

Immunoglobulin G4-Related Disease Mimicking Unresectable Gallbladder Cancer

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Immunoglobulin G4 (IgG4)-related disease is a novel disease entity that can involve diverse organs, causing specific diseases, including autoimmune pancreatitis, sclerosing cholangitis, cholecystitis, inflammatory aortic aneurysm, and inflammatory pseudotumor. IgG4-related disease is characterized by elevated serum IgG4 concentrations, abundant IgG4 lymphoplasmacytic infiltration, and dramatic steroid responses. It is clinically important to differentiate this rare disease from primary sclerosing cholangitis and cholangiocarcinoma, because the treatment and prognosis of these two diseases are completely different. However, the preoperative diagnosis is challenging, and the disease is frequently misdiagnosed. If the serum level of IgG4 is within the normal range, the diagnosis of IgG4-related disease is more difficult. This article reports on a 59-year-old man with IgG4-related disease mimicking unresectable gallbladder cancer with normal serum IgG4 concentrations. (*Gut Liver* 2013;7:616-620)

Key Words: Immunoglobulin G; Cholangitis, sclerosing; Gallbladder neoplasms; Cholecystitis

INTRODUCTION

Immunoglobulin G-related disease (IgG4-RD) is a novel disease entity which is a steroid responsive, autoimmune disorder. And it is well known that IgG4-RD can involve diverse organs

causing specific diseases including autoimmune pancreatitis, sclerosing cholangitis, cholecystitis, inflammatory aortic aneurysm, and inflammatory pseudotumor.^{1,2} There are many reports of misdiagnosis of IgG4-related sclerosing cholangitis (SC) as pancreatic and biliary cancer.³⁻⁵ However, clinical presentation mimicking gallbladder (GB) cancer is rarely reported. We report herein a case of IgG4-RD mimicking GB cancer that was successfully treated with an oral steroid.

CASE REPORT

A 59-year-old man was referred to our emergency room with jaundice and right upper abdominal discomfort for 1 month. He complained of nausea, fatigue, loss of appetite, and yellowish discoloration of the skin. However, he did not complain of chills and his body temperature was within normal limit.

Laboratory data were as follows (values in parentheses indicate normal range): white blood cell count 7,780/mm³ (range, 4,000 to 10,000/mm³), hemoglobin 14.3 g/dL (range, 13 to 17 g/dL), hematocrit 40.1% (range, 39% to 52%), platelet count 233,000/mm³ (range, 130,000 to 400,000/mm³), aspartate aminotransferase 80 IU/L (range, 0 to 40 IU/L), alanine aminotransferase 138 IU/L (range, 0 to 40 IU/L), alkaline phosphatase 402 IU/L (range, 30 to 115 IU/L), total bilirubin 6.0 mg/dL (range, 0.2 to 1.2 mg/dL), direct bilirubin 5.0 mg/dL (range, 0 to 0.5 mg/dL), amylase 55 U/L (range, 30 to 100 U/L), lipase 60 U/L (range, 23

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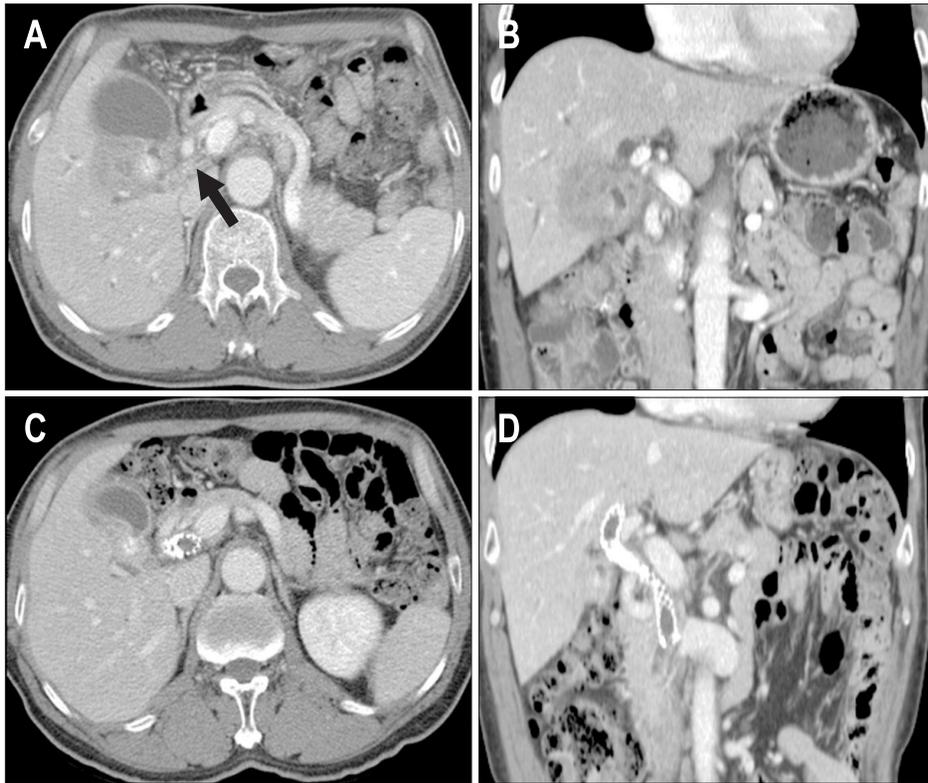


Fig. 1. Computed tomography (CT) image (A, B) before and (C, D) after treatment. (A, B) CT before treatment with steroids reveals an infiltrative low density mass involving the neck portion of the gallbladder and adjacent hepatic parenchyma, along with multiple radio-opaque gallstones and diffuse wall thickening of the common bile duct (annotated with a black solid arrow). (C, D) Abdominal CT after 4 weeks of treatment with steroids indicates resolution of the hepatic mass lesion and a decreased degree of GB wall thickening. The biliary metal stent can also be observed. (A, C) Axial image. (B, D) Coronal image.

to 300 U/L), total protein 8.0 g/dL (range, 6 to 8 g/dL), albumin 4.3 g/dL (range, 3.3 to 5.2 g/dL), hepatitis B surface antigen negative, hepatitis B surface antibody negative, and urine bilirubin 3 positive (negative). The serum levels of carcinoembryonic antigen and α -fetoprotein were within normal limits; however, carbohydrate antigen 19-9 was 90 U/mL (range, 0 to 37 U/mL).

Abdominal computed tomography (CT) revealed an infiltrative low density mass involving the neck portion of GB and adjacent hepatic parenchyma along with multiple radio-opaque gallstones in the fundus and neck portion (Fig. 1A and B). However, there were not any abnormalities in pancreas and other organs on abdominal CT scan. As there was contiguous soft tissue infiltration involving the right and common hepatic artery, right and main portal vein, it was initially interpreted as unresectable GB cancer. The mass showed mild enhancement in the arterial phase and further delayed enhancement. In addition, there was diffuse symmetrical wall thickening of the extrahepatic bile duct and cystic duct. Magnetic resonance cholangiopancreatography (MRCP) revealed short segmental stricture at the proximal common hepatic duct with upstream bile duct dilatation (Fig. 2). Under the impression of GB cancer with direct hepatic invasion, ultrasonography-guided 18-gauge core needle biopsy was done at the hypoechoic lesion at S5 of the liver adjacent to the thickened wall of GB for pathologic confirmation. Histologic examination showed no malignant cells but only moderate periportal fibrosis with portal inflammation. In order to differentiate IgG4-

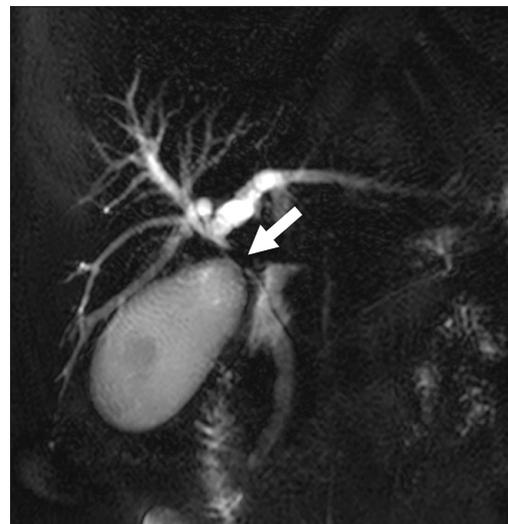


Fig. 2. Magnetic resonance cholangiopancreatography reveals a short segmental stricture at the proximal common hepatic duct (annotated with a white solid arrow) with upstream bile duct dilatation.

related disease, we performed additional laboratory tests for autoimmune disorders as follows (values in parentheses indicate normal range): antinuclear antibody was negative: IgG 1,280 mg/dL (range, 700 to 1,700 mg/dL), IgA 381 mg/dL (range, 90 to 400 mg/dL), IgM 71.7 mg/dL (range, 45 to 230 mg/dL), IgG subtype IV 75 mg/dL (range, 6 to 121 mg/dL). Since the serum

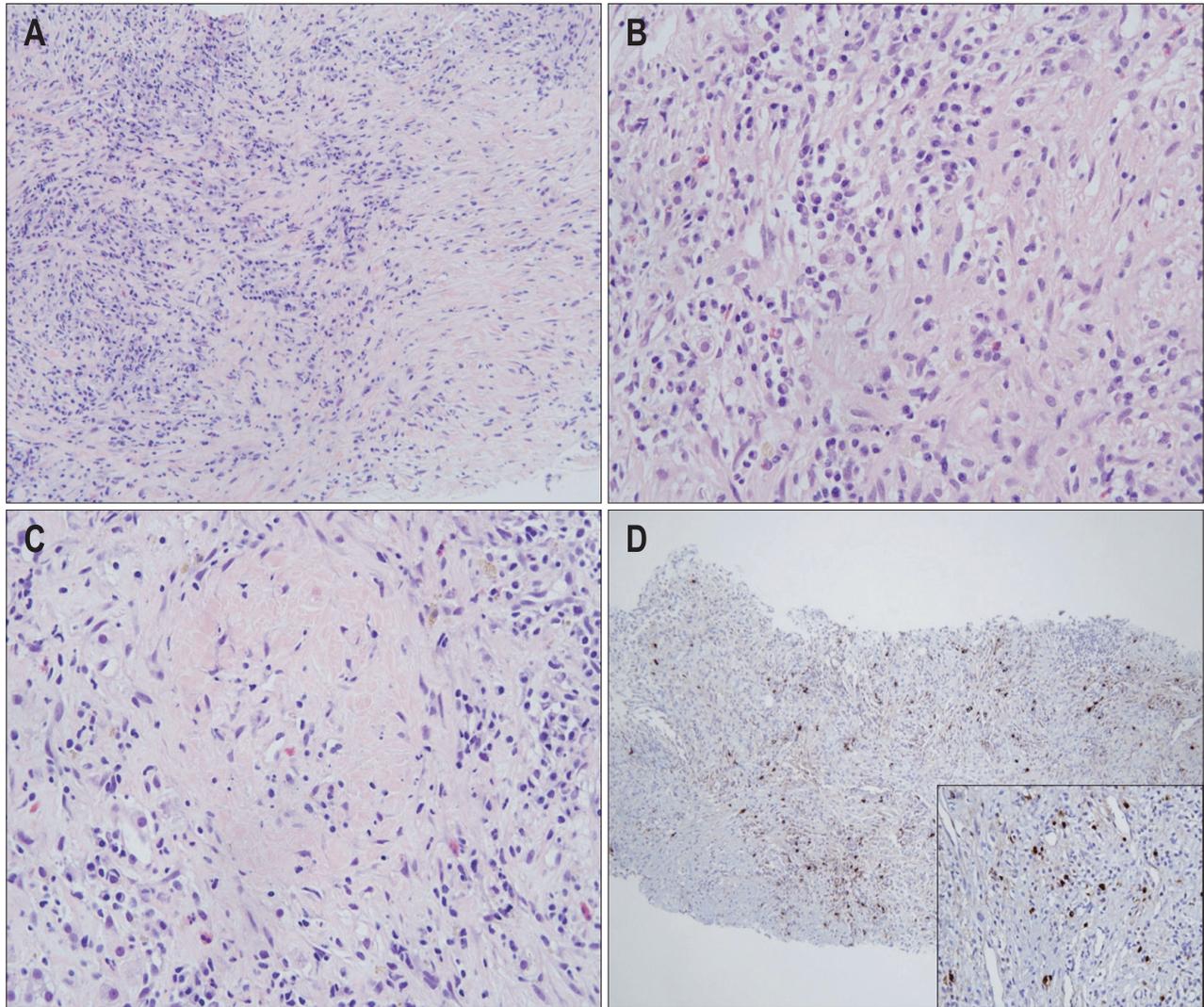


Fig. 3. Pathology of the gallbladder bed from the patient. (A) Inflammatory cell infiltration within a background of fibrosis (H&E stain, $\times 200$), (B) many plasma cells and a few eosinophils (H&E stain, $\times 400$), (C) subocclusive vasculitis with inflammatory infiltrate in the thickened vessel wall (H&E stain, $\times 400$), and (D) abundant immunoglobulin G4+ (IgG4+) plasma cells (immunohistochemistry of IgG4, $\times 100$).

concentrations of autoimmune markers including the IgG4 were within normal range, the possibility of IgG4-RD was considered to be low. On our multidiscipline team conference this case was concluded as inoperable GB cancer. Therefore, biliary self-expandable metal stent was inserted to treat the obstructive jaundice. After that, we took the biopsy once more in order to confirm the pathology. The microscopic examination of the second GB bed biopsy revealed diffuse lymphoplasmacytic infiltration and dense fibrosis (Fig. 3A and B). Obliterative phlebitis and infiltration of some eosinophils were also found (Fig. 3C). On immunohistochemical stain, the number of the IgG4+ plasma cells was counted up to 30/high power field (Fig. 3D). Based on the characteristic findings of pathology, CT, and MRCP, the final diagnosis was IgG4-RD involving bile duct (SC), GB (cholecystitis),

and hepatic parenchyma (inflammatory pseudotumor). And oral prednisolone therapy was started at a dose of 40 mg/day. After 4 weeks treatment it was tapered at 7 days interval with 5 mg dose. After total 11 weeks steroid treatment, it was stopped. And the symptoms had completely resolved without any complications. Abdominal dynamic CT after 4 weeks steroid treatment showed resolution of the hepatic mass lesion and decreased degree of GB wall thickening (Fig. 1C and D). And the resolution state was maintained on follow-up abdominal CT after 11 months. The patient has been closely followed for 13 months in terms of recurrence and stent-related long-term complications, such as recurrent stone formation or stent obstruction due to epithelial hyperplasia.

DISCUSSION

Since Kamisawa *et al.*⁶ proposed a new term of systemic IgG4-related autoimmune disease in 2003, IgG4-RD has become a novel clinicopathological disease entity.¹ There are many terms of IgG4 related conditions, such as IgG4-related autoimmune disease,⁶ IgG4-related sclerosing disease,⁷ IgG4-related multiorgan lymphoproliferative syndrome,⁸ and IgG4-RD,⁹ all of which refer to the same disease entity. IgG4-RD is a systemic disease which can involve multiple organs simultaneously or metachronously, such as the central nervous system, lacrimal/salivary glands, thyroid gland, lungs, pancreas, biliary duct, liver, gastrointestinal tracts, kidneys, prostate gland, retroperitoneum, skin, arteries, and lymph nodes. The key histopathologic findings are abundant IgG4 lymphoplasmacytic infiltrate, obliterative phlebitis, and an eosinophil infiltrate.² Although increased level of serum IgG4 is a characteristic, it is not highly diagnostic. The sensitivity and accuracy of serum IgG4 for IgG4-related SC was reported as 50% and 60%, respectively.¹⁰ In our case, the level of serum IgG4 was within normal range. But, histopathological finding showed all of the key findings. Therefore, IgG4-RD involving bile duct (SC), GB (cholecystitis), and hepatic parenchyma (inflammatory pseudotumor) could be diagnosed based on combination of histology, radiological image, serology, the presence of other organ involvement and steroid responsiveness.

Recently, there are several reports that hepatic inflammatory pseudotumor is associated with IgG4-related SC, in which extrahepatic manifestations were reported including lymph node swelling, sialoadenitis, and pancreatitis.^{5,11-13} However, cholecystitis mimicking GB cancer has never been reported like in this case.

Our patient was treated with steroid according to the treatment protocol of Mayo Clinic because it is well known that IgG4-related SC has a dramatic steroid response.¹¹ After 4 weeks treatment, the symptoms had completely resolved without any complications. Abdominal dynamic CT showed resolution of the hepatic mass lesion and decreased degree of GB wall thickening. The good response of steroid therapy was able to diagnose IgG4-related SC with confidence. Although steroid therapy is well known as the initial treatment of IgG4-related SC, there are no randomized trials and no data about the duration of treatment. And the rate of relapse on steroid withdrawal was reported to be about 54%.¹⁴ Mayo Clinic proposed that azathioprine or mycophenolate mofetil could be used as maintenance drugs.¹⁴ The maintenance therapy is used only in those patients who relapse after an initial course of steroid at the Mayo Clinic, unlike Japan, Korea, or Europe. And it needs further study to be established. Therefore, we have closely followed up the patient without steroid or immunomodulatory drugs and the patient continues to be the remission status until now.

This case is unique in the point of that IgG4-RD could be presented as mimic of GB cancer with normal IgG4 concentration. Therefore, if initial pathology does not show malignant cells, additional special stain for IgG4 should be considered even in the case of normal IgG4 concentration. And IgG4-RD should be considered in the differential diagnosis even though GB cancer is suspected.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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