

CASE REPORT

Immunoglobulin G4-related disease mimicking gallbladder cancer with associated choledochal cyst: A case report of a malignant masquerade

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Introduction

Immunoglobulin G4 (IgG4)-related disease is a novel disease entity that may affect diverse organs such as liver, pancreas, bile duct, esophagus, salivary glands, and retroperitoneum.¹ IgG4 sclerosing cholangitis mimicking hilar cholangiocarcinoma is a well-described phenomenon.² In contrast, there have been only a handful of reports of IgG4 sclerosing cholecystitis with a clinical presentation as a gallbladder mass.^{3,4} It is important to recognize IgG4-related disease preoperatively as this condition tends to respond dramatically to steroid therapy. However, due to the overlapping clinical and radiological features, this distinction may be difficult in many instances. We report a rare case of a middle-aged male presenting with a soft-tissue mass in the gallbladder with a dilated common bile duct, which we suspected to be gallbladder cancer secondary to a choledochal cyst.

Abstract

Immunoglobulin G4 (IgG4)-related disease is a recently described autoimmune disease that can involve diverse organ systems, causing pancreatitis, cholangitis, retroperitoneal fibrosis, and thyroiditis to name a few. Key histological features include storiform fibrosis, obliterative venulitis, and intense inflammatory infiltrate composed of lymphoplasmacytic cells. The disease has a tendency to present with mass-forming lesions, often difficult to differentiate from malignant processes. We report the case of a 48-year-old male from an area endemic for gallbladder cancer (north India). He presented with a short history of abdominal pain and was found to have asymmetric thickening of the gallbladder wall with a soft-tissue mass invading the adjacent liver. In addition, the bile duct was dilated throughout its extent. A clinical and radiological diagnosis of gallbladder cancer with choledochal cyst was made, and the patient underwent radical cholecystectomy with bile duct excision. Histopathology surprisingly demonstrated IgG4-related disease with no evidence of malignancy. Notably, serum levels of immunoglobulins were found to be normal. Preoperative diagnosis was challenging due to the absence of other manifestations. IgG4-related disease is a possible diagnostic pitfall and should be included as a possible differential diagnosis for gallbladder masses.

Case Report

A 48-year-old male, who was an ex-smoker and occasional alcohol user, with no known medical or surgical comorbidities, presented to our hospital with complaints of upper abdominal pain for the last 1 month. The pain was localized to the right hypochondrium and epigastrium, occasionally radiating to the back. It was aggravated on food intake and relieved by oral analgesics. There was no history of vomiting, jaundice, or upper/lower gastrointestinal bleed. There was no history of anorexia or unintentional weight loss. Physical examination was unremarkable. Laboratory investigations were notable for elevated serum carbohydrate antigen 19-9 (CA 19-9) levels – 87.8 U/mL (0–27 U/mL). The remaining investigations were unremarkable—hemoglobin 13.1 g/dL (12–14 g/dL), white blood cell count 6400/mm³ (4000–11 000/mm³), platelet count 238 000/mm³ (150 000–450 000/mm³), total bilirubin 1.07 mg/dL (0.3–1.2 mg/dL), direct bilirubin 0.1 mg/dL (0–0.4 mg/dL), aspartate

aminotransferase 30.4 IU/L (2–40 IU/L), alanine aminotransferase 36.9 IU/L (2–41 IU/L), alkaline phosphatase 121 IU/L (42–128 IU/L), amylase 74.1 U/L (28–100 U/L), total protein 8.32 g/dL (6.4–8.3 g/dL), and albumin 4.6 g/dL (3.4–4.8 g/dL).

The patient underwent an ultrasound of the abdomen, which showed multiple gallbladder calculi with an asymmetrically thickened gallbladder wall (4 mm thickness). There was dilatation of the common bile duct, with mild dilatation of the central intrahepatic biliary radicles. A contrast-enhanced computed tomography (CT) scan was performed, which demonstrated moderately distended gallbladder with multiple calculi within thickened walls. A focal soft-tissue mass measuring 2.6 × 1.5 cm was noted near the fundus, which was infiltrating the adjacent liver parenchyma (segment IV) (Fig. 1a). The pancreas was normal. The mass showed moderate heterogeneous postcontrast enhancement (35 Hounsfield Units) with a central nonenhancing hypodense area (arrow) (Fig. 1b). In view of the ultrasound findings, the patient underwent magnetic resonance cholangiopancreatography, which showed fusiform dilation of the common bile duct (15 mm) with smooth distal tapering at the lower end (Fig. 1c). Intrahepatic biliary radicles were reported to be normal. The remaining findings were similar to findings on CT scan.

In view of the short history of symptoms, elevated tumor markers, and suggestive imaging findings, a clinical diagnosis of carcinoma gallbladder secondary to Type I choledochal cyst was made. The patient was taken for surgery. Intraoperatively, the common bile duct was dilated until its lower end (2 cm diameter). The gallbladder was thickened and packed with stones. There was a hard mass palpable in the fundus, with infiltration into the liver parenchyma. There were multiple enlarged lymph nodes in periportal, portacaval, and posterosuperior pancreatoduodenal locations. Extended cholecystectomy (with formal segment IVb/V resection) with lymphadenectomy along with cyst excision and Roux-en-Y hepaticojejunostomy was performed.

Gross pathological examination demonstrated multiple stones within the gallbladder. The gallbladder walls were thickened (Fig. 1d). There was a 3 × 2 × 2 cm tumor mass from the fundus of the gallbladder, which was densely adherent to liver parenchyma. On microscopic examination, the gallbladder wall was thickened with intact epithelium lining. The lamina propria, muscularis layer, and adventitial tissue showed inflammatory changes, along with marked fibrosis with lymphoplasmacytic infiltrate mixed with eosinophils (Fig. 1e). Obliterative changes in vessels were also noted. There was no evidence of invasive malignancy. On immunohistochemical staining, an increased number of IgG4-positive plasma cells was seen (more than 30/high-power field) (Fig. 1f). Similar histopathological findings were noted in the wall of the common bile duct. Overall, the findings were suggestive of inflammatory pathology, that is, IgG4-related disease.

After the histopathology was reported, the serum IgG and IgG4 levels were measured. Both these levels were within normal limits (serum IgG4 – 0.63 g/L; range, 0.3–2 g/L and serum IgG – 14.7 g/L; range, 7–16 g/L). The postoperative course was uneventful, and the patient was discharged home 5 days after the surgery. He continues to be symptom-free on regular follow-up.

Discussion

IgG4-related sclerosing disease was first reported by Kamisawa *et al.* in 2003.⁵ Since then, IgG4 disease has been reported to

affect diverse organ systems, such as the salivary gland, lacrimal gland, thyroid, lungs, kidneys, prostate, skin, retroperitoneum, aorta, central nervous system, bile duct, liver, and gastrointestinal tract.¹ Diagnostic criteria for IgG4 disease were given by Deshpande *et al.*⁶ in 2012 and consist of three classical histological features, including dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative venulitis. Immunohistochemical findings include Infiltration of IgG4+ plasma cells with a ratio of IgG4+ to IgG+ cells >40% and >10 IgG4+ plasma cells per high-power field.

IgG4 disease of the hepatopancreatobiliary system can present in myriad ways. The majority of cases of IgG4-related disease involve the pancreas, causing autoimmune pancreatitis (AIP). IgG4 disease involving the biliary tree can present as sclerosing cholangitis, with strictures and upstream dilatation similar to cholangiocarcinoma. Involvement of the gallbladder has been documented in only around 5.5% of patients.⁷ It is often difficult to differentiate the two conditions, which is of importance because the lesions of IgG4 disease tend to respond dramatically to steroids as opposed to malignancy, which would need surgical intervention.⁸

The Indian subcontinent, especially north India, has one of the highest incidences of gallbladder cancer throughout the world. So, clinical presentation with gallbladder mass is not uncommon. In our patient, the clinical suspicion of gallbladder cancer was strong. In a resectable case of gallbladder cancer, preoperative tissue diagnosis is not mandatory. Rather, it is discouraged in order to minimize the risk of needle-tract seeding. Hence, biopsy or fine-needle aspiration cytology was not performed in our patient. We also did not measure presurgery serum IgG and IgG4 levels in our patient as there was no suspicion of this entity preoperatively. However, these levels were obtained later and were found to be normal. Notably, IgG4-related disease may not always manifest with raised serum levels of immunoglobulin. The sensitivity and specificity of serum IgG4 for IgG4-related sclerosing disease is reported to be 50 and 60%, respectively.⁹

In our patient, in addition to gallbladder mass, the common bile duct was grossly dilated. However, alkaline phosphatase was normal, and there was no jaundice or evidence of cholestasis. Hence, our initial working diagnosis was of carcinoma gallbladder secondary to choledochal cyst. Choledochal cyst is a known premalignant condition that causes gallbladder cancer, and the gallbladder is the second most common site of malignancy (after cholangiocarcinoma) in a choledochal cyst. However, on histopathology, the bile duct was also found to be involved in the IgG4 inflammatory process. The absence of jaundice, normal serum bilirubin and alkaline phosphatase levels, and the absence of pancreatic involvement make stricture of distal bile duct unlikely. In the index case, the dilatation of the bile duct in the absence of cholestasis remains unexplained.

Follow-up of patients is essential as they can go on to have recurrent disease and/or involvement of new organ systems.¹⁰ Serum levels of IgG4 form a simple test for monitoring disease activity. However, approximately 30% of patients with IgG4-related disease have normal IgG4 serum levels. Imaging can also help in detecting recurrent disease or the involvement of new organs on follow-up; 18-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/CT, plain CT, and magnetic resonance imaging (MRI) can also be used to identify organ enlargement for monitoring disease progression and identifying

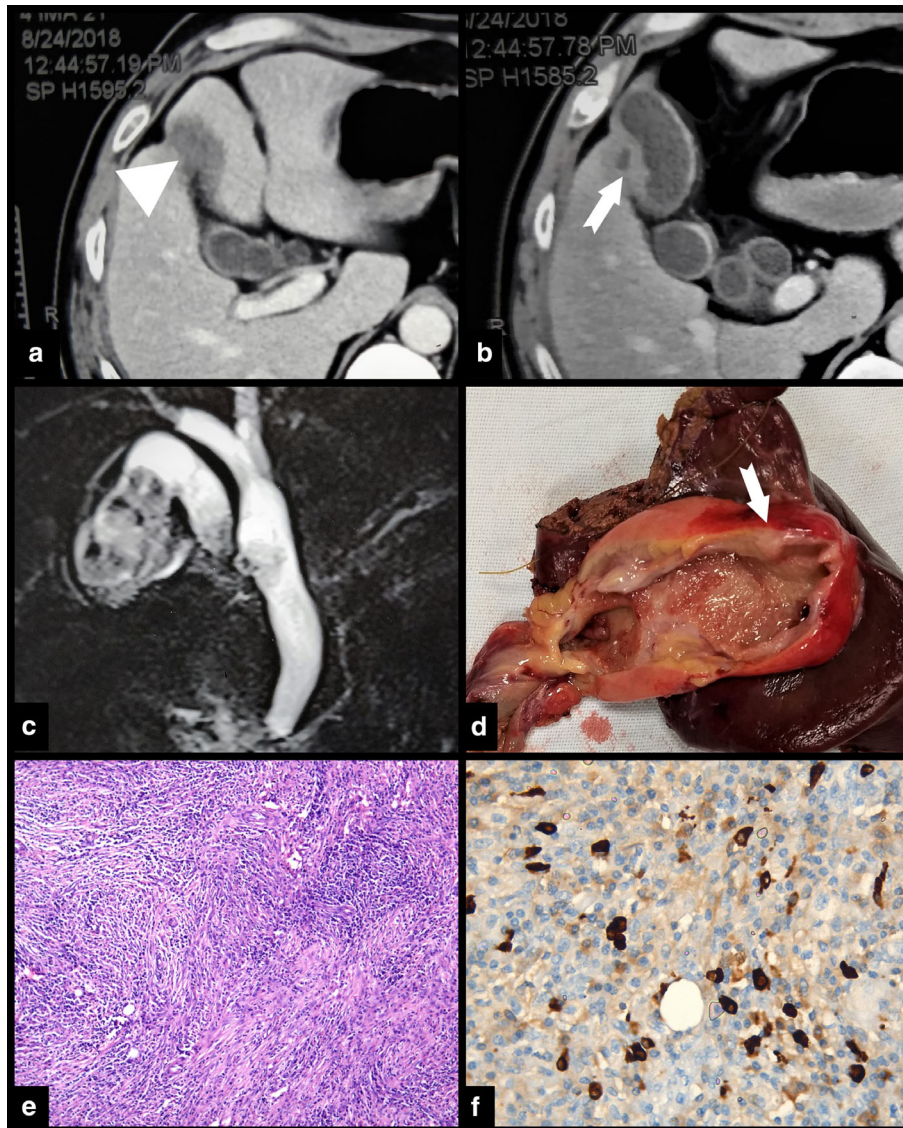


Figure 1 (a) CECT scan of the abdomen with axial sections showing eccentric gallbladder wall thickening with low-density soft-tissue lesion (arrow) infiltrating the liver parenchyma (arrowhead). (b) Contrast-enhanced computed tomography scan of the abdomen with axial sections showing eccentric gallbladder wall thickening with a soft-tissue mass lesion with central hypodensity (arrow). (c) Magnetic resonance cholangiopancreatogram showing a diffusely dilated common bile duct with distal tapering. The main pancreatic duct appears normal. (d) Gross specimen of extended cholecystectomy showing the gallbladder (cut open) with a thickened wall (arrow). A hard mass was present in the fundus; however, the overlying mucosa was normal. (e) Microscopic view of the gallbladder wall showing storiform, transmural fibrosis, and intense mononuclear inflammatory infiltrate (HE stain, $\times 100$). (f) Microscopic view of the gallbladder wall showing abundant immunoglobulin G4+ (IgG4+) plasma cells (immunohistochemistry of IgG4, $\times 400$).

new sites of involvement.¹⁰ Newer modalities for the detection of disease activity include IgG4/IgG RNA ratio and quantitation of circulating plasmablasts using flow cytometry. In our case, we plan to follow up with the patient using serum IgG4 levels and PET/CT annually.

To summarize, IgG4-related cholecystitis can rarely present as a mass-forming lesion, which may mimic gallbladder cancer clinically and radiologically. Hence, IgG4-related cholecystitis should be included in the differential diagnosis of a thick-walled gallbladder. Serum IgG and IgG4 levels,

endoscopic ultrasound with FNAC or biopsy, and CT-guided biopsy are all useful modalities of confirming the diagnosis. However, if there are no other concurrent sites of IgG4-related disease (AIP) and malignancy cannot be excluded, it is necessary to consider surgical resection for such patients. Follow-up of these patients is crucial to ensure disease-free status in the future.

Written informed consent by the patient was obtained for publication of the case details. A copy of the consent form is available for viewing by the editor-in-chief of the journal.

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