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Case Report

Usefulness of Steroid Administration for Diagnosis of IgG4-Related Sclerosing Cholangitis

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Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is one of the IgG4-related systemic sclerosing diseases and responds well to steroid therapy. A 58-year-old male was admitted with hilar bile duct stenosis revealed by computed tomography. We performed percutaneous transhepatic right portal vein embolization (PTPE) and scheduled a right hepatectomy because a hilar cholangiocarcinoma was first suspected. However, there was no cytologic evidence of malignancy and serum IgG4 was elevated. Steroid therapy was initiated after PTPE. There was no evidence of bile duct stenosis after 4 weeks. Improving diagnostic technique, IgG4-SC was diagnosed and treated with steroid therapy. In some cases, we couldn't deny the malignancy and performed unnecessary resection. We recommend that steroid administration while waiting for the liver volume to increase after PTPE is useful. The therapy aids in the diagnosis of bile duct stenosis, which has value for a hilar bile duct limit type of IgG4-SC, as in the case reported here.

Key words: IgG4-related sclerosing cholangitis – IgG4, diagnostic administration – steroid therapy – bile duct stenosis

Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) has been described as an IgG4-related systemic sclerosing disease and has been classified into 6 groups by Zen *et al.*[1] IgG4-related systemic sclerosing disease includes sclerosing pancreatitis, hepatic inflammatory pseudotumor, hypophysitis, hypothyroidism, retroperitoneal fibrosis, interstitial nephritis, and prostatitis.[2,3] IgG4-SC mainly affects middle-aged and elderly men.[2] In many cases, the patients present with icteric. The bile duct stenosis lesions of IgG4-SC are often misdiagnosed as cholangiocarcinoma, and some patients, according to reports, have undergone unnecessary surgical resection. IgG4-SC has been recently diagnosed by laboratory examination, diagnostic imaging, and biopsy with intraductal ultrasonography (IDUS). Steroids have been used to treat the

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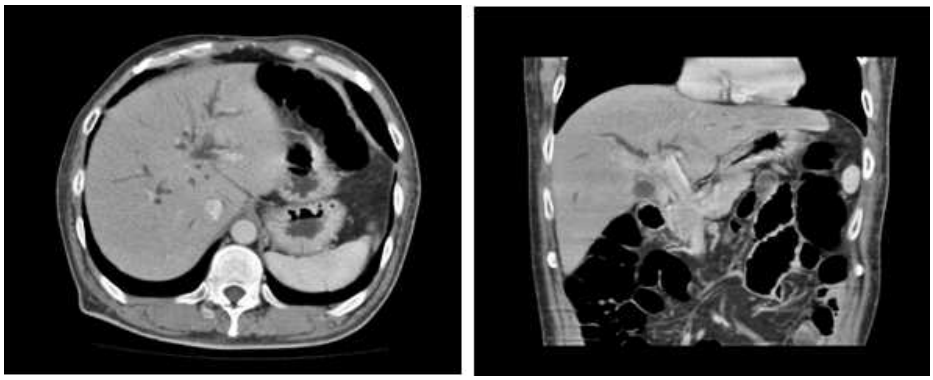

Fig. 1 Abdominal computed tomography image of the patient before steroid therapy. (left) Transverse section shows the dilation of the intrahepatic bile duct. (right) Coronal section shows wall thickening and imaging effect from the middle to the hilar bile duct.

stenosis with good results. In this article, we present the case of an individual diagnosed with IgG4-SC by steroid administration, while awaiting an increase in liver volume after portal vein embolization (PTPE), and the successful treatment. A review of current literature on IgG4-SC is also included.

Case Report

A 58-year-old male was admitted to the Gunma University Hospital for further investigation of bile duct stenosis. Liver function disorder had been diagnosed during a medical checkup, and computed tomography (CT) had shown bile duct stenosis, hypertrophic change of the bile duct wall, and dilation of the intrahepatic bile duct (Fig. 1). The patient exhibited no symptoms on admission; his body temperature was 36.3°C; his pulse, 68 beats per minute; and his blood pressure, 107/65 mmHg. A physical examination of the patient revealed mild icterus of the bulbar conjunctiva, and no mass was palpable in the abdomen. The laboratory data upon admission were as follows (Table 1): total bilirubin, 2.4 mg/dL; aspartate aminotransferase, 344 IU/L; alanine aminotransferase, 167 IU/L; lactate dehydrogenase, 190 IU/L; alkaline phosphatase, 1132 IU/L; and γ-glutamyltransferase, 1477 IU/L. The levels of the tumor markers were normal; the carcinoembryonic antigen (CEA) was <1.0 ng/mL; and the carbohydrate antigen 19-9 (CA19-9) was <7 U/mL. Endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) revealed bile duct stenosis in the upper to hilar portion of the bile duct (Figs. 2 and 3a), dilatation of the intrahepatic bile duct, and no narrowing of the main pancreatic duct. Gall bladder stones were detected by magnetic resonance imaging. No malignant cells were detected during brush cytology from the bile duct. Abdominal angiography revealed no tumor stain and no encasement of the hepatic artery and portal vein. (18)F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) revealed accumulation in the hilar bile duct (HBD), and the maximum standardized uptake value (SUVmax) of the HBD was 5.3 (Fig. 3b).

We performed PTPE and scheduled a right hepatectomy because hilar cholangiocarcinoma was suspected. At the same time, we suspected IgG4-SC and examined the blood; IgG was elevated to 2104 mg/dL; IgG subclass IgG4 was elevated to 522 mg/dL; IgM was 123 mg/dL; antinuclear antibody was negative; antimitochondrial antibody was negative; and anti–smooth muscle antibody was negative.

While awaiting an increase in liver volume, steroid therapy was initiated on the patient at a dosage of 30 mg/d. After 4 weeks of steroid therapy, the levels of serum IgG4 decreased to 316 mg/dL, and total bilirubin was 0.8 mg/dL. After 3 additional weeks, the levels of serum IgG4 decreased to 210 mg/dL, and MRCP revealed no bile duct stenosis (Fig. 3). Prednisolone was tapered to 20 mg/d. We believed that the bile duct stenosis had been caused by IgG4-SC. After that, for work-related reasons, the patient was transferred to another hospital, where follow-up continued. After 3 months, prednisolone was tapered to 5 mg, and the bile duct stenosis recurred. Prednisolone was increased to 10 mg, and the stenosis disappeared. Since then, the patient has been treated with prednisolone (10 mg/d) and no bile duct stenosis has occurred.

Discussion

IgG4-SC is recognized as a systemic sclerosing disease characterized by elevated serum levels of IgG4 and

Table 1 Laboratory findings in the present case[a]

Peripheral blood counts	
RBC ($\times 10^4$)	437
Hb (g/dL)	13.9
Ht (%)	41.7
Plt ($\times 10^4$)	233
WBC (per μL)	5,300
Coagulation	
PT (%)	99
PT-INR	0.99
APTT (seconds)	2.94
Tumor markers	
CEA (ng/mL)	<1.0
CA19-9 (ng/mL)	<7
Biochemistry	
TP (g/dL)	8.0
Alb (g/dL)	3.7
T-Bil (mg/dL)	2.4
D-Bil (mg/dL)	0.9
AST (IU/L)	344
ALT (IU/L)	167
LDH (IU/L)	190
ALP (IU/L)	1132
γ-GTP (IU/L)	1477
AMY (IU/L)	86
LIP (IU/L)	7.7
FBS (mg/dL)	95
BUN (mg/dL)	15
Cr (mg/dL)	0.45
Na (mEq/L)	138
K (mEq/L)	4.6
Cl (mEq/L)	102
Ca (mEq/L)	9.7
Immunology	
CRP (mg/L)	1.05
IgG (mg/dL)	2104
IgG4 (mg/dL)	522
IgM (mg/dL)	123
antinuclear antibody	negative
antimitochondrial antibody	negative
anti-smooth muscle antibody	negative

RBC, red blood cells; Hb, hemoglobin; Ht, hematocrit; Plt, platelet; WBC, white blood cells; PT, prothrombin time; PT-INR, prothrombin time–international normalized ratio; APTT, activated partial thromboplastin time; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; TP, total protein; Alb, albumin; T-Bil, total bilirubin; D-Bil, direct bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyltransferase; AMY, amylase; LIP, lipase; FBS, fasting blood sugar; BUN, blood nitrogen urea; CRP, C-reactive protein.

[a]T-bil, AST, ALT, ALP, and γ -GTP had increased. IgG and IgG4 were elevated in immunologic findings.

has been classified into 6 groups by Zen *et al*.[1] In the past, such biliary lesions of IgG4-SC were often misdiagnosed as primary sclerosing cholangitis (PSC) or cholangiocarcinoma; in some other cases, malignancy could not be ruled out, and unnecessary

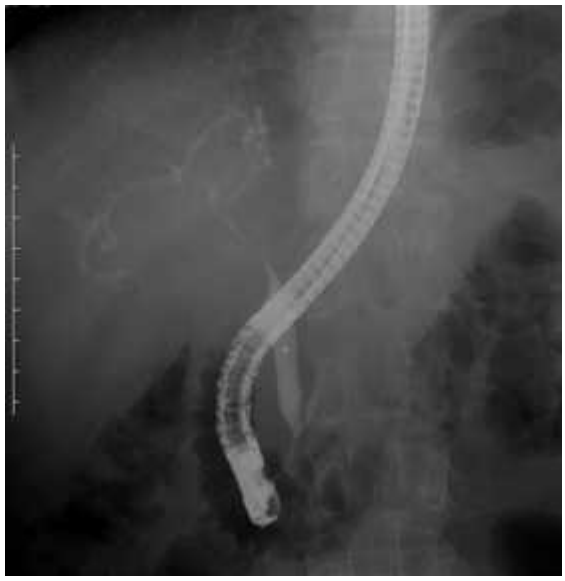

Fig. 2 ERCP shows middle to hilar bile duct stenosis. The inner and outer margins were smooth.

surgical resection took place.[4] Before surgery, it was difficult to deny the possibility of cancer because the imaging of IgG4-SC was similar to cancer. PSC was suspected in cases in which bile duct stenosis occurred. It is difficult to discriminate between IgG4-SC with HBD limit type and bile duct cancer. Elevated serum IgG4 has been observed in 9% of patients diagnosed with PSC, which complicates diagnosis.[5] It is very important to identify each disease, because the treatment differs and bile duct cancer occurs in PSC.[6]

Cholangiography and IDUS findings with biopsy have been useful to distinguish IgG4-SC from cholangiocarcinoma and PSC.[7–11] A bile duct wall thicker than 0.8 mm in regions of non-stricture on a cholangiogram and IDUS is suggestive of IgG4-SC.[8] Bile duct biopsies are useful for ruling out malignant disease in some cases.[8] The tumors can be used to predict malignancy when their size exceeds 10.0 mm or they interrupt the wall structure on IDUS images.[10] FDG-PET has been useful in checking for the presence of other lesions as well as in evaluating the response to steroid therapy.[12]

Because of the improved diagnostic technique, IgG4-SC was easily diagnosed and then treated with steroid therapy with good results.[13–14] Twenty-nine out of 30 IgG4-SC patients (97%) were responsive to steroid therapy.[14]

In this case report, CT and endoscopic findings revealed bile duct stenosis without sclerosing pancreatitis, pancreatic inflammatory pseudotumor (IP), and hepatic IP. The lesion was then classified as the bile duct

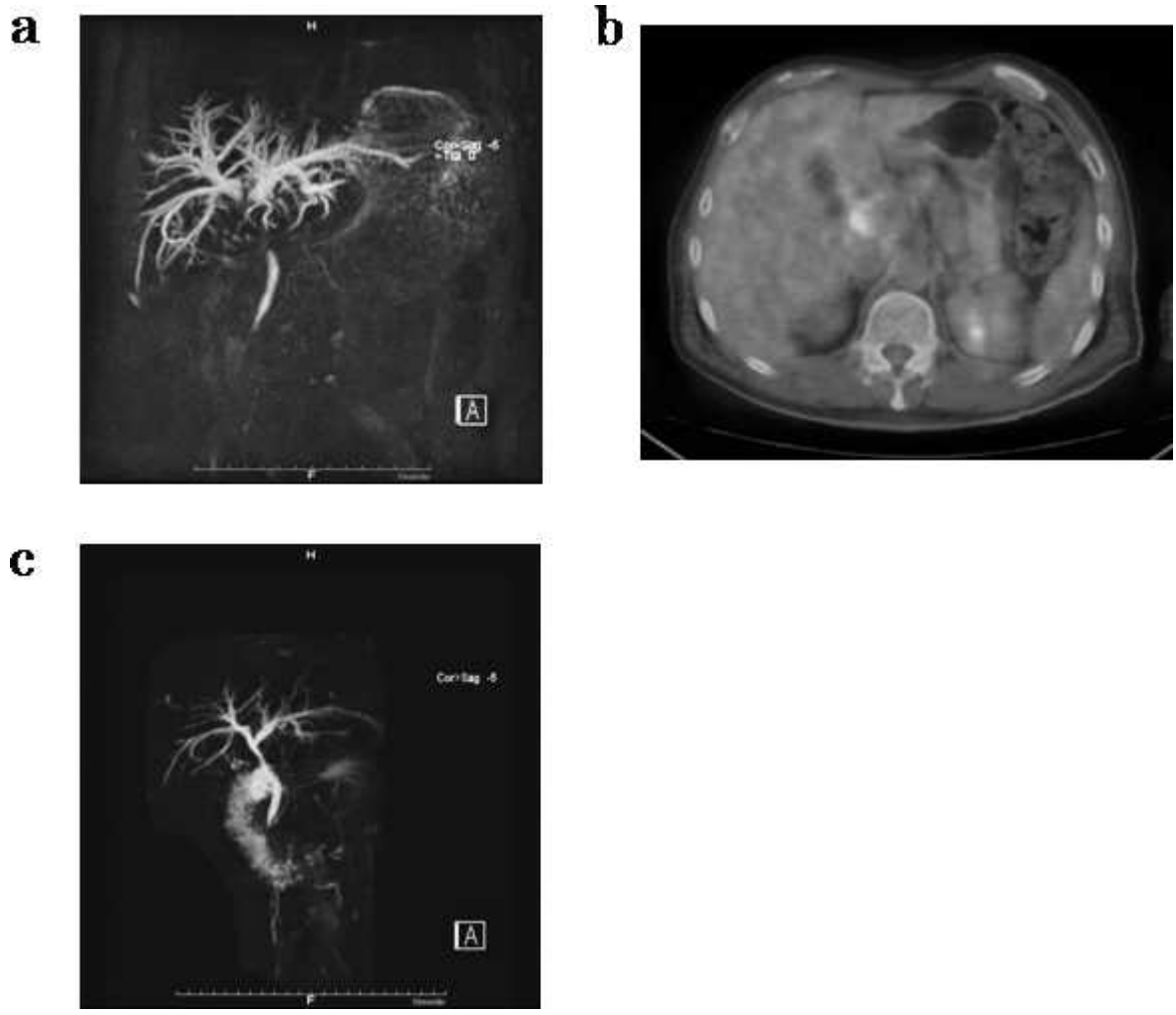

Fig. 3 (a) Cholangiography with MRCP shows bile duct stenosis before the steroid therapy. (b) PET/CT revealed accumulation in the hilar bile duct, and SUVmax was 5.3. (c) MRCP showed no stenosis after the therapy.

limit type according to Zen *et al.*[1] At Gunma University Hospital, brush cytology with ERCP is available, but IDUS is not. Elevated serum IgG4 and a good reaction to steroid therapy together suggested IgG4-SC.

Histologically, IgG4-SC shows lymphoplasmacytic infiltration with extensive fibrosis in the affected bile duct.[2] Immunostaining of IgG4 reveals diffuse infiltration of IgG4-positive plasma cells. The ratio of IgG4 to IgG1-positive plasma cells was significantly higher in specimens obtained from patients with IgG4-SC than in those with PSC, autoimmune hepatitis, and PBC.[15] However, PSC and cholangiocarcinoma sometimes show infiltration of IgG4-positive plasma cells.[8,16] PSC with an infiltration of abundant IgG4-positive plasma cells in the liver was unresponsive to steroid therapy.[16] In one case, an individual with cholangiocarcinoma had abundant IgG4-positive plasma cells.[8] IgG4-SC cannot be ascertained solely by infiltration of IgG4-positive plasma cells. It is necessary to carefully observe the reaction to steroids.

The HBD-limited type of IgG4-SC is difficult to differentiate from bile duct cancer. There have been some patients who underwent surgical resection without final diagnosis. The Mayo Clinic issued a recommendation that steroids be administered to diagnose autoimmune pancreatitis.[17] Similarly, it was useful to evaluate the reaction of the bile duct stenosis to the steroid therapy before surgical resection, while PTPE was enforced to increase liver volume. The morbidity rate for PTPE was only 2.2% without mortality.[18] About 4 weeks were required to increase the liver volume following PTPE and to use the period effectively. When the steroid was administered to an IgG4-SC patient, liver function and bile duct stenosis were reported to have improved;

however, with the administration of ursodeoxycholic acid, no improvement was observed. An opposite outcome was reported for PSC.[19] We believe that the use of steroids for diagnostic purposes has value.

In this case, serum IgG4 decreased approximately 2 months after the beginning of the steroid therapy, and the bile duct stenosis also began to improve. Bile duct stenosis occurred again with an increase of serum IgG4 after steroid was tapered. We believe that serum IgG4 indicated the occurrence of bile duct stenosis. After steroid treatment, 54% of patients had relapsed, and some of them needed steroids or immunomodulatory drugs.[14]

In one case report, a patient with a background of IgG4-SC and autoimmune pancreatitis was diagnosed with bile duct cancer.[20] Benign cases must be decided carefully. It is important to follow up the patient with IgG4-SC.

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