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Severe acute cytolytic hepatitis revealing IgG4-related liver disease in a young woman

M. Tahiri Joutei Hassani[1], M. Fartmissi[1], Meryem Thaili[1] Z. Boukhal[1], F.Z. Elrhaoussi[1], F. Haddad[1], W. Hliwa[1], A. Bellabah[1], W. Badre[1]

[1]Gastroenterology department, Ibn Rochd University Hospital, Casablanca, Morocco

ABSTRACT

IgG4-related disease is a systemic immune-mediated fibroinflammatory condition that can involve multiple organs, with hepatobiliary manifestations being increasingly recognized. While IgG4-related sclerosing cholangitis represents the most frequent hepatic presentation, **primary parenchymal liver involvement, known as IgG4-related hepatitis, remains rare and poorly characterized**. Its presentation may mimic other causes of acute hepatitis, posing significant diagnostic challenges.

We report the case of a 37-year-old woman with no past medical history who presented with generalized asthenia and episodes of lipothymia, without jaundice, pruritus, fever, or abdominal pain. Physical examination was unremarkable. Laboratory investigations revealed **progressive and severe isolated hepatocellular injury**, with alanine aminotransferase levels peaking at 1294 U/L and aspartate aminotransferase at 803 U/L, while cholestatic enzymes and bilirubin remained near normal. An extensive etiological workup excluded viral hepatitis, including hepatitis A, B, C, and E, as well as Epstein–Barr virus infection. Autoimmune liver disease antibodies were negative, and abdominal ultrasound showed no abnormalities.

Given the absence of an identifiable cause, serum IgG4 levels were assessed and found to be markedly elevated at 3.751 g/L, approximately four times the upper limit of normal. Corticosteroid therapy was initiated, resulting in a **rapid and dramatic biochemical response** with near-complete normalization of liver enzymes. Owing to this favorable evolution, liver biopsy was not performed. Azathioprine was subsequently introduced as maintenance therapy during steroid tapering.

This case highlights **IgG4-related hepatitis as a rare but important cause of severe acute cytolytic hepatitis**, even in the absence of biliary involvement or histological confirmation. Markedly elevated serum IgG4 levels combined with a striking response to corticosteroids can strongly support the diagnosis after careful exclusion of alternative etiologies.

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KEYWORDS:

IgG4-related disease, IgG4-related hepatitis, acute hepatitis, hepatocellular injury, corticosteroids

INTRODUCTION

IgG4-related disease (IgG4-RD) is a systemic immune-mediated fibroinflammatory disorder characterized by tumefactive lesions, lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells, storiform fibrosis, and often elevated serum IgG4 levels [1]. Initially described in association with autoimmune pancreatitis, it is now recognized as a multisystem condition that can involve the pancreas, biliary tract, liver, kidneys, salivary glands, lungs, and retroperitoneum [2,3]. Because it can mimic malignant, infectious, or inflammatory diseases, diagnosis is frequently delayed. Early recognition is crucial due to its typically excellent response to corticosteroid therapy [2,3].

Corresponding Author: Fartmissi Manar

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Hepatobiliary involvement is a well-recognized manifestation of IgG4-RD. The most common hepatic presentation is IgG4-related sclerosing cholangitis, which usually manifests with cholestatic liver enzyme abnormalities and biliary strictures that may closely resemble primary sclerosing cholangitis or cholangiocarcinoma [4,5] .

In contrast, direct involvement of the liver parenchyma—known as IgG4-related hepatopathy or IgG4-related hepatitis—is much less common and remains poorly defined in the literature [6] .

Accordingly, the hepatic manifestations of IgG4-RD are heterogeneous and less well defined, making the diagnosis particularly challenging, especially in the absence of histological confirmation [7].

We report in a case of a a 37-year-old woman with severe isolated cytolytic hepatitis associated with markedly elevated serum IgG4 levels and a dramatic response to corticosteroid therapy.

CASE REPORT

This is a 37-year-old woman with no past medical history. She denied alcohol consumption, medication use, herbal products, or recent travel. She presented with progressive generalized fatigue occurring three days prior to evaluation. She reported no abdominal pain, nausea, vomiting, fever, jaundice, pruritus, or weight loss.

On clinical examination, the patient was hemodynamically stable. There was no jaundice or peripheral stigmata of chronic liver disease. Abdominal examination was unremarkable, with no hepatomegaly or tenderness.

Initial laboratory tests revealed a marked hepatocellular pattern of liver injury, with progressively increasing transaminases. Aspartate aminotransferase (AST) rose from 463 U/L to 803 U/L, and alanine aminotransferase (ALT) increased from 605 U/L to 1294 U/L over several days. Alkaline phosphatase and gamma-glutamyl transferase were only mildly elevated, and bilirubin levels remained within the normal range. Inflammatory markers were low (ESR 3 mm/h and CRP 4.5 mg/L).

A complete etiological workup was performed. Viral hepatitis panels, including hepatitis A, B, C, and E, were negative. Serologic tests for Epstein–Barr virus were also negative. Autoimmune screening, including antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and antimitochondrial antibodies (AMA), was negative.

Given the unexplained and severe cytolytic hepatitis, serum IgG4 was measured and found to be markedly elevated at 3.75 g/L (reference range 0.015–0.959 g/L). Total IgG was normal.

Abdominal ultrasonography showed a normal liver without biliary dilation or focal lesions. No pancreatic abnormalities were identified.

In the absence of an identifiable cause, the patient was started on prednisone 40 mg daily. Within days, a rapid and significant biochemical improvement was observed. AST decreased from 803 U/L to 99 U/L and subsequently normalized, while ALT decreased from 1294 U/L to 96 U/L, confirming an excellent response to corticosteroid therapy.

Azathioprine 50 mg daily was introduced two weeks after initiation of corticosteroids as maintenance therapy. During two months of follow-up, liver function tests remained stable, with complete normalization of transaminases and no evidence of relapse.

DISCUSSION

IgG4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory condition that can affect multiple organs and lead to tumefactive, tissue-destructive lesions and organ failure
[1].

Although hepatobiliary involvement is a recognized feature of IgG4-RD, isolated parenchymal liver involvement remains rare**.** Two main hepatic patterns have been described: secondary hepatic injury associated with IgG4-related sclerosing cholangitis and primary hepatic parenchymal disease, referred to as IgG4-related hepatopathy
[6,7].

Primary IgG4-related hepatopathy typically presents with predominant hepatocellular injury and may clinically resemble autoimmune hepatitis or acute viral hepatitis. When histology is available, it demonstrates portal and lobular lymphoplasmacytic inflammation enriched in IgG4-positive plasma cells, whereas the classic features of autoimmune hepatitis are not consistently observed [1,6].

A key diagnostic issue is distinguishing IgG4-related hepatopathy from IgG4-associated autoimmune hepatitis**.** In the latter, patients fulfill established autoimmune hepatitis diagnostic criteria, including positive autoantibodies and interface hepatitis on histology, with additional IgG4 enrichment. In contrast, IgG4-related hepatopathy is considered a manifestation of systemic IgG4-RD and frequently occurs in the absence of autoimmune antibodies [6] . In our case, the complete negativity of autoimmune serologies supported this distinction.

Furthermore, our patient had no radiological evidence of pancreatic or biliary involvement**,** and the biochemical profile was purely hepatocellular. These findings, combined with the markedly elevated serum IgG4 level, strongly supported a diagnosis of primary IgG4-related hepatic involvement rather than secondary liver injury**.**

Another major feature reinforcing the diagnosis was the rapid and dramatic biochemical response to corticosteroid therapy, which is characteristic of IgG4-RD. Corticosteroids remain the first-line treatment for remission induction, and early biochemical improvement after their initiation is considered a strong supportive diagnostic element [2,3].

Prednisone is usually started at **30–40 mg/day**, maintained for approximately **2–4 weeks**, and then gradually tapered according to clinical and biochemical response. Although spontaneous remission has been described, early corticosteroid treatment is generally recommended to achieve rapid disease control [9].

For long-term management, steroid-sparing immunosuppressive agents such as azathioprine are commonly employed, particularly in patients with severe or relapsing disease. However, robust evidence supporting their efficacy remains limited [10].

In our case, azathioprine was introduced after corticosteroid induction, and the favorable biochemical evolution was maintained.

This case illustrates that **IgG4-related hepatopathy should be considered in patients presenting with severe unexplained cytolytic hepatitis and markedly elevated serum IgG4 levels, even in the absence of pancreatic or biliary disease**. Early recognition is essential because of the excellent response to corticosteroids and the availability of maintenance treatment options.

CONCLUSION

IgG4-related hepatitis is a rare but important cause of acute cytolytic hepatitis. This case emphasizes that markedly elevated serum IgG4 levels and a dramatic steroid response can support the diagnosis when other etiologies have been excluded. Recognizing this condition early allows timely initiation of therapy and may prevent unnecessary investigations or disease progression.

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