manifestation of IgG4-related sclerosing systemic disease [7]. Because of the non-specific symptoms such as abdominal pain and obstructive jaundice, IgG4-related sclerosing cholangitis is not suspected at the outset. Even if IgG4-related sclerosing cholangitis is suspected, the definitive diagnosis is still controversial. Unlike for primary sclerosing cholangitis (PSC), laboratory studies do not show specific results, except for the serum IgG4

Table 1 Reported cases of intrahepatic bile duct stenosis of IgG4-related sclerosing cholangitis

	First author[Ref]	Years	Age (years)	Sex	Clinical diagnosis	AIP	Hepatic IPT	Suppurative cholangitis	Treatment
1	Zen [1]	2004	59	M	Liver cancer	(−)	(+)	(−)	Segmentectomy of the liver
2	Zen [1]	2004	56	M	ICC	(−)	(+)	(−)	Lobectomy of the liver
3	Zen [1]	2004	64	M	ICC	(−)	(+)	(−)	Lobectomy of the liver
4	Naitoh [2]	2009	77	M	ICC	(−)	(+)	(−)	Lobectomy of the liver
5	Oh [3]	2010	51	M	ICC	(−)	(−)	(−)	Liver resection
6	Oh [3]	2010	76	M	ICC	(−)	(−)	(−)	Liver resection
7	Present case	2010	78	M	Cholangitis	(−)	(−)	(+)	Lobectomy of the liver

ICC intrahepatic cholangiocarcinoma, *AIP* autoimmune pancreatitis, *IPT* inflammatory pseudotumor

level; however, because the diagnostic sensitivity is not high [3, 8], IgG4 examination can also be problematic. Despite recent advances in diagnostic methods, such as transpapillary cytology and intraductal ultrasonography, a definitive or exclusive diagnosis remains elusive. The fact that immunohistochemical staining for IgG4 in biopsy samples is not effective for diagnosing bile duct stenosis limits the scope of examination. Moreover, the biopsied samples are so small that immunohistochemical analysis is impractical [3]. Most patients with IgG4-related sclerosing cholangitis also suffer pancreatic symptoms [9], so to find the features of auto immune pancreatitis (AIP) would be helpful when IgG4-related sclerosing cholangitis is suspected. However, when bile duct stenosis occurs only in the hilar or intrahepatic bile duct without pancreatic lesions, a misdiagnosis of cholangiocarcinoma could be made [10]. Most of those lesions were in fact resected and confirmed to be non-malignant and diagnosed as IgG4-related sclerosing cholangitis by postoperative immunohistochemical staining. Because IgG4-related sclerosing cholangitis has characteristic histology and positive staining for IgG4, the diagnosis using resected specimens poses no difficulty [1].

IgG4-related sclerosing cholangitis is classified by cholangiography into four types [10]. Although type 2 involves intrahepatic bile duct stenosis, the stenosis is in the lower part of the common bile duct. Conversely, in the present case, the bile duct stenosis was limited to the intrahepatic portion (Fig. 1d); thus, our case cannot be categorized as any other type. Intrahepatic stricture is rare, with an incidence of 8–12.5 % [3, 9]. Table 1 summarizes the six reported cases, as well as the present case of IgG4-related sclerosing cholangitis limited to the intrahepatic portion [1–3]. All of the patients were male and the disease was not associated with AIP, but it was misdiagnosed as liver cancer or intrahepatic cholangiocarcinoma. Moreover, all of the patients underwent surgical resection. In the present case, biliary cytology did not show malignancy, but the serum CA19-9 level was high and the stenosis had led to sepsis; therefore, we considered that surgical resection was indicated. The fact that the CA19-9 level returned to normal after surgery suggests that CA19-9 was augmented by the inflammation, so its elevation was not useful for the differential diagnosis [11, 12].

Even if the cause of the stricture is benign, it should be resected when it results in an adverse event, such as suppurative cholangitis or sepsis. Clinically, IgG4-related sclerosing disease responds well to steroid therapy and a proposed treatment strategy for suspicious IgG4-related sclerosing cholangitis includes a short trial of steroids [9]. However, as our patient exhibited signs of sepsis, we were hesitant to give him steroids.

Acute obstructive suppurative cholangitis is a severe inflammatory event caused by obstruction of the bile duct; however, it is rarely caused by IgG4-related sclerosing cholangitis. Because the sepsis manifested 6 months after our patient's initial presentation, we concluded that ERCP was not the cause of the inflammation. As our patient's condition was complicated by sepsis and pre-DIC from the suppurative inflammation, IgG4-related sclerosing cholangitis should be considered in the differential diagnoses, even if the bile duct stricture is located only in the intrahepatic portion without pancreatic involvement.

Acknowledgments We thank Noralyn Dudt MA for her editorial assistance.

Conflict of interest M. Saito and his co-authors have no conflict of interest.

References

1. Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, et al. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-

associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? Am J Surg Pathol. 2004;28:1193–203.
2. Naitoh I, Nakazawa T, Ohara H, Ando T, Hayashi K, Tanaka H, et al. IgG4-related hepatic inflammatory pseudotumor with sclerosing cholangitis: a case report and review of the literature. Cases J. 2009;2:7029.
3. Oh HC, Kim MH, Lee KT, Lee JK, Moon SH, Song TJ, et al. Clinical clues to suspicion of IgG4-associated sclerosing cholangitis disguised as primary sclerosing cholangitis or hilar cholangiocarcinoma. J Gastroenterol Hepatol. 2010;25:1831–7.
4. Mori A, Doi R, Yonenaga Y, Nakabo S, Yazumi S, Nakaya J, et al. Xanthogranulomatous cholecystitis complicated with primary sclerosing cholangitis: report of a case. Surg Today. 2010;40(8):777–82.
5. Kamisawa T, Okamoto A. IgG4-related sclerosing disease. World J Gastroenterol. 2008;14:3948–55.
6. Kamisawa T, Nakajima H, Egawa N, Funata N, Tsuruta K, Okamoto A. IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. Pancreatology. 2006;6:132–7.
7. Kamisawa T, Takuma K, Egawa N, Tsuruta K, Sasaki T. Autoimmune pancreatitis and IgG4-related sclerosing disease. Nat Rev Gastroenterol Hepatol. 2011;7:401–9.
8. Ghazale A, Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, et al. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. Am J Gastroenterol. 2007;102:1646–53.
9. Ghazale A, Chari ST, Zhang L, Smyrk TC, Takahashi N, Levy MJ, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology. 2008;134:706–15.
10. Nakazawa T, Ohara H, Sano H, Ando T, Joh T. Schematic classification of sclerosing cholangitis with autoimmune pancreatitis by cholangiography. Pancreas. 2006;32:229.
11. Giannaris M, Dourakis SP, Alexopoulou A, Archimandritis AJ. Markedly elevated CA 19-9 in the pus and the serum of a patient with pyogenic liver abscess. J Clin Gastroenterol. 2006;40:657.
12. Sheen-Chen SM, Sun CK, Liu YW, Eng HL, Ko SF, Kuo CH. Extremely elevated CA19-9 in acute cholangitis. Dig Dis Sci. 2007;52:3140–2.