

Seronegative Autoimmune Hepatitis: A Case Series of Four Patients

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Abstract

Autoimmune hepatitis (AIH) is a relatively rare chronic liver disease, with a global incidence ranging from 0.7 to 2 cases per 100,000 individuals, and a marked female predominance. It is classically characterized by the presence of specific circulating autoantibodies. However, approximately 10% of AIH cases lack detectable specific autoantibodies.

Currently, there is no established diagnostic algorithm for seronegative AIH. Delayed or incorrect diagnosis may lead to severe disease progression, including fulminant hepatitis or cirrhosis.

Keywords: Seronegative autoimmune hepatitis; Liver biopsy; Immunosuppressive therapy

Introduction

Autoimmune hepatitis (AIH) is a relatively rare chronic liver disease, with a global incidence ranging from 0.7 to 2 cases per 100,000 individuals, and a marked female predominance. It is classically characterized by the presence of specific circulating autoantibodies. However, approximately 10% of AIH cases lack detectable specific autoantibodies.

Currently, there is no established diagnostic algorithm for seronegative AIH. Delayed or incorrect diagnosis may lead to severe disease progression, including fulminant hepatitis or cirrhosis.

Materials and Methods

This was a retrospective study conducted over a four-year period (2020–2024), including all patients admitted to the Hepato-Gastroenterology Department of Moulay Ismail Military Hospital in Meknes who were diagnosed with seronegative autoimmune hepatitis based on histological criteria.

Results

Among 15 patients admitted for AIH, four patients (26%) had negative autoantibody serology. The mean age was 39 years (range: 20–62 years), with a female-to-male ratio of 3:1.

We report the following four clinical cases:

Case 1:

A 62-year-old woman with a history of diabetes mellitus was admitted for severe acute hepatitis. Clinical examination was unremarkable. Laboratory findings showed AST/ALT levels 12 times the upper limit of normal (ULN), prothrombin time (PT) of 35%, negative hepatitis B and C serologies, negative autoimmune panel, serum protein electrophoresis showing IgG levels $1.5 \times$ ULN, and normal abdominal

ultrasound.

Case 2:

A 47-year-old woman followed for primary biliary cholangitis treated with ursodeoxycholic acid presented with chronic cytopenia. Clinical examination was normal. Laboratory tests revealed AST/ALT $\geq 5 \times$ ULN, PT of 92%, negative viral serologies, negative autoimmune markers, and IgG levels $2 \times$ ULN.

Case 3:

A 34-year-old woman with multiple sclerosis was admitted for acute cholestatic hepatitis. Clinical examination was normal. Laboratory findings included AST/ALT $\geq 10 \times$ ULN, total bilirubin 100 mg/L, elevated GGT and alkaline phosphatase, PT of 80%, negative viral and autoimmune serologies, normal abdominal ultrasound and MR cholangiography, and FibroScan showing F2 fibrosis.

Case 4:

A 20-year-old man with no significant medical history was admitted for severe acute hepatitis. Clinical examination was normal. Laboratory tests showed AST/ALT $20 \times$ ULN, PT of 30%, negative viral and autoimmune serologies, IgG levels $1.5 \times$ ULN, and normal abdominal ultrasound.

Liver biopsy was performed for all the patients after correction of PT and confirmed autoimmune hepatitis.

All patients were treated with corticosteroids and azathioprine according to EASL guidelines, with favorable clinical and biochemical outcomes.

Discussion

Seronegative autoimmune hepatitis (snAIH) represents a particular form of AIH in which diagnosis is especially challenging. While AIH is typically diagnosed based on the presence of serum autoantibodies—such as antinuclear antibodies (ANA), smooth muscle antibodies (SMA), or anti-liver kidney microsomal type 1 (LKM1) antibodies—some patients do not exhibit these markers despite clinical and histological features strongly suggestive of AIH.

This absence of autoantibodies, reported in approximately 7–34% of AIH cases, was observed in 26% of patients in our study, making snAIH prone to underdiagnosis. Consequently, it represents a diagnostic challenge, as it escapes standard serology-based diagnostic approaches. [1]

In our series, patient age ranged from 20 to 62 years, with a mean age of 39 years. Other studies have reported higher mean or median ages, ranging from approximately 50 to 53 years. A marked female predominance was observed in our study (75%), consistent with previously published data reporting female proportions exceeding 75%. [1,2,3,4,5]

Clinical presentation of AIH is highly variable, ranging from asymptomatic or mild disease to acute or fulminant hepatitis. Common symptoms include asthenia, abdominal pain, and jaundice, though these are nonspecific. Acute presentations may mimic viral hepatitis or progress to hepatic failure. Extrahepatic manifestations such as arthralgia and myalgia may also occur. [6,7]

Clinical examination is often unremarkable, especially in early stages. Advanced disease may present with signs of cirrhosis such as ascites or splenomegaly.

The typical biochemical profile includes elevated transaminases and gamma-glutamyl transferase levels, with normal or mildly elevated alkaline phosphatase. Elevated serum gamma globulins, particularly IgG, are present in approximately 85% of cases and constitute a key diagnostic clue. [8,9,10,11]

Although autoantibodies serve as important biomarkers, AIH can rarely occur without detectable autoantibodies. [12] In seronegative forms, repeated serological testing is recommended, as antibodies may appear during disease progression.

Liver biopsy remains an essential diagnostic tool, particularly in seronegative cases. Typical histological features include interface hepatitis with periportal inflammation, hepatocyte necrosis, and a lymphoplasmacytic infiltrate. [13] In our study, liver biopsy confirmed AIH in three cases and overlap syndrome in one case, consistent with findings reported in the literature.

All patients in our study received corticosteroids combined with azathioprine, in accordance with EASL recommendations, [8] and achieved biochemical normalization at 12 months. Comparable response rates have been reported in other studies, demonstrating similar treatment efficacy between seronegative and seropositive AIH. [1,2,3,4,5]

Conclusion

Seronegative autoimmune hepatitis is frequently underrecognized and may be diagnosed late. It should be considered in cases of acute hepatitis or chronic cytolysis with a negative etiological and immunological workup. Liver biopsy plays a pivotal role in establishing the diagnosis and guiding treatment.

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