

Case report

A rare case of localized IgG4-related sclerosing cholecystitis mimicking gallbladder cancer

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Abstract

Objective: IgG4-related sclerosing cholecystitis is generally associated with IgG4-related sclerosing cholangitis and presents with diffuse, circumferential thickening of the gallbladder wall. We report a rare case of localized IgG4-related sclerosing cholecystitis without IgG4-related sclerosing cholangitis, which was difficult to differentiate from gallbladder cancer preoperatively.

Patient: A 56-year-old man with suspected IgG4-related disease or gallbladder cancer was admitted to our ward. The serum IgG4 level was elevated at 721 mg/dL. Computed tomography (CT) demonstrated focal wall thickening of the gallbladder fundus. Drip infusion cholecystocholangiography with CT revealed no dilation, stenosis, or border irregularity of the bile duct.

Results: For diagnostic and treatment purposes, cholecystectomy with wedge resection of the gallbladder bed was performed. The pathological diagnosis was IgG4-related sclerosing cholecystitis.

Conclusion: It is difficult to differentiate IgG4-related sclerosing cholecystitis from gallbladder cancer in cases involving localized thickening of the gallbladder wall. In similar cases, surgical resection with cancer in mind might be performed based on present clinical knowledge.

Key words: IgG4-related cholecystitis, IgG4-related disease, gallbladder cancer

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Introduction

In general, IgG4-related sclerosing cholecystitis is associated with IgG4-related sclerosing cholangitis. In addition, the condition mainly presents with diffuse, circumferential thickening of the gallbladder wall¹⁾. We report a rare case of localized IgG4-related sclerosing cholecystitis without IgG4-related sclerosing cholangitis, which was difficult to differentiate from gallbladder cancer preoperatively.

Patient

A 56-year-old man was diagnosed with a tumor in his left jaw in May 2016. He was referred to the otolaryngology department in our hospital and was observed as an outpatient with ultrasonography. Because the submandibular gland tumor showed a tendency to enlarge, tumor resection was performed in January 2017. Pathological examination revealed IgG4-related sclerosing sialadenitis. Computed tomography (CT) performed as part of systemic screening revealed thickening of the gallbladder wall. Sclerosing cholecystitis associated with IgG4-related disease and gallbladder cancer were considered in the differential diagnosis. The patient was admitted to our ward for detailed examination and surgical intervention in May 2017.

Laboratory testing revealed the following results (values in parentheses indicate normal range): amylase 163 U/L (43–116 U/L), lipase 150 IU/L (13–55 IU/L), aspartate aminotransferase 50 U/L (0–30 U/L), and alanine aminotransferase 104 U/L (0–30 U/L). The serum IgG4 level was elevated at 721 mg/dL (4.5–117 mg/dL), while the levels of tumor markers, including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), were within the normal ranges.

Abdominal CT images revealed focal wall thickening of the gallbladder fundus compared to the images from one year previously. No enhancement was observed in the ar-

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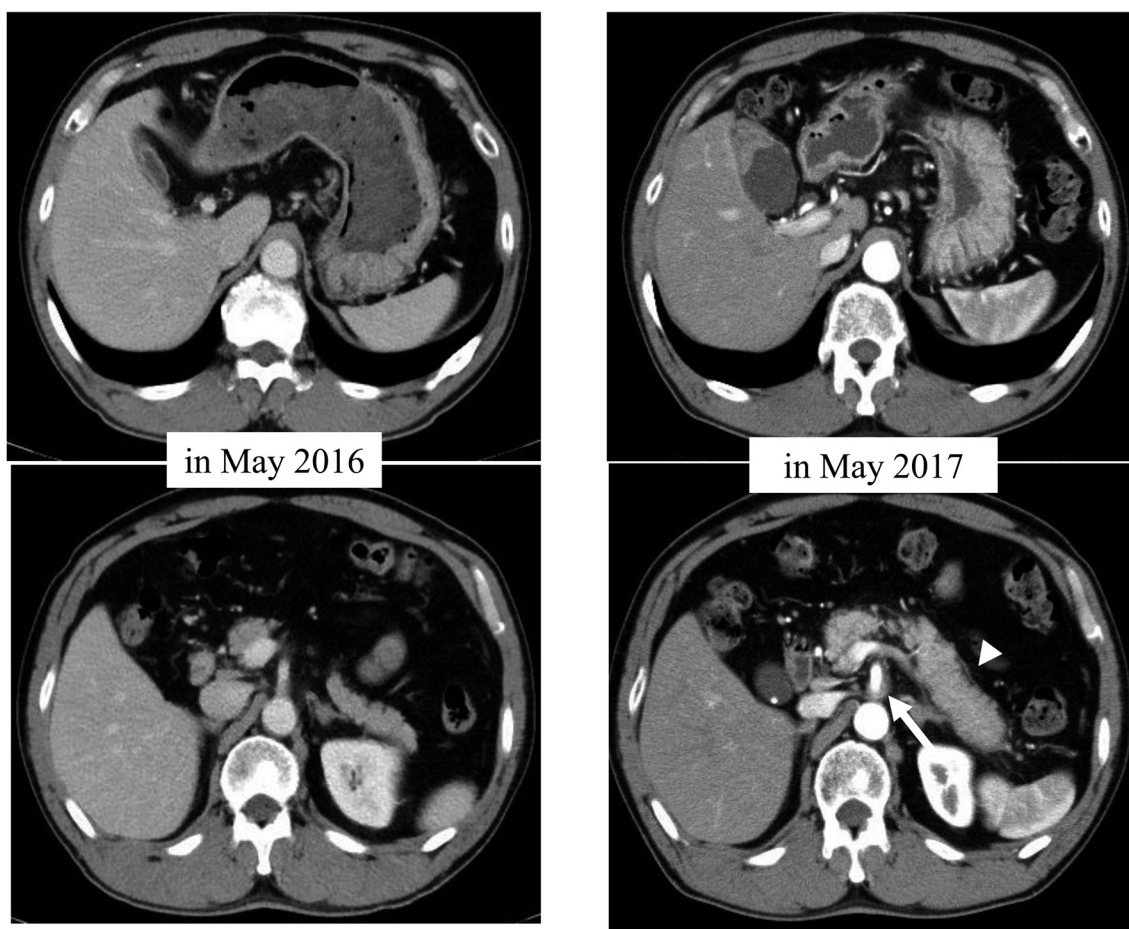


Figure 1 Left column: Computed tomography (CT) image in May 2016, Right column: CT image in May 2017. CT in 2017 revealed localized wall thickening of gallbladder fundus compared to 1 year ago. There was no enhancement in arterial phase, and lesion showed a relatively homogenous concentration and smooth margins. Diffuse swelling in pancreatic tail (arrow head) suggested autoimmune pancreatitis, and low-density area around superior mesenteric artery was characteristic of retroperitoneal fibrosis (arrow).

terial phase, and the lesion demonstrated a relatively homogenous concentration and smooth margins. Two small stones in the gallbladder were identified. In addition, diffuse swelling in the pancreatic tail (arrow head) suggested autoimmune pancreatitis, and the low-density area around the superior mesenteric artery was characteristic of retroperitoneal fibrosis (Figure 1).

Abdominal ultrasonography also revealed focal wall thickening of the gallbladder fundus similar to that shown by the CT images. The ultrasonography revealed a comet-like echo in the gallbladder wall and enlarged Rokitansky-Aschoff sinuses (Figure 2).

Drip infusion cholecystocholangiography with CT (DIC-CT) revealed no dilation, stenosis, or border irregularity of the bile duct. No anatomical abnormalities of the cystic duct were observed (Figure 3).

Based on these results, the most likely diagnosis was sclerosing cholecystitis associated with IgG4-related disease; however, we could not completely rule out the possibility of gallbladder cancer. For diagnostic and treatment purposes, cholecystectomy with wedge resection of the gallbladder bed was performed.

Gross findings of the surgical specimen demonstrated a localized tumor similar in appearance to adenomyomatosis in the gallbladder fundus, firmly adhering to gallbladder bed (Figure 4).

Pathological findings revealed a high degree of infiltration of lymphocytes and plasma cells, lymphoid follicle formation, collagen fiber proliferation, and a fibrotic spiral growth pattern spread around the Rokitansky-Aschoff sinuses and under the epithelium of the gallbladder (Figure 5A, B). Immunohistochemical staining was positive for



Figure 2 Abdominal ultrasonography also showed localized wall thickening of gallbladder fundus similar to that observed with CT. It revealed comet-like echo in gallbladder wall and enlarged Rokitansky-Aschoff sinuses.



Figure 3 Drip infusion cholecystocholangiography with CT (DIC-CT) revealed no dilation, stenosis, or border irregularity of bile duct. No anatomical abnormality of cystic duct was observed.

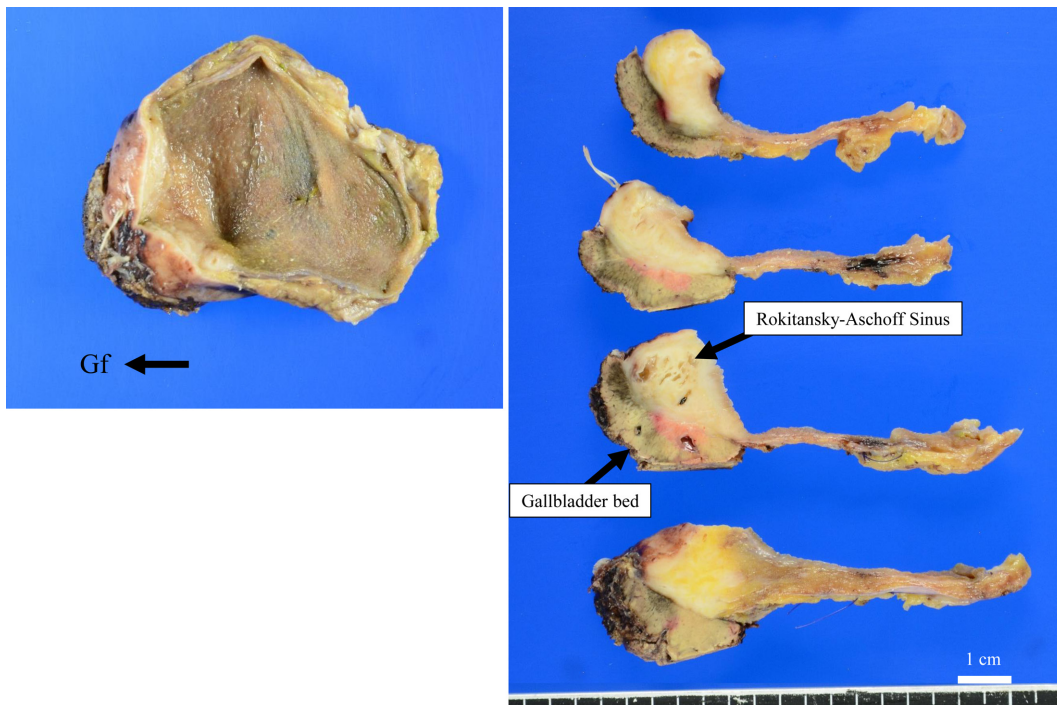


Figure 4 Gross findings of surgical specimen demonstrated localized tumor with similar appearance to adenomyomatosis in gallbladder fundus, firmly adhering to gallbladder bed.

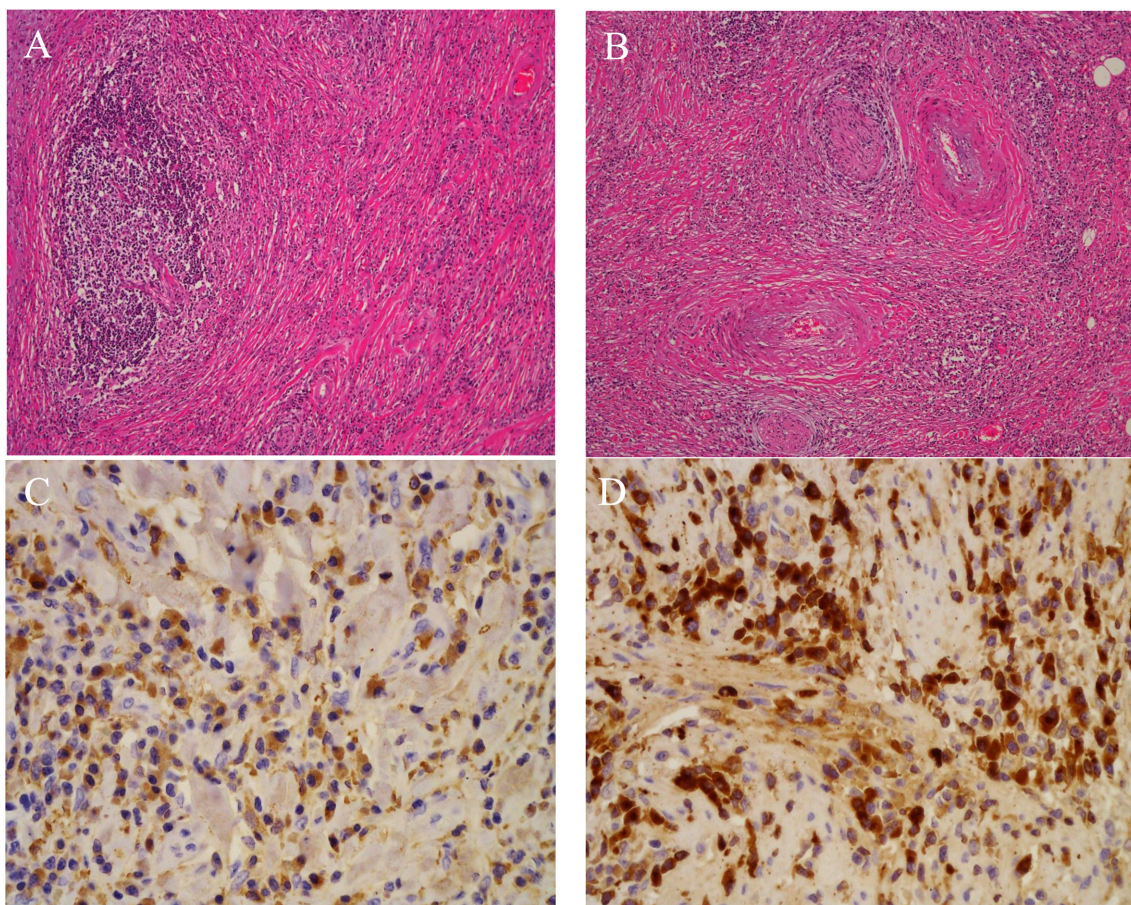


Figure 5 A, B (H&E stain, $\times 100$): Pathological findings revealed high degree infiltration of lymphocytes and plasma cells, lymphoid follicle formation, collagen fiber proliferation, and fibrotic spiral growth pattern spread around Rokitan-sky-Aschoff sinuses and under gallbladder epithelium. C (immunohistochemistry for IgG $\times 400$), D (immunohistochemistry for IgG4 $\times 400$): The number of IgG4-positive cells was 60 to 100 per high-power field. Ratio of IgG4 to IgG was nearly 1.

CD138, with approximately equal staining for κ type and δ type, and a high degree of infiltration of polyclonal plasma cells was observed. The number of IgG4-positive cells was 60 to 100 per high-power field. The ratio of IgG4 to IgG was closed to 1; thus, the final diagnosis was IgG4-related sclerosing cholecystitis (Figure 5C, D). Infiltration of IgG4-positive cells was also observed in the peripheral gallbladder mucosa, without tumor formation, as well as in the lymph nodes around the cystic duct.

The patient's postoperative course was uneventful. No postoperative steroid was administered, and he was discharged six days after the surgery without any additional treatment. The serum IgG4 level has remained in the range of 303 to 1300 mg/dL in the first year after surgery, and no signs of cholangitis or exacerbation of pancreatitis have been observed on CT imaging to date.

Discussion

IgG4-related sclerosing disease, a recently described clinicopathological entity, is a systemic inflammatory syndrome characterized by extensive infiltration of IgG4-positive plasma cells and lymphocytes with fibrosis and obliterative phlebitis in the pancreas, gallbladder, bile duct, liver, lacrimal/salivary glands, retroperitoneum, lungs, thyroid, mammary gland, prostate, gastrointestinal tract, central nervous system, skin, arteries and lymph nodes²⁻⁴. Features include preponderance in elderly men, frequent elevation of serum IgG4 levels, and dramatic response to steroid therapy⁵. Although increased serum IgG4 is a characteristic of the condition, it is not highly diagnostic. The sensitivity and accuracy of serum IgG4 for IgG4-related sclerosing cholangitis have been reported as 50% and 60%, respectively⁶.

IgG4-related sclerosing cholecystitis is a manifestation of IgG4-related sclerosing disease in the gallbladder.

There have been few cases of patients presenting with symptoms of usual cholecystitis, such as fever or right hypochondralgia, and the condition is often revealed by imaging findings, as in the case described here. IgG4-related sclerosing cholecystitis generally accompanies IgG4-related pancreatitis and/or sclerosing cholangitis; cases of sclerosing cholecystitis alone are rare. To the best of our knowledge, in fact (based on a literature search using “IgG4-related cholecystitis” as a keyword in PubMed and Ichushi-Web between 2000 and 2018), there has been only one case⁷⁾. In a study of 43 patients with autoimmune pancreatitis, no thickening of the gallbladder wall was noted in nine patients without bile duct lesions, whereas 69% (9/13) and 19% (4/21) of patients with diffuse stenosis of the bile duct and lower bile duct involvement only demonstrated thickening of the gallbladder wall, respectively⁸⁾. The case presented here was a case of IgG4-related cholecystitis in the absence of sclerosing cholangitis; therefore it should be classified as a rare case.

The characteristic radiologic findings of IgG4-related sclerosing cholecystitis include continuity of the mucous layer and the homogenous contrast effect of the gallbladder wall on CT⁷⁾; however, it is challenging to differentiate the condition from gallbladder cancer in the case of localized thickening of the gallbladder wall. Kawakami *et al.*⁹⁾ and Inoue *et al.*¹⁰⁾ speculated that the combined changes induced by adenomyomatosis and IgG4-related cholecystitis may promote the development of localized tumors, thus requiring close diagnostic attention.

In most cases of IgG4-related sclerosing cholecystitis, surgical interventions have been selected and extended cholecystectomy has frequently been performed as part of the operative procedure⁵⁾. In the present case, although the most probable diagnosis was sclerosing cholecystitis associated with IgG4-related disease, we could not completely rule out the possibility of gallbladder cancer. Therefore, after obtaining sufficient informed consent, surgical intervention was selected.

Conclusion

We report a case of IgG4-related sclerosing cholecystitis with difficulty in preoperative diagnosis. Diffuse thickening of the gallbladder wall is often accompanied by autoimmune

pancreatitis and/or sclerosing cholangitis; however, it is difficult to differentiate the condition from gallbladder cancer in the case of localized thickening of the gallbladder wall. In similar cases, surgical resection with cancer in mind might be performed based on present clinical knowledge.

Conflicts of Interest: All authors report no conflicts of interest with respect to this article.

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