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Title: Metachronic Development of Cholangiocarcinoma During Treatment for IgG4-related Sclerosing Cholangitis

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Abstract

We report a case of obstructive jaundice due to recurrent distal biliary stricture during 3 years of treatment for immunoglobulin G4 (IgG4)-related sclerosing cholangitis (IgG4-SC) associated with autoimmune pancreatitis. Although a relapse of IgG4-SC was initially suspected, imaging findings, laboratory tests, and histopathological examinations led to the diagnosis of metachronous cholangiocarcinoma. The patient underwent pancreaticoduodenectomy, and no cancer recurrence was noted 6 months postoperatively. Distal cholangiocarcinoma and IgG4-SC remission were observed in the resected specimen. In patients with recurrent biliary strictures during IgG4-SC treatment, comprehensive evaluations are essential because of the risk of disease relapse and development of metachronous cholangiocarcinoma.

Keywords: Autoimmune pancreatitis; IgG4-related sclerosing cholangitis; Cholangiocarcinoma; Metachronous carcinogenesis

Introduction

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is a chronic, multi-organ disorder histopathologically characterized by the infiltration of lymphocytes and IgG4-positive plasma cells, elevated serum IgG4 levels, and tissue fibrosis. It primarily affects the central nervous system, lacrimal and salivary glands, lungs, pancreas, bile ducts, retroperitoneum, and kidneys [1]. Several studies have investigated the association between IgG4-RD and malignancy. Approximately 10% of patients with IgG4-RD develop malignancies such as malignant lymphoma, lung cancer, and colorectal cancer during follow-up for IgG4-RD [2]. Among malignancies, cholangiocarcinoma occurred in 0.7–1.4% of patients with IgG4-related sclerosing cholangitis (IgG4-SC) [3, 4]. Furthermore, the standardized incidence ratio (SIR) following a diagnosis of autoimmune pancreatitis (AIP) or IgG4-SC is relatively high [4]. Therefore, during the treatment and follow-up of IgG4-SC, careful monitoring for the development of malignancies, particularly cholangiocarcinoma, is essential. Here, we present a rare case of recurrent distal biliary stricture due to cholangiocarcinoma that developed during 3 years of treatment for IgG4-SC with AIP.

Case report

A 79-year-old man with hypertension and diabetes mellitus presented with brown-colored urine and anorexia for 1 week. He had a history of occasional alcohol consumption but no history of smoking. Abdominal examination revealed mild discomfort upon deep palpation in the right upper quadrant with no palpable mass or peritoneal signs.

Laboratory tests revealed elevated levels of total bilirubin (5.9 mg/dL, reference range: 0.4–1.5 mg/dL), direct bilirubin (4.5 mg/dL, reference range: < 0.4 mg/dL), carbohydrate antigen 19-9 (CA19-9: 40.0 U/mL, reference range: < 37.0 U/mL), and IgG4 (358 mg/dL, reference range: 11–121 mg/dL). Contrast-enhanced computed tomography (CE-CT) revealed a distal biliary stricture accompanied by a slightly enhanced tumor at the pancreatic head-body junction, where contrast enhancement was relatively poor compared with other pancreatic regions (Fig. 1a, b). Duodenoscopy revealed normal ampulla (Fig. 2a). Endoscopic retrograde cholangiopancreatography (ERCP) showed a distal bile duct stricture and narrowing of the pancreatic duct from the pancreatic head to the body, with findings suggestive of AIP (Fig. 2b, c). Intraductal ultrasonography revealed circumferential wall thickening (Fig. 2d). Endoscopic transpapillary biopsy (Radial Jaw™, Boston

Scientific, MA, USA) for biliary stricture and juice cytology revealed no malignancy. Endoscopic biliary stenting (Flexima™ Biliary Stent System 7Fr, Boston Scientific, Marlborough, MA, USA) was performed. Endoscopic ultrasonography (EUS) revealed a low-echoic parenchyma in the pancreas (Fig. 2e), and EUS-guided tissue acquisition (Acquire® 22-gauge, Boston Scientific, Boston, MA, USA) showed IgG4-positive plasma cells without atypical cells (Fig. 3a, b). The patient was diagnosed with IgG4-SC with focal-type AIP and treated with prednisolone 30 mg/day.

Three months later, while the patient was receiving 12.5 mg/day of prednisolone, duodenoscopy revealed no apparent malignant features at the papilla after sphincterotomy; ERCP showed improvement of the biliary stricture (Fig. 4a, b), and prednisolone was tapered. After 15 months of steroid induction, 50 mg/ day of azathioprine was added to maintain remission. The serum IgG4 levels gradually decreased (Fig. 5). However, 3 years later, the patient presented with fever, anorexia, and upper abdominal pain. He was administered a prednisolone dose of 3 mg/day. Laboratory tests revealed elevated levels of C-reactive protein (12.54 mg/dL, reference range: < 0.14 mg/dL), total bilirubin (2.8 mg/dL), direct bilirubin (1.4 mg/dL), and CA19-9 (60.2 U/mL), whereas the IgG4 level was normal (55 mg/dL). CE-CT revealed a newly enhanced tumor in the distal bile duct near the papilla (Fig. 6a). ERCP revealed a newly developed distal biliary stricture located further

85 downstream from the original site, with a granular appearance on the ampulla of Vater following
86 endoscopic sphincterotomy (Fig. 6b, c). EUS demonstrated a hypoechoic mass consistent with a
87 biliary stricture, along with contiguous mild wall thickening, which appeared to reflect benign
88 conditions such as suppurative cholangitis or IgG4-SC. Moreover, the lesion was in contact with the
89 thickened proper muscular layer of the duodenum (Fig. 6d). These findings raised suspicion of
90 invasion of the proper muscular layer of the duodenum by the lesion. Endoscopic biliary stenting
91 (Flexima™ Biliary Stent System 7Fr) was performed for acute cholangitis, and endoscopic
92 transpapillary biopsy (Radial Jaw^{TM}, Boston Scientific, MA, USA) for the biliary stricture confirmed
93 cholangiocarcinoma. This patient underwent pancreaticoduodenectomy for distal
94 cholangiocarcinoma, with resection at the level of the hepatic hilum, thereby removing the initially
95 diagnosed IgG4-SC lesion as well (Fig. 7a). While histopathological evaluation near the ampulla
96 revealed adenocarcinoma (Fig. 7b, c), examination at the level of the IgG4-SC lesion (pancreatic
97 upper margin) showed no evidence of malignancy, with only mild lymphocytic infiltration.
98 Immunostaining showed minimal infiltration of IgG4-positive plasma cells, which did not meet the
99 diagnostic criteria for IgG4-SC, suggesting that the disease is in a state of maintained remission (Fig.
100 7d, e). Steroid therapy was completed over 3 years, and postoperative treatment was limited to

adjuvant chemotherapy with S-1 (tegafur/gimeracil/oteracil, 80mg/body) for cholangiocarcinoma, without further steroid and azathioprine therapy, as the IgG4 levels and histopathological findings indicated remission of IgG4-SC. No cancer recurrence occurred 6 months postoperatively.

Discussion

We present a case of recurrent biliary stricture detected 3 years after the initiation of steroid therapy for IgG4-SC. Laboratory data revealed abnormalities, including a slightly elevated CA19-9 level, and EUS revealed irregular bile duct wall thickening. Based on these findings, cholangiocarcinoma, rather than recurrent IgG4-SC, was suspected. The diagnosis was subsequently confirmed via bile duct biopsy. During the follow-up of IgG4-SC, intensive surveillance is essential not only for detecting disease relapse but also for identifying the potential development of cholangiocarcinoma [3-5]. Tanaka et al. found that cholangiocarcinoma occurred in only 4 (0.7%) of 527 patients with IgG4-SC during a median follow-up period of 4.1 years [3]. Similarly, Kurita et al. reported that 3 (1.4%) of 201 patients were diagnosed with bile duct cancer, and the SIR for cholangiocarcinoma following a diagnosis of AIP or IgG4-SC was 6.89 (95% CI: 6.20–7.75) during a mean follow-up period of 5.7 years [4]. An association between IgG4-SC and cholangiocarcinoma has been suggested. Therefore, during long-term follow-up, careful monitoring of imaging and blood test results is important.

IgG4-SC, commonly observed in patients with AIP, is characterized by bile duct wall thickening and biliary strictures. Compared with cholangiocarcinoma, wall thickening in IgG4-SC is typically

circumferential and symmetrical, with smooth inner and outer margins and homogeneous internal echogenicity [6]. However, even with an endoscopic bile duct biopsy, diagnosing IgG4-SC can be challenging in some cases. Kawakami et al. demonstrated that a diagnosis was possible through papillary and bile duct biopsies in 15 of 29 patients (52%) with IgG4-SC [7]. As AIP recurs in approximately one-third of the cases, a definitive diagnosis should be established not only at the initial presentation but also at the time of relapse [5]. Harada et al. demonstrated that distal cholangiocarcinomas are often accompanied by significant IgG4-positive plasma cell infiltration, indicating that such infiltration is not always a definitive histological hallmark of IgG4-SC [8]. As an additional diagnostic marker, Ohara et al. reported that in differentiating IgG4-SC from cholangiocarcinoma, setting the IgG4 cutoff value at 182 mg/dL resulted in a specificity of 97% and a specificity of 100% at 207 mg/dL [9].

Malignant tumors can be associated with IgG4-RD, and paraneoplastic syndromes and persistent inflammation have been suggested as possible underlying mechanisms [10, 11]. Shiokawa et al. found that 15 of 108 patients with AIP (13.9%) developed malignancies during a median follow-up period of 3.3 years. The SIR of cancer in the first year after AIP diagnosis was 6.1 (95% confidence interval [CI]: 2.3–9.9), while in the subsequent years, it was 1.5 (95% CI: 0.3–2.8). In

addition, the relative risk of cancer among patients with AIP at the time of AIP diagnosis was 4.9 (95% CI: 1.7–14.9), suggesting that IgG4-RD is a paraneoplastic syndrome [10]. Kamisawa et al. demonstrated that significant K-ras mutations frequently occur because of persistent inflammation in the pancreatobiliary regions of patients with AIP, which may be a risk factor for metachronous pancreatobiliary cancer [11]. PubMed search using the terms "IgG4-related sclerosing cholangitis," "bile duct cancer," and "carcinogenesis" identified only 4 case reports in which bile duct cancer developed more than 1 year after the diagnosis of IgG4-SC [12-15] (Table 1). The reported cases typically involve older adult males aged over 75 years. The latency period between AIP treatment and the development of cholangiocarcinoma varies widely, ranging from 3 to over 12 years. In some cases, cancer is diagnosed at an advanced stage, when surgical resection is no longer an option. A noteworthy finding is the similarity between anatomical sites affected by IgG4-SC and those involved in cholangiocarcinoma in 4 cases. This suggests a potential link between chronic bile duct inflammation and carcinogenesis. Therefore, long-term imaging follow-up and tumor marker monitoring may be warranted, especially as cholangiocarcinoma should be considered when recurrent biliary stricture occurs at previously affected sites. Therefore, long-term imaging surveillance and monitoring of tumor markers are required.

In the present case, recurrent biliary stricture was detected following the sudden onset of acute cholangitis symptoms 3 years after initiating steroid therapy for IgG4-SC, suggesting a low likelihood of paraneoplastic syndrome. Laboratory tests revealed a slightly elevated CA19-9 level, whereas serum IgG4 levels remained within the normal range. EUS revealed irregular wall thickening with a hypoechoic mass near the ampulla of Vater. Based on laboratory and imaging findings, the cholangiocarcinoma was suspected to be an IgG4-SC, and adenocarcinoma was ultimately confirmed by endoscopic biopsy. Although cholangiocarcinoma presenting with biliary strictures over a prolonged period of three years is considered extremely rare, the possibility of malignancy cannot be completely excluded based on biopsy or cytology alone, and false-negative results remain a potential concern. These points represent limitations of this case report.

In conclusion, in patients with recurrent biliary strictures during treatment for IgG4-SC, comprehensive evaluations, including serum IgG4 levels, tumor markers, CE-CT imaging, and bile duct biopsy, are essential for assessing the potential risk of metachronous bile duct cancer.

Conflict of Interests: The authors declare that they have no conflict of interest.

168 **References**

169 1. Okazaki K, Kawa S, Kamisawa T, et al. Amendment of the Japanese consensus guidelines for
170 autoimmune pancreatitis, 2020. J Gastroenterol. 2022;57:225–45.
171 2. Yamamoto M, Takahashi H, Tabeya T, et al. Risk of malignancies in IgG4-related disease. Mod
172 Rheumatol. 2012;22:414–8.
173 3. Tanaka A, Tazuma S, Okazaki K, et al. Clinical features, response to treatment, and outcomes of
174 IgG4-related sclerosing cholangitis. Clin Gastroenterol Hepatol. 2017;15:920–926.e3.
175 4. Kurita Y, Kubota K, Fujita Y, et al. IgG4-related pancreatobiliary diseases could be associated with
176 onset of pancreatobiliary cancer: A multicenter cohort study. J Hepato-Bil Pancreat Sci.
177 2024;31:173–82.
178 5. Kubota K, Kamisawa T, Okazaki K, et al. Low-dose maintenance steroid treatment could reduce
179 the relapse rate in patients with type 1 autoimmune pancreatitis: a long-term Japanese multicenter
180 analysis of 510 patients. J Gastroenterol. 2017;52:955–64.
181 6. Naitoh I, Nakazawa T, Ohara H, et al. Endoscopic transpapillary intraductal ultrasonography and
182 biopsy in the diagnosis of IgG4-related sclerosing cholangitis. J Gastroenterol. 2009;44:1147–55.

183 7. Kawakami H, Zen Y, Kuwatani M, et al. IgG4-related sclerosing cholangitis and autoimmune
184 pancreatitis: histological assessment of biopsies from Vater's ampulla and the bile duct. J
185 Gastroenterol Hepatol. 2010;25:1648–55.
186 8. Harada K, Shimoda S, Kimura Y, et al. Significance of immunoglobulin G4 (IgG4)-positive cells
187 in extrahepatic cholangiocarcinoma: molecular mechanism of IgG4 reaction in cancer tissue.
188 Hepatology. 2012;56:157–64.
189 9. Ohara H, Nakazawa T, Kawa S, et al. Establishment of a serum IgG4 cut-off value for the
190 differential diagnosis of IgG4-related sclerosing cholangitis: a Japanese cohort. J Gastroenterol
191 Hepatol. 2013;28:1247–51.
192 10. Shiokawa M, Kodama Y, Yoshimura K, et al. Risk of cancer in patients with autoimmune
193 pancreatitis. Am J Gastroenterol. 2013;108:610–7.
194 11. Kamisawa T, Tsuruta K, Okamoto A, et al. Frequent and significant K-ras mutation in the
195 pancreas, the bile duct, and the gallbladder in autoimmune pancreatitis. Pancreas. 2009;38:890–5.
196 12. Douhara A, Mitoro A, Otani E, et al. Cholangiocarcinoma developed in a patient with IgG4-
197 related disease. World J Gastrointest Oncol. 2013;5:181–5.

198 13. Maeda S, Marugami N, Anai H, et al. Bile duct cancer from IgG4-related sclerosing cholangitis:
199 CT and MRI findings [in Japanese]. Jpn J Clin Radiol. 2013;58:812–6.
200 14. Hasebe O, Ochi Y, Ito T, et al. Cholangiocellular carcinoma developed in a patient with
201 autoimmune pancreatitis and IgG4-related sclerosing cholangitis during long follow-up periods [in
202 Japanese]. J Jpn Biliary Assoc. 2014;28:785–93.
203 15. Shinozaki H, Sasakura Y, Shinozaki S, et al. Cholangiocarcinoma presenting after eight years of
204 treatment of IgG4-related autoimmune pancreatitis with steroids. Case Rep Gastroenterol.
205 2021;15:154–62.
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Figure legends

Fig. 1

(a) Contrast-enhanced computed tomography (CECT) shows the wall thickness and focal stricture in the distal bile duct with autoimmune pancreatitis (red arrowheads). Upstream bile duct dilatation is noted.

(b) CE-CT shows a slightly enhanced area in the pancreatic head-body junction, suggestive of autoimmune pancreatitis (AIP).

Fig. 2

(a) Duodenoscopy reveals a normal papilla of Vater.

(b) Endoscopic retrograde cholangiopancreatography (ERCP) reveals a filling defect in the distal bile duct, which was consistent with findings of IgG4-related sclerosing cholangitis (IgG4-SC) (blue arrowheads).

(c) ERCP via the accessory pancreatic duct demonstrated a localized narrowing of the pancreatic duct (yellow arrowheads). Wirsung's canal was not visualized. These findings are considered to reflect AIP.

(d) Intraductal ultrasonography reveals the circumferential and symmetrical wall thickening in the bile duct.

(e) Endoscopic ultrasonography (EUS) reveals diffusely hypoechoic parenchyma with focal punctate hyperechoic spots in the pancreatic head-body junction, consistent with chronic pancreatitis.

Fig. 3

(a) Microscopic examination reveals no malignant cells on hematoxylin and eosin staining (×200).

(b) Histological findings demonstrate increased immunoglobulin G4 (IgG4)-positive plasma cells on IgG4 staining (×200).

Fig. 4

(a) Duodenoscopy revealed a mildly erythematous papilla immediately following biliary stent removal, with no evidence of malignancy.

(b) ERCP shows improvement in biliary stricture 3 months after the initiation of steroid therapy.

Fig. 5

This figure shows the improvement and maintenance of serum immunoglobulin G4 (IgG4) levels and dosage of steroids and azathioprine over 3 years of treatment. Red star indicates the occurrence of recurrent biliary stricture.

Fig. 6

(a) CECT demonstrates a hyperenhancing nodule in the bile duct near the ampulla, showing stronger contrast enhancement than the surrounding duodenum and pancreas, accompanied by contiguous wall thickening (red arrowheads). Although the site of biliary stricture differs from that at the diagnosis of IgG4-SC, upstream bile duct dilatation is similarly observed.

(b) Duodenoscopy shows a granular appearance on the ampulla of Vater following endoscopic sphincterotomy.

(c) ERCP reveals a new distal biliary stricture that was located further downstream from the original site (blue arrowheads).

(d) EUS reveals a hypoechoic mass consistent with biliary stricture (yellow arrowheads). The lesion is in contact with the thickened proper muscular layer of the duodenum (orange arrowheads). There is no evidence of disruption in the duodenal mucosa (hyperechoic layer). Mild irregular wall thickening is observed in the part of the upstream bile duct.

Fig. 7

(a) The surgical specimen includes a portion of the duodenum, common hepatic duct, common bile duct, gallbladder, and pancreatic head. Red arrowheads indicate a tumor near the papilla,

accompanied by bile duct wall thickening. Blue arrowheads indicate improvement of a distal biliary stricture caused by AIP, located at the level of the upper border of the pancreas.

(b, c) Histological analysis of the bile duct at the superior margin of the pancreas in surgical specimens shows no malignancy and few immunoglobulin G4 (IgG4)-positive plasma cells (blue square) (b: hematoxylin and eosin [HE], ×4; c: IgG4, ×200).

(d, e) Histological analysis of the bile duct near the papilla in the surgical specimens shows adenocarcinoma (red square) (d: HE, ×4, e: HE, ×200).

Table 1 Case reports of metachronous development of cholangiocarcinoma in patients with immunoglobulin G4-related sclerosing cholangitis (IgG4-SC)

Author	Year	Age	Sex	Initial IgG4 value (mg/dL)	IgG4-SC classification	Treatment for IgG4-SC	Cancer diagnosis from IgG4-SC	Location of cancer	Treatment for cancer	Follow-up
Douhara [12]	2013	77	Male	299	Type 1	4 years of steroids	4 years	Distal	Surgery	Not reported
Maeda [13]	2013	78	Male	55	Type 3	4 years of steroids	4 years	Hilar	Surgery	Not reported
Hasebe [14]	2014	81	Male	535	Type 3	15 years of steroids	15 years	Hilar	Palliative therapy	Died 9 months after diagnosis
Shinozaki [15]	2020	76	Male	> 1000	Not reported	8 years of steroids	8 years	Distal	Chemotherapy	Died 4 months after diagnosis
Our case	2025	82	Male	358	Type 1	3 years of steroids combined 2 years of azathioprine	3 years	Distal	Surgery	Alive 6 months after surgery

The age refers to the age at the time of cholangiocarcinoma diagnosis.