Case Report

Isolated IgG4-related sclerosing cholangitis

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Isolated IgG4-related sclerosing cholangitis mimicking hilar cholangiocarcinoma: A case report and review

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Abstract

Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is a rare autoimmune disease characterized by fibroinflammatory lesions and bile duct strictures, often associated with type 1 autoimmune pancreatitis (AIP). Isolated IgG4-SC, occurring without AIP, is particularly uncommon and can clinically and radiologically mimic hilar cholangiocarcinoma, presenting with jaundice and bile duct strictures. Accurate differentiation between these conditions is essential, as surgical resection is the standard treatment for cholangiocarcinoma, whereas steroid therapy is the first-line treatment for IgG4-SC. This case report discusses a 55-year-old female patient who underwent left hepatectomy due to a hilar bile duct stricture initially suspected to be cholangiocarcinoma but was ultimately diagnosed as isolated IgG4-SC based on postoperative histopathological and immunohistochemical findings. The report highlights the diagnostic challenges of isolated IgG4-SC and emphasizes the importance of integrating histology, imaging, and serology to prevent unnecessary surgical interventions.

Keywords: Cholangiocarcinoma; cholangitis; IgG4.

Introduction

Immunoglobulin G4-associated sclerosing cholangitis (IgG4-SC) is a rare autoimmune disorder that manifests with fibroinflammatory lesions and strictures in the bile ducts.[1] It is frequently associated with type 1 autoimmune pancreatitis (AIP), forming part of the spectrum of IgG4-related disease (IgG4-RD). However, in the absence of AIP, the condition is classified as isolated IgG4-SC. Isolated IgG4-SC is a clinically uncommon entity and poses a diagnostic challenge due to its resemblance to hilar cholangiocarcinoma. Both conditions present radiologically as bile duct strictures and clinically with symptoms such as jaundice, making differentiation difficult. While hilar cholangiocarcinoma typically requires surgical resection, the primary treatment for IgG4-SC is corticosteroid therapy, as recommended by international consensus.[2] Accurate diagnosis is therefore essential to avoid unnecessary surgical interventions.

This case report presents a patient with isolated IgG4-SC who underwent surgical treatment due to diagnostic uncertainty with hilar cholangiocarcinoma. The report also reviews current diagnostic and therapeutic strategies, emphasizing the importance of distinguishing isolated IgG4-SC from malignant conditions.

Case Report

A 55-year-old female with no significant medical or surgical history presented with progressive right upper quadrant pain and jaundice. On clinical examination, she exhibited scleral icterus, but no palpable masses or signs of hepatosplenomegaly were observed. Laboratory investigations revealed the following: CRP 27 mg/L (reference range: 0.0–5 mg/L), sedimentation rate 81 mm/h, total bilirubin 2.24 mg/dL (reference range: 0.1–1.2 mg/dL), direct bilirubin 1.84 mg/dL (reference range: 0–0.3 mg/dL), alkaline phosphatase (ALP) 118 U/L (reference range: 45–125 U/L), gamma-glutamyl transferase (GGT) 221 U/L (reference range: 10–60 U/L), alanine aminotransferase (ALT) 7 U/L (reference range: 9–50 U/L), and aspartate aminotransferase (AST) 12 U/L (reference range: 15–40 U/L). Tumor markers, including alpha-fetoprotein (AFP) at 1.58 ng/mL (reference range: 0–7 ng/mL), carcinoembryonic antigen (CEA) at 1.96 U/mL (reference range: 0–20 U/mL), and CA 19-9 at 38.5 U/mL (reference range: 0–40 U/mL), were within normal limits. Tests for hepatitis A, B, C, and E were negative. Serum IgG4 levels were measured at 4.41 mg/dL (reference range: 3.92–86.4 mg/dL).

Abdominal ultrasonography showed intrahepatic bile duct dilatation without evidence of mass lesions. Contrast-enhanced magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) identified significant narrowing in the left hepatic duct at the bifurcation and soft tissue density with malignant characteristics, resulting in intrahepatic bile duct dilatation (Fig. 1). No abnormalities were observed in the extrahepatic bile ducts or pancreas. To further evaluate the biliary stricture, endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) were performed. EUS revealed bile duct wall thickening, while ERCP confirmed luminal narrowing at the left hepatic duct bifurcation. Biopsies obtained during ERCP were nondiagnostic due to insufficient tissue.

Given the diagnostic uncertainty and the high suspicion for hilar cholangiocarcinoma based on imaging and clinical presentation, surgical intervention was deemed necessary. The patient underwent an exploratory laparotomy, which revealed thickened, edematous walls

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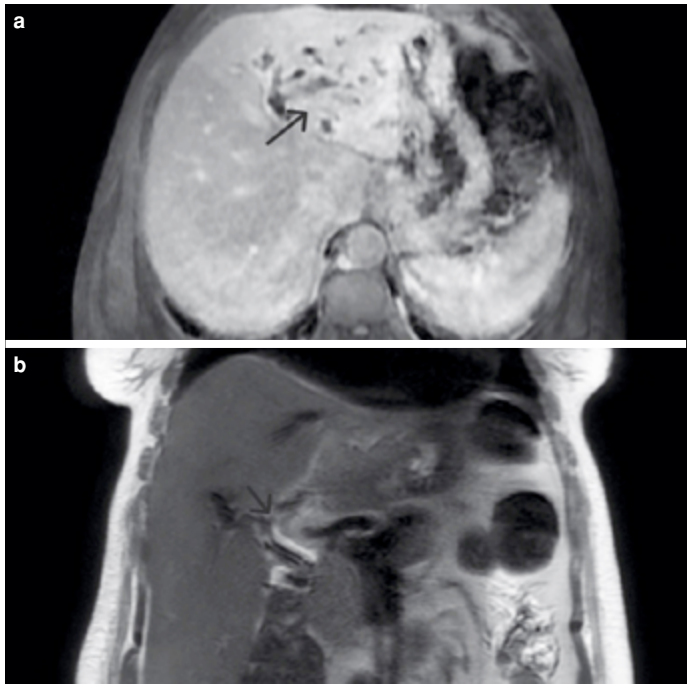

Figure 1. Contrast-enhanced magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) examinations revealed dilated bile ducts in the left lobe **(a)**, significant stenosis at the bifurcation of the left hepatic duct, and malignant soft tissue density **(b)**.

of the gallbladder and a fibrotic stricture involving the hepatic bifurcation and the common bile duct. A left hepatectomy was performed, with intraoperative frozen section analysis confirming benign surgical margins. Postoperative recovery was uneventful, and the patient was discharged on postoperative day 7.

Macroscopic examination of the resected specimen revealed fibrotic thickening of the perihilar bile ducts (Fig. 2). Histopathological analysis confirmed extensive fibrosis and inflammation, consistent with IgG4-SC. Immunohistochemical staining showed an elevated IgG4+ plasma cell count (>10 cells per high-power field) and a high IgG4/IgG ratio (>40%), leading to a definitive diagnosis of isolated IgG4-SC (Fig. 3).

Discussion

IgG4-SC is a chronic fibroinflammatory disease associated with IgG4-RD. It predominantly affects middle-aged to elderly males, with a male-to-female ratio of approximately 4:1.[3] Isolated IgG4-SC, defined as IgG4-SC occurring in the absence of AIP or other organ involvement, is extremely rare, accounting for about 8% of IgG4-SC cases.[3] The condition's clinical presentation and imaging findings often mimic those of hilar cholangiocarcinoma, especially in Type 4 IgG4-SC, where strictures are confined to the hilar bile ducts.[4] This diagnostic overlap frequently leads to unnecessary surgical resections.

IgG4-SC is categorized based on its association with AIP and the location of biliary strictures.[5] When associated with AIP, it often responds well to corticosteroid therapy. However, in isolated IgG4-SC, the absence of systemic or pancreatic involvement complicates the diagnosis.

The disease is further classified into four types based on the location of strictures: Type 1 involves the distal bile ducts; Type 2a includes

Figure 2. Left hepatectomy specimen showing fibrotic wall thickening around perihilar bile ducts.

intrahepatic bile duct strictures with dilation; Type 2b features strictures without dilation and reduced bile duct branches; and Type 3 involves strictures in both the hilar and distal bile ducts. Type 4, as observed in this patient, is limited to hilar bile ducts and is the least common subtype, accounting for approximately 10% of cases.[6]

The differentiation of IgG4-SC from malignant conditions such as hilar cholangiocarcinoma is critical to avoid overtreatment. Imaging modalities, including MRI, MRCP, and EUS, play essential roles in the evaluation of biliary strictures. On MRI and MRCP, IgG4-SC typically demonstrates bile duct wall thickening, homogeneous enhancement, and long-segment strictures without the mass effect seen in cholangiocarcinoma.[7] However, these findings are not always conclusive. EUS and intraductal ultrasound provide high-resolution images and enable fine-needle aspiration, though biopsies may yield nondiagnostic results due to sampling limitations, as occurred in this case.

Serological markers such as serum IgG4 levels are an integral part of the diagnostic criteria. According to the Japanese Biliary Association (JBA) guidelines, an IgG4 level ≥135 mg/dL is diagnostic, although levels below this threshold can occur in isolated cases.[8] In this patient, serum IgG4 levels were within normal limits, underscoring the importance of integrating clinical, radiological, and histopathological findings for accurate diagnosis.

Histopathology remains the gold standard for diagnosing IgG4-SC. Key features include dense lymphoplasmacytic infiltrates, storiform fibrosis, and obliterative phlebitis. Immunohistochemical staining for

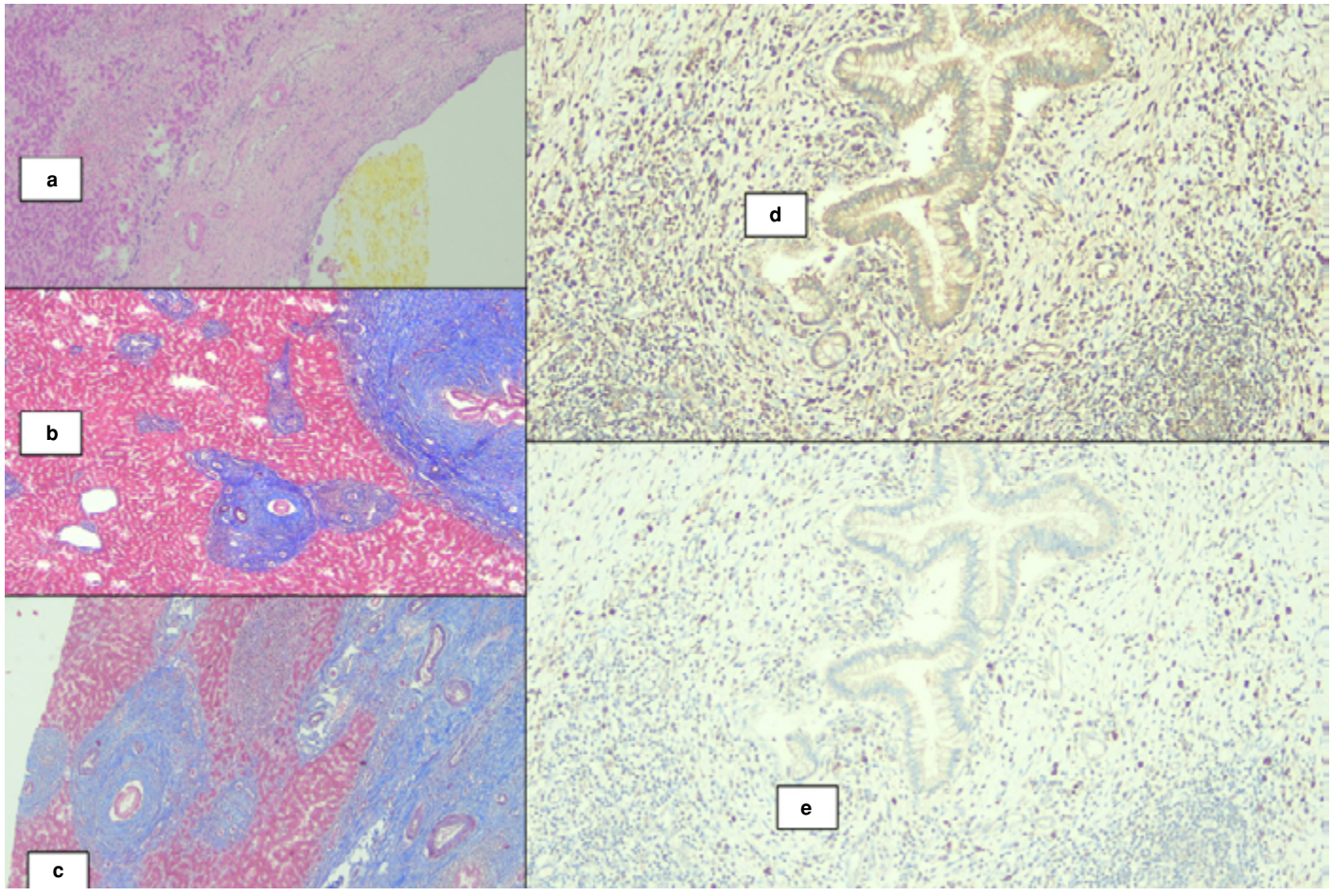

Figure 3. Lithiasis findings are observed within the lumen of perihilar large bile ducts (**a**; H&E; x40). Portal fibrosis and occasional onion skin fibrosis around bile ducts are seen (**b–c**; Masson trichrome; x40). Lymphoplasmacytic infiltration around bile ducts, showing IgG(+) plasma cells component (**d**; x100). Lymphoplasmacytic infiltration around bile ducts, showing IgG4(+) cell component (**e**; x100).

IgG4+ plasma cells and the IgG4/IgG ratio are essential for confirmation.[9] In this case, the resected specimen demonstrated all these findings, establishing the diagnosis of isolated IgG4-SC. Notably, the patient's advanced disease with significant fibrosis likely contributed to the absence of a marked IgG4 elevation in serum.

The literature includes cases of patients diagnosed with IgG4-related sclerosing cholangitis (IgG4-SC) incidentally who subsequently remained asymptomatic without requiring treatment.[10–13] However, corticosteroid therapy is the first-line treatment for IgG4-SC, achieving remission in the majority of patients during the inflammatory phase of the disease.[14,15] Early initiation of corticosteroids can mitigate inflammation and prevent progression to fibrosis. In patients who are unresponsive to steroids or who have already developed fibrosis, alternative therapeutic strategies, such as rituximab and azathioprine, are necessary.[16,17] Rituximab, a CD20 monoclonal antibody, effectively induces remission by depleting B cells and is particularly beneficial in cases of steroid resistance.

In this patient, surgical treatment was performed due to the high suspicion of malignancy. Although surgery is not the standard treatment for IgG4-SC, it provided definitive diagnosis and symptom relief in this case. Moving forward, the patient will require close follow-up to monitor for disease recurrence or progression in other organs.

Conclusion

This case highlights the diagnostic challenges associated with isolated IgG4-SC, particularly Type 4, which closely mimics hilar cholangiocarcinoma. Accurate diagnosis requires a multidisciplinary approach, integrating clinical, radiological, serological, and histopathological findings. While imaging and serology are valuable, histopathological confirmation remains the cornerstone of diagnosis. Early recognition of IgG4-SC is critical to initiating appropriate medical therapy and avoiding unnecessary surgical interventions. Clinicians should maintain a high index of suspicion for IgG4-SC in patients with biliary strictures to optimize outcomes.

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