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Acute Seronegative Autoimmune Hepatitis challenge Diagnosis Case Report

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Abstract

Autoimmune hepatitis (AIH) is a liver condition that is considered uncommon, with a global incidence ranging from 0.7 to 2 cases for every 100,000 individuals. This illness is marked by the existence of autoantibodies within the body. Nevertheless, roughly 10% of AIH individuals exhibit symptoms and pathological features associated with AIH but do not show autoimmune serology. Currently, there is no recognized diagnostic algorithm for identifying seronegative AIH (snAIH) cases. An incorrect or postponed diagnosis of snAIH can lead to a lack of treatment or unsuitable interventions, potentially resulting in the progression to severe hepatitis or cirrhosis. This review seeks to analyze the existing research and provide an update on seronegative autoimmune hepatitis, focusing on its underlying mechanisms, clinical features, diagnostic procedures, and treatment options to enhance awareness and highlight the importance of prompt management.

Keywords: Seronegative autoimmune hepatitis, Autoantibody negative, liver biopsy, Autoimmune hepatitis

Introduction

Autoimmune hepatitis (AIH) is a chronic progressive immunemediated inflammatory disease of the liver that is associated with a high mortality rate if left untreated (6-fold higher in the first year after diagnosis and 2-fold higher after 1 year). (1)1 This is even more pronounced in the paediatric population, with an 8-fold higher mortality risk (2). AIH affects females and males of all ages and all ethnicities.3–9 While AIH is traditionally considered a rare disease, recent population-based studies indicate a rising trend in both incidence and prevalence. (3,4).

The diagnosis of AIH is established through scoring systems developed by The International Autoimmune Hepatitis Group (IAIHG) exclude other diseases and histological features that reflect a chronic inflammatory state. (5).

The incidence and prevalence of AIH vary between continents and even between countries. One of the challenges of obtaining accurate incidence and prevalence is the lack of a signature diagnostic marker. AIH can be suspected after ruling out viral etiologies, drug-induced hepatotoxicity, liver diseases, and genetic conditions such as Wilson's disease and hereditary hemochromatosis. As of 2021, New Zealand reported an incidence of 1.93 per 100,000 persons. A literature review estimated AIH yearly incidence in America to be 1 per 100,000 persons as of April 2019 [6]. The overall prevalence of AIH is 3 per 100,000 in the adult population (7).

In recent years, a new form of disease has been described, seronegative AIH, on which few data have been published in the paediatric literature (8,9). It is similar to classic AIH, but is characterised by the absence of antibodies and may present in association with other autoimmune diseases (9,10). It manifests with clinical and biochemical signs of chronic hepatitis in the absence of features indicative of other aetiologies (infectious, metabolic, toxic, etc.). Blood tests usually reveal elevated transaminase levels and absence of antibodies, with additional absence of hypergammaglobulinaemia in up to 25% of cases. Liver biopsy reveals features compatible with AIH, and affected patients respond well to immunosuppressive therapy, as do patients with classic AIH (11,12).

We present a case of a 48-year-old woman who presented with 2 weeks history with elevated enzymes and jaundice, AIH markers were negative and liver biopsy diagnosed seronegative autoimmune hepatitis.

Case presentation

A 48-year-old female, who is obese and has hypertension, came in with a two-week history of upper abdominal discomfort, fatigue, nausea, and jaundice. For hyperlipidemia, she had been taking Rvastatin at a dosage of 20 mg daily for the past year, along with Selokenzoc for hypertension and praxilene as an anti-ischemic vasodilator.

The patient does not consume alcohol and has no recent travel background. The physical examination was largely normal, except for tenderness in the epigastric area and the right upper quadrant.

Laboratory tests conducted one week prior to her admission showed no significant elevation in liver enzymes (ALT 98 IU and AST 81 IU), with alkaline phosphatase (ALP) at 291 IU and a total bilirubin level of 9.2 (with direct bilirubin at 6.1).

An ultrasound of the abdomen revealed signs of chronic non-calculous cholecystitis, while MRCP indicated no obstruction. ruling out the possibility of ductal stricture, choledocholithiasis, biliary ductal enlargement, primary sclerosing cholangitis, and portal vein thrombosis

On the day of admission, liver function tests showed a notable increase in total bilirubin to 13.4 (with direct bilirubin at 11.4), along with ALT levels at 558 IU, AST levels at 677 IU, and alkaline phosphatase (ALP) at 302 IU.

There was suspicion of viral hepatitis, leading to further investigation the same day. Tests for HAV IgM, HBsAg, IgM Anti HBcAb, anti-HCV, HCV PCR, and HEV IgM returned negative results. Conventional serological tests for autoimmune hepatitis yielded unremarkable results with negative ANA, ASMA, IgG, and AMA profiles. The serum ceruloplasmin and tests for hemochromatosis were also negative, in addition to normal levels of EBV, CMV, and HSV IgM antibodies, with the lipid profile appearing to be normal.

Liver function assessments were conducted before, after starting, and after stopping the oral prednisone treatment, as outlined in Table 1.

She was advised to discontinue any medications prior to her hospital admission but did not show improvement, with significantly elevated liver test results. A trial of ursodeoxycholic acid was initiated, but it failed to alleviate symptoms, and five days later, there were still notably elevated liver tests, including a total bilirubin level of 22.6 (with direct bilirubin at 15.5), along with ALT at 332 IU and AST at 234 IU and alkaline phosphatase (ALP) at 302 IU.

According to her medical history, she had been taking Rvastatin 20 mg daily for a year to manage hyperlipidemia, along with Selokenzoc for hypertension and praxilene as an ant ischemic vasodilator.

A preliminary diagnosis was made of drug-induced cholestatic hepatitis potentially related to Rvastatin, praxilene, and Selokenzoc, as these medications are known for causing liver toxicity. Consequently, steroid therapy was initiated at a dose of 60 mg per day for the toxic hepatitis. Follow-up investigations after two days of steroid treatment indicated improvement, with total bilirubin dropping to 15.9 mg/dL and direct bilirubin to 13.9 mg/dL; ALT was 150 IU/L and AST was 156 IU/L. After five days, total bilirubin measured at 7.4 mg/dL, and direct bilirubin was 7.1 mg/dL.

After a complete two-week period, significant improvement was observed (total bilirubin at 2.0 mg/dL, direct bilirubin at 0.8 mg/dL, ALT at 89 IU/L, and AST at 95 IU/L). The steroid dosage was then gradually reduced until it was completely discontinued, and liver function tests were conducted every two weeks. These tests later showed a relapse with elevated liver test results (total bilirubin at 5.2 mg/dL, direct bilirubin at 3.8 mg/dL, ALT at 125 IU/L, and AST at 141 IU/L), followed by ongoing monitoring.

One month after stopping the steroid, liver function tests indicated elevated results (total bilirubin at 9.06 mg/dL; direct bilirubin at 7.88 mg/dL; ALT at 276 IU/L; AST at 98 IU/L). Two days later, total bilirubin reached 10.2 mg/dL, direct bilirubin was 9.86 mg/dL, ALT was 167 IU/L, and AST was 236 IU/L.

Table 1.

Day	5/11 Befor admission	8/9	13/9 Start steroid	14/9	18/9	27/9 tapering	24/10	3/11 After stoped

TB DB	9.2 6.1	13.9 11.4	22.6 16.5	15.9 13.9	7.3 7.1	2.0 0.8	5.2 3.8	9.06 7.88
ALT	98	558	232	150		89	125	276
AST	81	677	234	156		95	141	397

AIH must be considered in all individuals exhibiting raised aminotransferases without a known cause, regardless of the degree of elevation, particularly when there are increased IgG levels and the presence of circulating autoantibodies. Additionally, AIH should also be assumed in cases of cirrhosis with an unknown origin, even if there are no raised aminotransferases, regardless of the absence of circulating autoantibodies.

A liver biopsy performed via percutaneous method demonstrated expansion due to periportal fibrosis (2 / 6) and indicated a significant infiltration of diverse acute and chronic inflammatory cells that included clusters of plasma cells, eosinophils, and various inflammatory cells. The degree of interface hepatitis was moderate (3 / 4). The liver parenchyma showed instances of hepatocyte ballooning accompanied by feathery degeneration, cholestasis, and isolated necrosis leading to a diagnosis of chronic hepatitis, mild fibrosis (2 / 6), and moderate activity (10 / 18). The cause of AIH is yet to be determined.

Based on these findings, the pathology report indicated that the cases were compatible with seronegative AIH, Treatment was commenced following the clinical guidelines of the American Association for the Study of Liver Diseases (AASLD)(13). Prednisone was administered at a dosage of 60 mg/day, and the patient responded favorably, exhibiting clinical and biochemical improvement. This was evidenced by the decrease in bilirubin and transaminase levels by day four of corticosteroid therapy. After seven days of hospitalization, the patient was discharged, and azathioprine at a dose of 50 mg was introduced at week two of treatment. At the one-month follow-up, the patient remained asymptomatic and demonstrated biochemical remission. they remained within the normal range at 6 months with the patients receiving minimum doses of Prednisone10mg/day and azathioprine at a dose of 100 mg/day.

Table 2

Day	3/11	5/11	7/11 Steroid	9/11	13/11	7/12 taper	25/1 maintenance	10/4	20/6	10/8
SB	9.06 7.88	10.76 9.86	10.78 8.63	6.7 3.88	3.64 2.73	0.52 0.37	0.60.43	0.55 0.39	0.64 0.41	0.25 0.05
ALT	276		167	104		18	22	23	20	17

AST	397		230	79		15	20	19	23	14
ALP	178	163	161	135						99
GGT	71	56	55	57						49

Liver function studies before, after liver biopsy and steroid initiation and tapering and maintenance Table (2)

Discussion

HAI is observed globally, crossing cultural and age divides with a bimodal distribution; one peak appears in individuals aged 10 to 18, while another emerges between the ages of 40 and 60. This condition mainly impacts women, presenting a ratio of three females for every male affected. Worldwide incidence rates are approximated to be between 0.67 and three occurrences for every 100,000 person-years (14,16,17). As noted in a recent retrospective cohort analysis from Colombia, 80% of the participants were women with an average age of 49 years (118).

The lack of clear defining features makes diagnosing HAI more challenging, leading it to be identified primarily through exclusion. The range of clinical symptoms is extensive and varies among different ethnicities, presenting anywhere from asymptomatic liver issues to intense cases of hepatitis (16,17). An acute onset, which occurs within 30 days, affects around 25% to 75% of individuals, with 3% to 6% facing acute liver failure (14). Most patients will exhibit chronic and vague symptoms such as exhaustion, discomfort, and joint pain prior to clinical evaluation. A physical examination might appear normal, or it could occasionally show hepatomegaly, painful splenomegaly, and in cases of advanced cirrhosis, identifiable signs of ongoing liver disease, including palmar erythema, spider angiomas, and gynecomastia (14,16,17).

During episodes of acute HAI, autoantibodies play a role in diagnosis. Antinuclear antibodies (ANAs) are found in 80% of cases, smooth muscle antibodies (SMAs) in 63%, and anti-LKM1 in 3% (16). Isolated serological results showing ANA, SMA, or anti-LKM1 are present in 49% of patients, while 51% have a mix of antibodies. ANAs may be absent or exist in low levels in 30% to 40% of patients (19). Serum IgG levels are typically normal in 25% to 39% of instances(15,16,17).

In recent years, a new form of disease has been described, seronegative AIH, on which few data have been published in literature (8,9). It is similar to classic AIH, but is characterised by the absence of antibodies and may present in association with other autoimmune diseases (9,10). It manifests with clinical and biochemical signs of chronic hepatitis in the absence of features indicative of other aetiologies (infectious, metabolic, toxic, etc.). Blood tests usually reveal elevated transaminase levels and absence of antibodies, with additional absence of hypergammaglobulinaemia in up to 25% of cases. Liver biopsy reveals features compatible with AIH, and affected patients respond well to immunosuppressive therapy, as do patients with classic AIH (11,12).

Histological findings for AIH need to be differentiated from drug-induced liver injury (DILIL); however, the hallmark of AIH is defined as interfaced hepatitis. Some histological features that favor AIH more than DILI are severe portal inflammation, prominent intra-acinar eosinophils, prominent portal plasma cells, rosette formation, any level of fibrosis, and severe focal necrosis (20). Our patient's liver biopsy pathology report was consistent interface hepatitis was moderate (3 / 4). The liver parenchyma showed instances of hepatocyte ballooning accompanied by feathery degeneration, cholestasis, and isolated necrosis leading to a diagnosis of chronic hepatitis, mild fibrosis (2 / 6), and moderate activity (10 / 18).

Concerning AIH, corticosteroids decrease gene expressions involved in pro-inflammatory cytokine production and stimulate the proliferation of Treg cells, which reduce liver cell injuries and decrease T-cell immune-mediated damages described in the previous section (21). Our patient was started on prednisone 60 mg / day, according to the American Association for the Study of Liver Diseases (AASLD) guideline for acute seronegative AIH, with notable improvement in her liver enzymes 4days later (21). There is usually an 80% improvement or reduction in the transaminase levels within the first eight weeks; however, if no improvement in transaminase levels is noted, then the clinician should suspect an alternative diagnosis (22,23) .

Conclusions

Seronegative autoimmune hepatitis is a condition that is frequently overlooked or diagnosed later than it should be. It should be evaluated sooner in cases resembling AIH but showing negative autoantibody tests, once other hepatitis causes and the need for immunosuppressive therapy are ruled out. Further evaluation includes applying the IAIHG comprehensive diagnostic scoring criteria, examining liver histology, and showing a favorable response to corticosteroid treatment. These elements are essential in supporting a diagnosis of snAIH. Nevertheless, there is no conclusive test presently available for this condition. Further research into the pathogenesis of snAIH may provide insight into

earlier and more specific diagnostic modalities.

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All authors are responsible for the modification and giving final approval of the manuscript. Abdelmoneim Elhadidy was a contributor in writing the manuscript. All authors read and approved the final manuscript.

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