

IgG4-Related Sclerosing Cholecystitis Mimicking Locally Advanced Gallbladder Carcinoma: A Case Report

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Abstract

Background: Immunoglobulin G4-related disease (IgG4-RD) is a systemic fibroinflammatory disorder that can involve multiple organs. Gallbladder involvement is uncommon and may closely resemble gallbladder carcinoma, particularly when it produces focal wall thickening, a mass-like lesion, or apparent invasion of adjacent organs.

Case presentation: A 60-year-old man presented with malaise, anorexia, weight loss, and intermittent abdominal pain for three months. Contrast-enhanced computed tomography (CECT), ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET), and magnetic resonance cholangiopancreatography (MRCP) demonstrated an irregular infiltrative lesion involving the gallbladder wall, with suspected extension into the adjacent liver and transverse colon. A diagnosis of locally advanced gallbladder malignancy was therefore considered. The patient underwent radical cholecystectomy with wedge resection of the adjacent liver, right hemicolectomy, and regional lymph node dissection. Gross examination revealed an irregular, firm, grey-white lesion involving full-thickness of the gallbladder wall with focal extension into the adjacent liver and adherent transverse colon. Histological examination demonstrated dense transmural lymphoplasmacytic inflammation, prominent fibrosis with focal indistinct storiform architecture. The inflammatory and fibrotic process extended into the adjacent hepatic parenchyma and colonic muscularis propria. No malignant epithelial proliferation was identified. Immunohistochemistry demonstrated approximately 25 IgG4-positive plasma cells per high-power field.

Conclusion: The combination of characteristic lymphoplasmacytic inflammation, storiform-pattern fibrosis, tissue extension, and increased IgG4-positive plasma cells supported a diagnosis of probable IgG4-related sclerosing cholecystitis. This case emphasizes that IgG4-related cholecystitis should be considered in the differential diagnosis of mass-forming or infiltrative gallbladder lesions, particularly when imaging suggests locally advanced malignancy. Recognition of this entity is clinically important because IgG4-RD may respond well to corticosteroid therapy and, in appropriately selected patients, early recognition may prevent unnecessarily extensive surgery.

Keywords: IgG4-related disease; IgG4-related cholecystitis; sclerosing cholecystitis; gallbladder carcinoma; storiform fibrosis; lymphoplasmacytic inflammation; IgG4-positive plasma cells.

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a chronic systemic fibroinflammatory condition characterized by tumefactive lesions, dense lymphoplasmacytic inflammation, fibrosis, and variable accumulation of IgG4-positive plasma cells. The disease may involve virtually any organ, with the pancreas, biliary tract, salivary glands, lacrimal glands, kidneys, lungs, and retroperitoneum among the commonly affected sites. The characteristic pathological findings include a dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis, although the relative prominence of these features varies according to the involved organ. [1,2]

Hepatobiliary involvement is most commonly recognized in the form of autoimmune pancreatitis and IgG4-related sclerosing cholangitis. In contrast, isolated involvement of the gallbladder is uncommon. IgG4-related cholecystitis may manifest as diffuse gallbladder wall thickening or, less frequently, as localized thickening that produces a mass-like lesion. The latter presentation can closely mimic gallbladder carcinoma on radiological examination. [3]

The differentiation between IgG4-related cholecystitis and malignancy can be particularly difficult when the inflammatory process appears to extend beyond the gallbladder into the liver or adjacent bowel. CECT, MRI, and MRCP are useful for defining the extent of gallbladder and biliary tract abnormalities, while FDG-PET/CT may demonstrate increased metabolic activity and identify additional sites of disease. However, neither anatomical imaging nor FDG uptake is sufficiently specific to reliably distinguish IgG4-related inflammation from malignancy. [3,4]

Histopathological examination therefore remains central to diagnosis. The presence of dense lymphoplasmacytic inflammation and

storiform fibrosis, together with an increased population of IgG4-positive plasma cells and appropriate clinicoradiological correlation, strongly supports IgG4-RD. The 2020 revised comprehensive diagnostic criteria incorporate clinical/radiological findings, serum IgG4 concentration, and characteristic pathological findings. [5]

We report an unusual case of IgG4-related sclerosing cholecystitis presenting as an infiltrative gallbladder lesion with apparent extension into the liver and transverse colon, resulting in a preoperative radiological diagnosis of locally advanced gallbladder carcinoma.

CASE REPORT

A 60-year-old man presented with a three-month history of malaise, reduced appetite, weight loss, and intermittent abdominal pain. In view of the constitutional symptoms and abdominal complaints, imaging was performed.

CECT demonstrated irregular and infiltrative thickening of the gallbladder wall with suspected involvement of the adjacent hepatic parenchyma and transverse colon. FDG-PET showed metabolic activity corresponding to the gallbladder lesion, while MRCP was performed to evaluate the biliary tract and the extent of the lesion. Taken together, the imaging findings raised strong suspicion of a locally advanced gallbladder malignancy with involvement of adjacent structures.

Considering the radiological possibility of locally advanced gallbladder carcinoma, the patient underwent radical cholecystectomy with wedge resection of the adjacent liver, right hemicolectomy, and regional lymph node dissection.

Gross examination

The resected gallbladder measured 8 × 6 × 2 cm. There was an irregular, firm, grey-white area involving entire wall thickening measuring approximately 4.3 × 3 cm. The lesion showed focal extension for approximately 0.5 cm into the adjacent hepatic tissue and the wall of the adherent transverse colon. The gallbladder was densely adherent to both the liver and colon. A globular grey-black calculus measuring 1.8 cm was identified within the gallbladder lumen.

Histopathological examination

Microscopic examination demonstrated mucosal denudation with dense transmural lymphoplasmacytic inflammation involving the entire gallbladder wall. The inflammatory infiltrate was accompanied by broad areas of fibrosis, with focal areas showing an indistinct storiform pattern.

The inflammatory and fibrotic process extended beyond the gallbladder into the adjacent hepatic parenchyma, resulting in focal distortion of the hepatic architecture and showed reactive ductular proliferation. Sections from the adherent transverse colon demonstrated lymphoplasmacytic inflammation extending into the muscularis propria, while the colonic mucosa remained intact. Importantly, no malignant epithelial proliferation was identified in the examined sections. There was no histological evidence of gallbladder adenocarcinoma.

Immunohistochemistry

Immunohistochemical staining for IgG4 demonstrated approximately 25 IgG4-positive plasma cells per high-power field, with satisfactory internal control staining. IgG immunostaining was not performed; therefore, the IgG4/IgG-positive plasma cell ratio could not be calculated.

In the appropriate clinicopathological setting, the combination of dense lymphoplasmacytic inflammation, storiform-pattern fibrosis, extension of the inflammatory process into adjacent tissues, absence of malignancy, and increased IgG4-positive plasma cells supported a diagnosis of probable IgG4-related sclerosing cholecystitis with inflammatory extension into the adjacent liver and transverse colon.



Figure 1A: Contrast-enhanced computed tomography (CECT) of the abdomen demonstrating an infiltrative, irregular gallbladder lesion with marked gallbladder wall involvement and extension into the adjacent hepatic region, producing a radiological appearance suspicious for locally advanced gallbladder malignancy.



Figure 1B: Gross specimen showing an irregular, firm, grey-white infiltrative lesion involving the gallbladder and extending into the adjacent tissues. The lesion demonstrates a poorly circumscribed appearance with dense fibrotic involvement, closely mimicking an advanced malignant process.

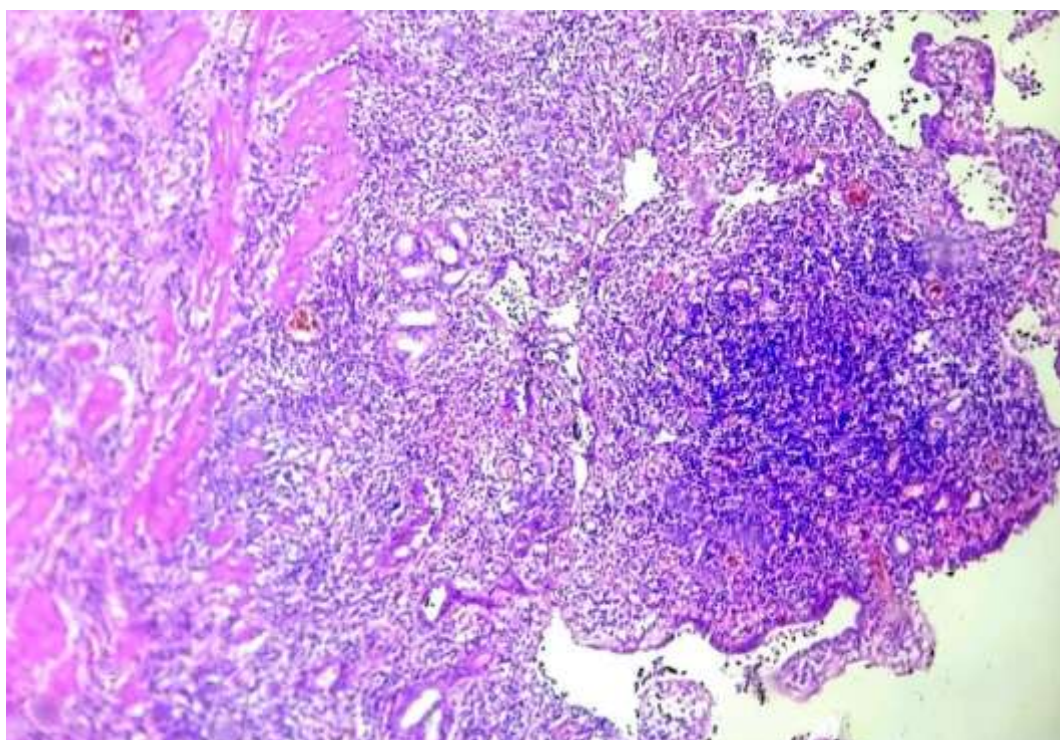


Figure 2A: Histopathological examination demonstrating extensive transmural involvement of the gallbladder wall by a dense fibroinflammatory lesion. The inflammatory infiltrate extends through the gallbladder wall with prominent lymphoplasmacytic inflammation and associated fibrosis.

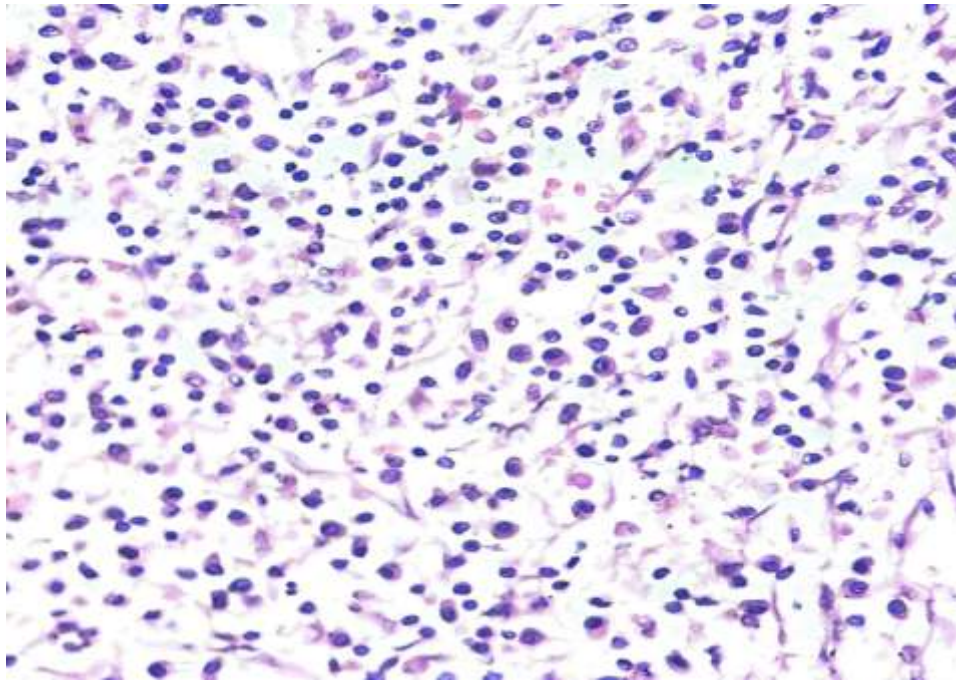


Figure 2B: High-power view demonstrating a dense lymphoplasmacytic inflammatory infiltrate, composed predominantly of lymphocytes and plasma cells within a fibrotic background. The infiltrate lacks significant cytological atypia or malignant epithelial proliferation, supporting a fibroinflammatory rather than malignant process.

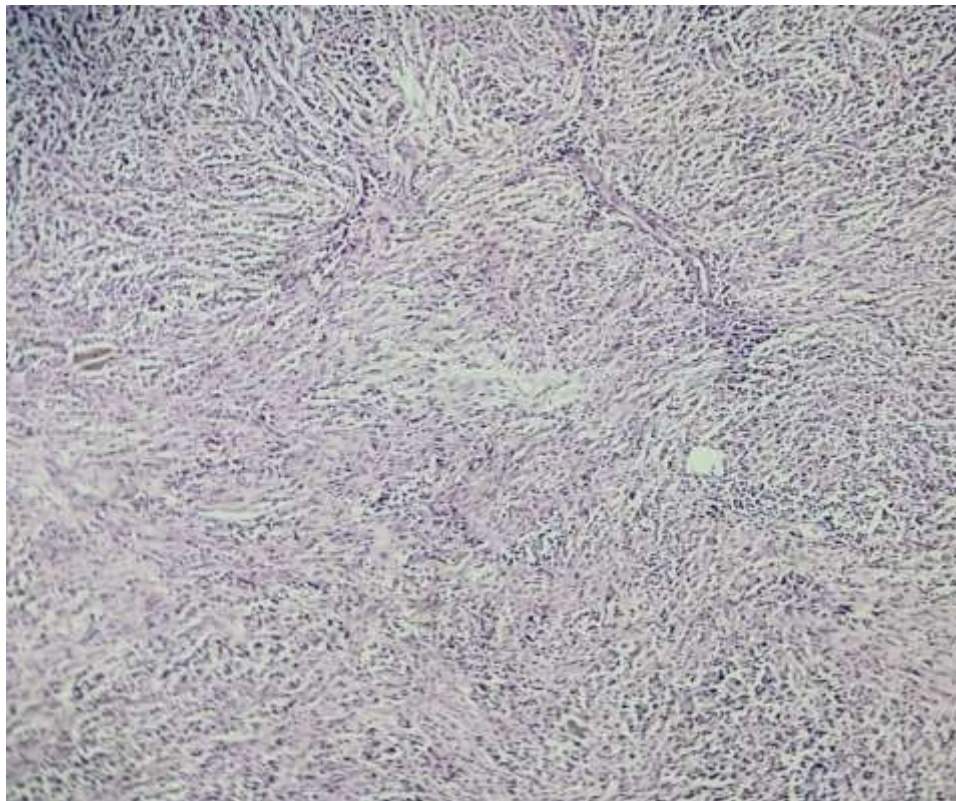


Figure 3A: Histopathological section demonstrating focal storiform-pattern fibrosis, characterized by irregular, whorled and radiating arrangements of collagen fibres surrounding the inflammatory infiltrate. This represents one of the characteristic morphological features associated with IgG4-related disease.

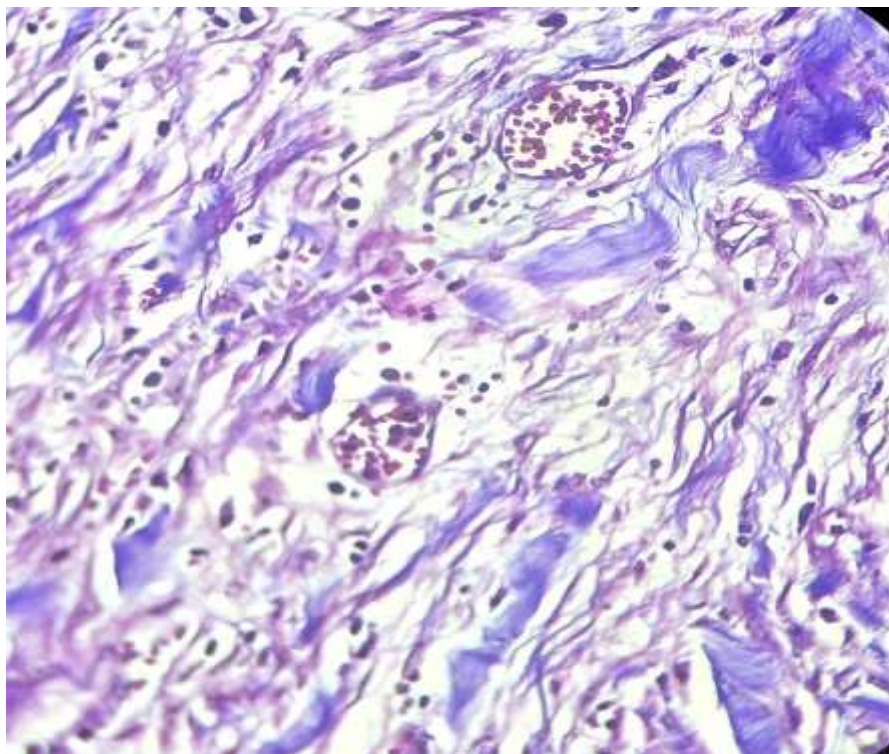


Figure 3B: Trichrome-stained section highlighting extensive fibrosis within the lesion, demonstrating the prominent collagenous component of the fibroinflammatory process. The extensive fibrosis corresponds to the dense fibrosing component identified on routine histopathological examination.

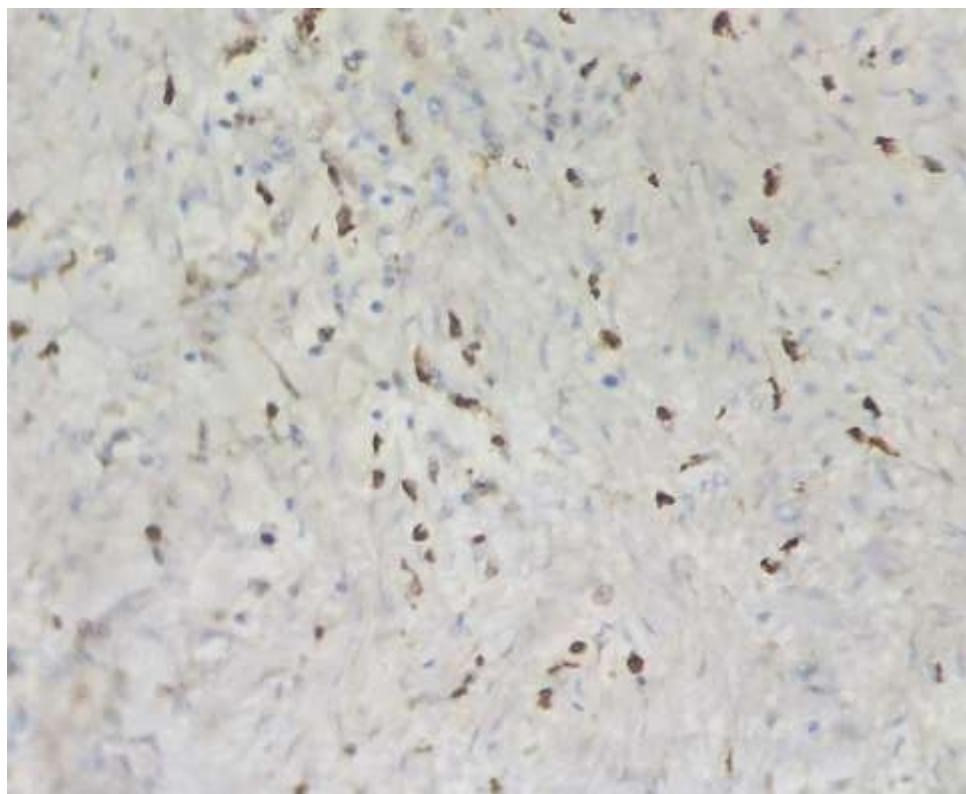


Figure 4: Immunohistochemical staining demonstrating increased IgG4-positive plasma cells within the fibroinflammatory lesion. Approximately 25 IgG4-positive plasma cells per high-power field were identified. The finding, in conjunction with dense lymphoplasmacytic inflammation and storiform-pattern fibrosis, provides supportive evidence for IgG4-related sclerosing cholecystitis.

DISCUSSION

Immunoglobulin G4-related disease (IgG4-RD) is a systemic fibroinflammatory disorder characterized by tumefactive lesions, dense lymphoplasmacytic inflammation, fibrosis, and variable accumulation of IgG4-positive plasma cells. It can involve multiple organs and may closely simulate malignant disease because of its mass-forming and infiltrative nature. The disease may affect the pancreas, biliary tract, kidneys, lungs, salivary glands, lacrimal glands, retroperitoneum, and other organs. Histopathologically, the characteristic features include dense lymphoplasmacytic inflammation, storiform fibrosis, and obliterative phlebitis, although the relative prominence of these features varies according to the involved organ. [1,2]

The present case demonstrates an unusual hepatobiliary manifestation of IgG4-RD in which the gallbladder lesion closely simulated locally advanced gallbladder carcinoma. Histologically, the lesion showed dense transmural lymphoplasmacytic inflammation, broad areas of fibrosis with focal storiform architecture, extension into the adjacent hepatic parenchyma and colonic muscularis propria, and approximately 25 IgG4-positive plasma cells per high-power field. Importantly, no malignant epithelial proliferation was identified. These findings are compatible with the characteristic fibroinflammatory pattern described in IgG4-RD. [2]

Gallbladder involvement is an uncommon manifestation of IgG4-RD. Isolated gallbladder disease is particularly rare, as hepatobiliary IgG4-RD more commonly occurs in association with autoimmune pancreatitis and/or IgG4-related sclerosing cholangitis. Harada et al. reported an isolated case of IgG4-related cholecystitis presenting with localized gallbladder wall thickening that mimicked gallbladder carcinoma. [4] Similarly, the present patient had an infiltrative gallbladder lesion that was interpreted radiologically as malignant, demonstrating that IgG4-related cholecystitis can closely reproduce the morphological appearance of gallbladder neoplasia.

The locally invasive appearance in the present case further increased the diagnostic difficulty. Imaging demonstrated apparent extension of the gallbladder lesion into the adjacent liver and transverse colon, resulting in a preoperative impression of locally advanced gallbladder carcinoma. A similar diagnostic problem was reported by Marichez et al., who described isolated IgG4-related cholecystitis mimicking advanced gallbladder cancer. [6] In the present case, histological examination demonstrated inflammatory and fibrotic extension into both the hepatic parenchyma and muscularis propria of the adherent transverse colon, while the colonic mucosa remained intact. This distribution favoured secondary inflammatory extension rather than a primary colonic neoplasm.

Radiological differentiation between IgG4-related cholecystitis and gallbladder carcinoma can be challenging. Gallbladder wall thickening, enhancement, mass-like lesions, and apparent infiltration of surrounding structures may occur in both conditions. Harada et al. similarly demonstrated that localized gallbladder wall thickening may be radiologically indistinguishable from malignancy. [4] The European guideline on IgG4-related digestive disease emphasizes that diagnosis should integrate clinical findings, imaging characteristics, serological evaluation, histopathology, and assessment for involvement of other organs rather than relying on a single diagnostic modality. [5] Therefore, the infiltrative appearance observed in the present case should be interpreted together with the pathological findings rather than regarded as definitive evidence of carcinoma.

FDG-PET may further complicate the distinction because IgG4-related inflammatory lesions can demonstrate increased ^{18}F -FDG uptake. Consequently, increased metabolic activity within the gallbladder wall or adjacent tissues does not by itself establish malignancy. In the present case, FDG uptake contributed to the overall suspicion of an aggressive neoplastic process; however, histopathological examination subsequently demonstrated a fibroinflammatory lesion without malignant epithelial proliferation. PET/CT is therefore valuable for assessing disease distribution and identifying additional sites of involvement, but it cannot reliably distinguish active IgG4-related inflammation from malignancy. [5]

Histopathological examination remains central to the diagnosis. The international consensus statement on the pathology of IgG4-RD identifies dense lymphoplasmacytic inflammation, storiform fibrosis, and obliterative phlebitis as the major morphological features, while increased tissue IgG4-positive plasma cells provide important supportive evidence. [2] In the present case, dense lymphoplasmacytic inflammation and broad areas of fibrosis with focal storiform architecture were prominent. The inflammatory and fibrotic process extended into the adjacent liver and colonic muscularis propria, while no malignant epithelial proliferation was identified. Thus, the morphological findings, together with the increased number of IgG4-positive plasma cells, provided substantial pathological support for IgG4-related disease.

An important differential diagnosis in this setting is xanthogranulomatous cholecystitis (XGC), another benign fibroinflammatory condition that can closely mimic gallbladder carcinoma and extend into adjacent organs. Goyal et al. demonstrated morphological overlap between XGC and IgG4-related cholecystitis, including increased IgG4-positive plasma cells, storiform fibrosis, increased IgG4/IgG ratios, and extra-cholecystic extension. [7] Importantly, increased IgG4-positive plasma cells alone are insufficient to establish a diagnosis of IgG4-RD. In the present case, the combination of dense lymphoplasmacytic inflammation, focal storiform fibrosis, extra-gallbladder extension, and increased IgG4-positive plasma cells supported IgG4-related disease; however, the absence of an IgG4/IgG ratio and serum IgG4 concentration appropriately limited the diagnostic certainty.

The 2020 revised comprehensive diagnostic criteria for IgG4-RD incorporate three major domains: characteristic clinical and radiological findings, serum IgG4 concentration, and characteristic pathological findings. [3] The pathological component includes dense lymphoplasmacytic inflammation and fibrosis together with increased IgG4-positive plasma cells, with an IgG4/IgG-positive plasma cell ratio greater than 40% and more than 10 IgG4-positive cells per high-power field considered supportive of the diagnosis.

[3] In the present case, approximately 25 IgG4-positive plasma cells per high-power field were identified. However, IgG immunostaining was not performed and therefore the IgG4/IgG ratio could not be calculated. Furthermore, serum IgG4 levels were not available. Consequently, it would be inappropriate to state that the case fulfills all components of the comprehensive diagnostic criteria. The most appropriate interpretation is therefore probable IgG4-related sclerosing cholecystitis, based on the characteristic histological pattern, increased tissue IgG4-positive plasma cells, absence of malignancy, and compatible radiological findings.

The possibility of establishing the diagnosis before definitive surgery is clinically important. Although surgery may be necessary when malignancy cannot be excluded, selected patients may benefit from tissue diagnosis when a safe and representative biopsy can be obtained. Kawakami et al. reported a case in which IgG4-related cholecystitis was diagnosed using transpapillary gallbladder biopsy, with histological and immunohistochemical findings supporting the diagnosis. [8] This report illustrates the potential role of targeted tissue sampling in selected patients when establishing the diagnosis could substantially alter management.

Similarly, Wu et al. described an EUS-assisted preoperative diagnosis of IgG4-related cholecystitis in a patient whose lesion mimicked gallbladder carcinoma. [9] These reports, together with the present case, suggest that minimally invasive tissue diagnosis may have an important role when technically feasible and when IgG4-related disease is included in the differential diagnosis. Nevertheless, the safety, accessibility, and diagnostic yield of biopsy must be considered individually, particularly when malignancy remains a significant clinical possibility.

Recognition of IgG4-RD has important therapeutic implications. Unlike gallbladder carcinoma, which requires oncological management, IgG4-related digestive disease may respond to glucocorticoid therapy when active inflammatory disease is identified before irreversible fibrosis or organ damage develops. The European guideline recommends an integrated diagnostic approach and recognizes glucocorticoids as an important component of treatment for symptomatic IgG4-related digestive disease. [5] Therefore, establishing the diagnosis before extensive surgery may potentially prevent unnecessary oncological resections in appropriately selected patients.

The recent report by Calvo et al. further emphasizes the diagnostic challenge posed by IgG4-related sclerosing cholecystitis, describing it as an important mimic of gallbladder neoplasia. [10] The present case is consistent with these observations but demonstrates an additional challenging feature: apparent extension into both the liver and transverse colon, producing a particularly convincing radiological picture of locally advanced malignancy. The discrepancy between the aggressive radiological appearance and the benign fibroinflammatory histology highlights the importance of multidisciplinary correlation among radiologists, surgeons, and pathologists. From a surgical and pathological perspective, careful evaluation of tissues adjacent to the gallbladder is important. In the present specimen, the inflammatory process extended into hepatic parenchyma and the muscularis propria of the adherent transverse colon, while the colonic mucosa remained intact. Such findings may be mistaken for direct malignant invasion if the underlying histological pattern is not carefully assessed. The absence of malignant epithelial proliferation, together with the characteristic lymphoplasmacytic and fibrosing process, favoured inflammatory extension rather than carcinoma.

Overall, the present case emphasizes that an infiltrative gallbladder lesion with apparent invasion of adjacent organs should not automatically be interpreted as gallbladder carcinoma. The combination of dense lymphoplasmacytic inflammation, storiform-pattern fibrosis, increased IgG4-positive plasma cells, and absence of malignant epithelial proliferation should prompt consideration of IgG4-related disease. However, IgG4-positive plasma cell counts alone are insufficient for diagnosis, and interpretation should incorporate serum IgG4 levels, IgG4/IgG ratio, radiological findings, assessment for other organ involvement, and appropriate clinicopathological correlation. [2,3,7]

The major clinical lesson from this case is that IgG4-related sclerosing cholecystitis represents a potentially treatable mimic of gallbladder malignancy. Recognition of this entity may facilitate accurate diagnosis, allow consideration of preoperative tissue sampling in selected patients, and potentially prevent unnecessarily extensive surgical procedures when the diagnosis can be established with sufficient confidence. [8-10]

CONCLUSION

IgG4-related sclerosing cholecystitis is an uncommon manifestation of IgG4-RD that can closely simulate locally advanced gallbladder carcinoma. Infiltrative gallbladder wall thickening with apparent extension into the liver or bowel does not invariably indicate malignancy. Dense lymphoplasmacytic inflammation, storiform-pattern fibrosis, increased IgG4-positive plasma cells, and the absence of malignant epithelial proliferation should prompt consideration of IgG4-RD. A definitive interpretation requires integration of histopathological, immunohistochemical, serological, and radiological findings. Awareness of this rare entity may facilitate accurate diagnosis and, in appropriate cases, avoid unnecessarily extensive surgical treatment.

LEARNING POINTS

- IgG4-related sclerosing cholecystitis is a rare manifestation of IgG4-related disease and can closely mimic gallbladder carcinoma.
- Mass-forming or infiltrative gallbladder lesions with apparent extension into adjacent organs may represent fibroinflammatory disease rather than malignancy.

- Dense lymphoplasmacytic inflammation and storiform fibrosis, together with increased IgG4-positive plasma cells, are important pathological clues.
- Imaging modalities such as CECT, MRI, MRCP, and FDG-PET/CT help define the extent and distribution of disease but cannot reliably distinguish IgG4-related inflammation from malignancy.
- Clinicoradiological, serological, histopathological, and immunohistochemical correlation is essential for an accurate diagnosis and may prevent unnecessarily extensive surgery in selected patients.

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