Localized IgG4-related Cholecystitis Mimicking Gallbladder Cancer

Tadahisa Inoue, Fumihiro Okumura, Takashi Mizushima, Hirotada Nishie, Hiroyasu Iwasaki, Kaiki Anbe, Takanori Ozeki, Kenta Kachi, Shigeki Fukusada, Yuta Suzuki, Kazuko Watanabe and Hitoshi Sano

Abstract

We encountered a case of localized IgG4-cholecystitis mimicking gallbladder cancer with focal/segmental type 1 autoimmune pancreatitis (AIP). In this case, we were unable to exclude a diagnosis of gallbladder cancer and thus performed radical cholecystectomy. Type 1 AIP is often associated with gallbladder lesions, accompanied by generally diffuse, circumferential thickening of the gallbladder wall. Although localized IgG4-related cholecystitis is extremely rare, differentiating this condition from gallbladder cancer is often very difficult.

Key words: IgG4-related cholecystitis, IgG4-related disease, autoimmune pancreatitis, gallbladder neoplasms, adenomyomatosis

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Introduction

In patients with autoimmune pancreatitis (AIP), various other organs may be involved, with pathological findings similar to those observed in the pancreatic tissue. The condition IgG4-related disease (IgG4-RD) is a recently described entity (1), and IgG4-related cholecystitis has been noted as a manifestation of IgG4-RD in the gallbladder (2, 3). In general, IgG4-related cholecystitis is associated with IgG4-sclerosing cholangitis (IgG4-SC), which presents with diffuse, circumferential thickening of the gallbladder wall (3). Although this disease is extremely rare, a case of localized IgG4-related cholecystitis has been reported (4). Differentiating localized IgG4-related cholecystitis from gallbladder cancer is often very challenging. We herein present a case of localized IgG4-related cholecystitis without bile duct lesions in which establishing a definitive diagnosis based on imaging results was very difficult. We believe that the present case provides useful information for managing patients in whom IgG4-related cholecystitis is suspected. In this report, we describe the current case with a review of the literature.

Case Report

A Japanese woman in her sixties visited our hospital for an evaluation of a gallbladder tumor detected on abdominal ultrasound (US) during a medical examination. She had no symptoms and had neither a relevant medical nor contributory family history. The serum IgG4 level was elevated at 813 mg/dL (normal range, 4.8 to 105 mg/dL) (Table), while the levels of tumor markers, including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), were within the normal ranges. Abdominal US revealed a 15×10-mm solid tumor at the fundus of the gallbladder (Fig. 1a) and a 40-mm low-echoic tumor in the pancreatic tail (Fig. 1b). In addition, computed tomography (CT) of the abdomen disclosed a localized, delayed-enhanced tumor in the gallbladder (Fig. 1a) and a 40-mm low-echoic tumor in the pancreatic tail (Fig. 1b). The pancreatic tail tumor exhibited delayed enhancement; however, the extent of enhancement was less than that observed in the surrounding pancreas (Fig. 2c, d). There were no abnormalities in any other organs, e.g., the bile duct, lymph nodes, salivary glands or kidneys, and magnetic resonance cholangiopancreatography.
Figure 1. Abdominal ultrasound (US) revealed a solid tumor (arrows) at the fundus of the gallbladder (a) and a low-echoic tumor (arrow) in the pancreatic tail (b).

showed no abnormalities in the bile duct (Fig. 3), although the main pancreatic duct of the pancreatic tail was not detected. Endoscopic ultrasonography (EUS) revealed a solid, localized tumor in the fundus of the gallbladder (Fig. 4a) as well as a hypoechoic and heterogeneous tumor in the pancreatic tail with narrowing of the main pancreatic duct caused by the tumor (Fig. 4b). No abnormalities of the bile duct, including thickening of the wall, were detected on EUS. Endoscopic retrograde cholangiopancreatography revealed a long segment of narrowing along the main pancreatic duct in the pancreatic tail (Fig. 5).

Based on these results, we suspected the pancreatic tail tumor to be focal/segmental AIP. This led to the speculation that the gallbladder tumor was a lesion of IgG4-related cholecystitis, although the possibility of gallbladder polyps (e.g., hyperplastic polyps and gallbladder adenoma) was also considered during the differential diagnosis. However, we could not exclude a diagnosis of gallbladder cancer because the tumor was localized and no thickening of the gallbladder wall, except in the fundus, or bile duct lesions were detected, including signs of stenosis or dilatation. Therefore, radical cholecystectomy with a simultaneous aspiration biopsy of the pancreatic tail tumor was performed.

An examination of the surgically resected specimen demonstrated a 15×10-mm tumor in the fundus of the gallbladder (Fig. 6). The excised section contained a yellow-white mass, and multiple small cystic lesions presenting as adenomyomatosis in the tumor were observed histologically. In addition, a histological examination revealed transmural lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis and abundant IgG4-positive plasma cells (>10 cells per high-power field), with no evidence of malignancy (Fig. 7).

These findings were not observed in areas other than the gallbladder tumor and regions in the vicinity. The biopsy specimen of the pancreatic tumor showed lymphoplasmacytic sclerosing pancreatitis without malignancy, similar to the histological findings of the gallbladder tumor. The final pathological diagnosis was focal/segmental type 1 AIP and IgG4-related cholecystitis. In the gallbladder tumor, transmural IgG4-related cholecystitis was interspersed with fundal-type adenomyomatosis, and the IgG4-related chole-
Figure 2. Computed tomography (CT) of the abdomen revealed a 15×10-mm localized, delayed-enhanced tumor (arrow) in the gallbladder (a, b). A 40-mm pancreatic tail delayed-enhanced tumor (arrow) was identified (c, d).

Figure 3. Magnetic resonance cholangiopancreatography (MRCP) showed no abnormalities in the bile duct. The main pancreatic duct of the pancreatic tail was not detected.

cystitis covered a slightly a wider area in the tumor than the adenomyomatosis. Oral prednisolone therapy was initiated after the surgery, and the pancreatic tail findings on CT improved. No signs of recurrence were observed for three years after the initiation of prednisolone.

Discussion

Type 1 AIP is characterized by enlargement of the pancreas, irregular narrowing of the pancreatic duct and an increased serum IgG4 level (5). Type 1 AIP is a systemic disease that affects multiple organs, in addition to the pancreas, including the central nervous system, lacrimal/salivary glands, thyroid gland, lungs, biliary duct, liver, gallbladder, gastrointestinal tract, kidneys, prostate gland, retroperitoneum, skin, arteries and lymph nodes. Therefore, the term “IgG4-RD” was recently coined, and type 1 AIP is acknowledged to be a pancreatic lesion of IgG4-RD (1). Bile duct lesions, in particular, are frequently associated with type 1 AIP, which occurs alongside IgG4-SC in approximately 60% to 80% of patients (6, 7). Regarding gallbladder lesions, Abraham et al. (2) reported that 12 of 20 cases (60%) of AIP showed intense inflammatory infiltration of the gallbladder wall and seven of 20 cases (35%) exhibited transmural chronic cholecystitis. In addition, Kamisawa et al. (3) reported that 10 of 19 cases (53%) of AIP demonstrated severe or moderate thickening of the gallbladder wall, as observed on radiological examinations, including US and/or CT, while six of eight patients (75%) with AIP undergoing surgery showed gallbladder wall thickening on histological examinations, including four patients with fibrosis, IgG4-positive plasma cells and the transmural inflammation of lymphocytes. IgG4-related cholecystitis is mainly associated with IgG4-SC (3, 8). In a report of biliary lesions in 43 patients with AIP (8), no gallbladder wall thickening was noted in nine patients, with no bile duct lesions, whereas
69% (9/13) and 19% (4/21) of the patients with extensive bile duct involvement and lower bile duct involvement only displayed gallbladder wall thickening, respectively. In the above-mentioned report of 19 patients with AIP (3), all patients with gallbladder wall thickening also showed severe stenosis of the extrahepatic bile duct. The present case is extremely rare, as gallbladder lesions were detected in the absence of bile duct lesions. Therefore, establishing a definitive diagnosis was challenging in this case.

In IgG4-RD patients, malignant tumors are often suspected, and obtaining the differential diagnosis is often very difficult (9). Most patients with IgG4-related cholecystitis exhibit diffuse, circumferential thickening of the gallbladder wall associated with IgG4-SC or AIP. Therefore, confirming the diagnosis is not difficult in typical cases of IgG4-related cholecystitis. However, in patients with localized gallbladder lesions or inflammation extending to the surrounding tissue in the gallbladder (mimicking the appearance of a malignant tumor), excluding the presence of gallbladder cancer is challenging. To date, eight cases of IgG4-related cholecystitis mimicking gallbladder cancer have been reported (4, 10-14). Most of the cases were not diagnosed preoperatively, and surgical treatment was therefore performed. To the best of our knowledge, only one case of a localized gallbladder lesion similar to the present case has been reported (4). In that report, the authors speculated that the localized tumor had developed as a result of the combined effects of adenomyomatosis and IgG4-related inflammation. In the present case, IgG4-related cholecystitis associated with fundal-type adenomyomatosis was observed, similar to that seen in the previously reported case (4). The combined changes induced by adenomyomatosis and IgG4-related cholecystitis may promote the development of localized tumors, thus requiring close diagnostic attention.

In the present case, the pancreatic tail tumor was consid-
Figure 7. Histopathological findings of the gallbladder tumor. (a) Inflammatory cell infiltration with fibrosis (Hematoxylin and Eosin (H&E) staining, ×100). (b) The gallbladder tumor exhibited storiform fibrosis (H&E staining, ×200). (c) Abundant IgG4-positive plasma cells were identified within the tumor (immunostaining for IgG4, ×400). (d) The gallbladder tumor showed obliterative phlebitis. (Elastica-Masson stain, ×200).

ered to be a lesion of AIP. Therefore, a diagnostic steroid trial was initially considered. However, according to the international consensus diagnostic criteria for AIP, such trials should be initiated only after obtaining negative findings on examinations for cancer, including endoscopic US-guided fine-needle aspiration (15). It is more difficult to obtain tissue for a histological diagnosis preoperatively in gallbladder lesions than in pancreatic lesions. The detection of AIP or IgG4-SC is an indication of IgG4-related cholecystitis; however, IgG4-related cholecystitis may occur without bile duct lesions, as observed in the present case and a previously reported case without AIP (12). Therefore, even if AIP or IgG4-SC is not observed when diagnosing gallbladder lesions, the presence of IgG4-related cholecystitis should be considered in the differential diagnosis. Hence, measuring the serum IgG4 level is relevant. The accumulation of cases of IgG4-related cholecystitis will help to clarify the typical features of IgG4-related cholecystitis on imaging, thereby assisting in the differential diagnosis of gallbladder cancer. As observed in the present case, the detection of a delayed-enhancement pattern on CT facilitates the ability to obtain a definitive diagnosis. However, if isolated or localized gallbladder lesions are detected and the possibility of gallbladder cancer cannot be excluded, it is necessary to consider appropriate treatment strategies, including surgical resection.

The authors state that they have no Conflict of Interest (COI).

References