CASE REPORT

Immunoglobulin (IgG4) Sclerosing Cholecystitis—Camouflaging Gall Bladder Cancer—a Case Report and Review of Literature

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Abstract
IgG4-related disease is a rare systemic disorder having an underlying autoimmune cause. These disorders mainly affects pancreatico biliary tree, i.e., pancreas, gall bladder, and biliary tree (extrahepatic as well intrahepatic), but can also affect other part of the body. Majority of disorders involving biliary tree are associated with autoimmune pancreatitis component. These disorders are difficult to diagnose clinically as they can mimic inflammatory as well malignancy and poses a real diagnostic challenge to manage and treat. Sixty-four-year-old female known diabetic evaluated for pain in right hypochondrium. Gall bladder cancer was suspected clinically as well on radiological basis. Patient underwent extended cholecystectomy as it was a resectable disease. Final histopathology revealed immunoglobulin G4 (IgG4)-related cholecystitis which was confirmed after immunohistochemistry for CD 138 and IgG4. This disease could be managed conservatively by giving oral steroids, if it has been picked up preoperatively and major surgical intervention have been avoided. No defined blood test or tumor markers are currently available to diagnose this entity except serum immunoglobulin G4 which is costly and not feasible to get done in all patients especially in developing nations like India. IgG4 cholecystitis is an immune-mediated disease whose pathophysiology is still not completely understood. Every clinician should keep possibility of IgG4 cholecystitis in mind whenever any patient with abnormal gall bladder thickening or gall bladder mass is encountered in their clinical practice, as both these entities have completely different options of treatment. We should not rely solely upon clinical and radiological picture.

Keywords Immunoglobulin G4 · Sclerosing cholecystitis · Gall bladder mass · Gall bladder cancer

Background
IgG4-related disease is a rare systemic disorder which can involve any organ of our body. To club these different organs’ involvement by this rare similar autoimmune phenomenon, Kamisawa et al. [1] proposed a new common term of systemic IgG4-related autoimmune diseases in 2003 as IgG4-related disorder (IgG4-RD).

These disorders are difficult to diagnose clinically as well radiologically due to the overlapping of clinical and radiological imaging features. These disorders mimic inflammatory as well malignancy and poses a real difficulty in diagnosis, treatment, and predicting the natural course of disease.

These disorders are immune mediated and mainly affects pancreatico biliary tree, i.e., pancreas, gall bladder, and biliary tree (extrahepatic as well intrahepatic). Association of gall bladder sclerosing cholecystitis along with concomitant choledochal cyst was shown by Aditya et al. in his case report [2].

Fifty-eight to 88% of patients show multiple organ involvement, with the remainder having isolated lesions, by radiological evaluation and clinical examination, respectively [3].

Apart from these organs, it can involve head and neck region, retroperitoneal organs, genito-urinary organs, salivary glands, and thorax [4]. But the incidence of involvement of all these organs/sites is less as compared to pancreas.
Autoimmune pancreatitis is a well-studied entity, and along with it, involvement of gall bladder and biliary tree, i.e., cholecystitis and cholangitis, respectively, is common. Approximately 20–30% of gall bladder involvement is in autoimmune pancreatitis [5, 6].

All these immune-related entities are covered under one umbrella and termed as IgG4-related diseases (IgG-RD) [7]. Isolated gall bladder involvement and its clinical manifestations are rare and still evolving entity, and literature also has paucity of data related to it. It is imperative to differentiate this autoimmune entity of gall bladder IgG4 sclerosing cholecystitis from other causes especially malignancy of gall bladder in order to avoid overtreatment as both of these have different treatment and completely different prognosis.

Diagnosis of this entity is really a head-scratching task as it has a totally similar presentation and most of the time it is misdiagnosed and wrongly treated.

Isolated IgG4 cholecystitis mimicking as cancer is not much reported in literature, and here, we are reporting a case report of IgG4 cholecystitis masquerading as gall bladder mass/cancer. Most of the case reports of IgG4 cholecystitis are associated with autoimmune pancreatitis (AIP) and reporting of isolated involvement of IgG4 cholecystitis are very few. Our case report will help in suspecting IgG4 cholecystitis whenever we encounter gall bladder mass on imaging and also adds up to the existing literature of isolated involvement of gall bladder in IgG4 cholecystitis.

Case Presentation

Sixty-four-year-old lady, postmenopausal, nonsmoker, and nonalcoholic residing in rural area of the state with known history of diabetes mellitus with poor glycemic control as patient, was not taking oral hypoglycemics in a regular manner. She was evaluated for pain in the right upper abdomen along with dyspeptic symptoms lasting for 1 year. Patient was referred to us in a tertiary care hospital. On examination, her vitals were stable and performance status was ¼ as per ECOG (Eastern Cooperative Oncology Group), her GPE (general physical examination) was within normal limits, and her abdomen was tender at the right hypochondriac and epigastric region.

Laboratory investigations: total leukocyte count 9800/mm³, total bilirubin 1.07 mg/dL, aspartate aminotransferase 21 U/L, alanine aminotransferase 27 U/L, alkaline phosphatase 169 U/L, albumin 4.2 g/dL and PT-11.8, INR 0.64. HbA1c was 7.3, carbohydrate antigen 19–9 (CA 19–9) levels were 70 U/mL, and serum carcino-embryonic antigen (CEA) level was within normal range.

Ultrasound abdomen showed focal gall bladder thickening at fundal approximately 5–6 mm along with gall bladder stones.

Patient was planned for triple-phase CECT scan abdomen which showed (Fig. 1) contracted gall bladder with irregular asymmetrical thickening of 6 mm along with calcification in fundal region of gall bladder. Fat planes with adjacent liver were ill defined. There were subcentimetric lymph nodes at inter-aortocaval region, in inter-aortocaval region. Pancreas and bile duct and rest of the organ were normal.

First possibility of gall bladder cancer was kept under the background of porcelain gall bladder and irregular thickness of 6 mm. Due to suspicion of gall bladder cancer, patient underwent ultrasound-guided fine needle aspiration cytology (FNAC) from gall bladder which was descriptive. In view of abnormal thickening and porcelain gall bladder, patient planned for surgery.

Patient underwent extended cholecystectomy after 3 weeks of acute attack of pain, and good glycemic control was obtained. On opening the abdomen, there was no ascites and metastasis. Gall bladder was thickened at fundal region along with multiple stones in lumen. Centimetric lymph nodes were found along hepatoduodenal ligament and inter-aortocaval region.

Patient had uneventful postoperative recovery and discharged on postoperative day 7.

Final histopathology report showed dense fibrosis (Fig. 2) arranged in a storiform pattern along with obliterator phlebitis and dense transmural lymphoplasmacytic infiltrate along with eosinophil and neutrophil (Fig. 3) [7]. Lymph nodes were harvested, and all showed sinus histocytic changes only. All these features were suggestive of IgG4 sclerosing cholecystitis. For confirmation, we performed immunohistochemistry (IHC) for IgG4 and CD138 which showed IgG4-positive 80 plasma cell, and CD138 was positive in plasma cells. IgG was inconclusive.

Fig. 1 Triple-phase computed tomogram scan of abdomen showing contracted gall bladder with irregular asymmetrical thickening of 6 mm along with calcification in fundal region of gall bladder. Fat planes with adjacent liver were ill defined.
Serum IgG4 was 0.972 (reference range 0.03–2.01).

Discussion

IgG4 cholecystitis is a total masquerader having a similar constellation of signs and symptoms as of gall bladder cancer. Etiopathogenesis of this entity is still not clear, but mostly, it is stated that this is manifestation of autoimmune process driven by lymphoplasmacytic interaction in the organ involved. Depending upon the organ or system involved, it really poses difficulty in making final diagnosis based on clinical and radiological features. To circumvent this dilemma, we need a complete and in-depth understanding of the clinical presentations of IgG4-related diseases. This will eventually lead to decrease unnecessary invasive forms of surgical interventions and ultimately benefits the patient and helps in reducing the futile exercise. It is prudent to put this rare entity in the list of differential diagnosis along with gall bladder cancer whenever any abnormal or suspicious features are there on clinically/radiologically [8].

Yamamoto et al. reported that 50% of IgG4-RD patients presented with new organ involvements at relapse. However, the specific organ in which IgG4-RD tends to recur remains unclear [9]. This entity is more common in older people having more predilections towards male [10]. Patients with IgG4 cholecystitis on sonography shows hypoechoic, diffuse, circumferential thickening of the gall bladder wall. As in our case, sonography showed gall stones along with asymmetrical thickening of 6 mm in gall bladder.

On CECT scan, it is mainly the delayed enhancement in IgG4-related cholecystitis which helps in differentiating it from gall bladder cancer. In our case, there was asymmetrical thickening of 6 mm along with porcelain bladder.

On MRI, it showed low-signal smooth diffuse gallbladder wall thickening on T2-weighted MR images, and delayed enhancement postcontrast [5, 11, 12]. This thickening or enlargement of organ on imaging is generally due to infiltration of organs by lymphocytes and plasma cells along with coexisting fibrosis. As per Deshpande et al. [13], the diagnostic criteria for diagnosing IgG4-related diseases are as mentioned in Table 1.

In order to diagnose IgG4 cholecystitis, there should be at least 2 out of 3 major criteria as mentioned above and also presence of more than 50% plasma cell per high power field. In our case, all the three major criteria were present. Among minimal criteria as mentioned above, IgG4 positive in 80 plasma cells, but serum IgG was within normal limit.

But Shin et al. reported only 15% plasma cell per high power field in their case study in the background of IgG4 cholecystitis [14].

Role of serum IgG4 is also advocated by many studies, but routinely, it is not practiced as it is not elevated in all cases of IgG4-related disease and also its accuracy only fits between 40 and 50%, and moreover, in developing countries like India, it is difficult to get done due to financial and cost constraints. To differentiate IgG4 or other benign conditions from ca gall bladder, role of carbohydrate antigen (CA 19–9), carcino-embryonic antigen (CEA), and carbohydrate antigen (CA-125) are more established [15]. Increased ratio > 40% of IgG4/IgG also favors IgG4-related disease and is considered as a salient feature to diagnose IgG4-related disease.

Treatment decision is of paramount importance in suspecting IgG4-related cholecystitis. The main diagnostic

Fig. 2 Histology and immunohistochemical stain for IgG4 of the gall bladder showed dense fibrosis arranged in a storiform pattern along with obliterative phlebitis (H&E stain, 200×)

Fig. 3 Histology and immunohistochemical stain for IgG4 of the gall bladder showed dense transmural lymphoplasmacytic infiltrate along with eosinophil and neutrophil (H&E stain, 400×)
ambiguity is with malignancy of gall bladder, as the treatment options for both these diseases are completely different. IgG4 cholecystitis is mainly treated by steroids and showed a dramatic response; duration and relapse rate are not yet documented as no randomized controlled trial has not been performed yet. About 20 to 30% of IgG4-RD present with a relapse during the reduction of CS; however, how and where disease relapse occurs has not yet been established [16].

Role of immunomodulators also has been tried in Mayo Clinic [17]. Even if patient requires surgery after steroid treatment, the extent of surgery is definitely less as compared to surgery for gall bladder cancer.

Radical surgery in the form of extended cholecystectomy and regional lymphadenectomy is mainly done for gall bladder cancer. Therefore, a firm and confident diagnosis is required before embarking upon any modality of treatment. Any misdiagnosis will overtreat IgG4 cholecystitis at the cost of other post perative surgical complications which can be completely avoided if we have ruled out IgG4 cholecystitis in case suspected to have gall bladder cancer.

**Conclusion**

IgG4 cholecystitis is an immune-mediated disease whose pathophysiology is still not completely understood. Every clinician should keep possibility of IgG4 cholecystitis in mind whenever any patient with abnormal gall bladder thickening or gall bladder mass is encountered in their clinical practice, as both these entities have completely different options of treatment. We should not rely solely upon clinical and radiological picture.

Histopathological picture completes the diagnosis confirmation. Role of serum IgG4 is still controversial, and needs more data to establish its role. Our case report will surely add some useful information in literature as an isolated case of IgG4 sclerosing cholecystitis without pancreas involvement.

### Table 1

| S. no | Major histopathological features associated with IgG4-RD | Other histopathological features associated with IgG4-RD are: | Minimal criteria for IgG4-RD in a new organ/site |
|-------|--------------------------------------------------------|----------------------------------------------------------------|-----------------------------------------------|
| 1.    | Dense lymphoplasmacytic infiltrate                      | Phlebitis without obliteration of the lumen                     | Characteristic histopathological findings with an elevated IgG4 plasma cells and IgG4-to-IgG ratio |
| 2.    | Fibrosis, arranged at least focally in a storiform pattern | Increased numbers of eosinophils                                 | High serum IgG4 concentrations                |
| 3.    | Obliterative phlebitis                                 |                                                                 | Effective response to glucocorticoid therapy    |
| 4.    |                                                       | Other organ involvement that is consistent with IgG4-RD        |                                               |

**Abbreviations**  
IgG4: Immunoglobulin G4; IgG4-RD: Immunoglobulin G4-related disorder

**Author Contribution**  
RS—drafted the case manuscript and was the main operating surgeon. PM—part of surgical team and helped in drafting the manuscript. RP, VR, JS, CK—all were part of surgical team and helped in citing references for the case report. JG—helped in framing discussion part. KM—reported the final histopathology report. All authors read and approved the final manuscript.

**Data Availability**  
Not applicable.

**Declarations**

**Ethics Approval and Consent to Participate**  
Not applicable for this section.

**Consent for Publication**  
Consent for publication has been obtained from the patient in a proper informed consent form.

**Conflict of Interest**  
The authors declare no competing interests.

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