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Atypical Presentation of Autoimmune Hepatitis: Diagnostic Challenges and the Role of Immunosuppressive Therapy in Clinical Stabilization

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ABSTRACT: **Background:** Autoimmune hepatitis (AIH) is a chronic, immune-mediated liver disease that can present with a spectrum of clinical symptoms ranging from asymptomatic transaminitis to acute liver failure. Serological markers, elevated liver enzymes, and liver histopathology often guide the diagnosis. However, in some cases, incomplete or nonspecific serological profiles complicate early diagnosis.

Case Summary: We report a case of a 45-year-old female who initially presented in 2023 with jaundice, fatigue, and significantly elevated liver enzymes. A weakly positive ANA and negative viral and other autoimmune markers were noted, but liver biopsy was deferred. After two years of being lost to follow-up, she re-presented in 2025 with recurrent symptoms and further deterioration in liver function. Imaging showed early signs of chronic liver disease. A liver biopsy revealed stage F2 fibrosis and classic histopathological features of AIH, confirming the diagnosis. Immunosuppressive therapy with prednisolone and azathioprine was initiated, resulting in clinical stabilization and biochemical improvement.

Discussion and Conclusion: This case underscores the importance of maintaining clinical vigilance and pursuing liver biopsy in uncertain cases, even with inconclusive serology. Early diagnosis and treatment are critical to preventing irreversible liver damage in AIH.

KEYWORDS: Autoimmune hepatitis, Liver Biopsy, Azathioprine, Prednisolone.

I. INTRODUCTION

Incidence and prevalence:

Waldenström was the first to characterize autoimmune hepatitis (AIH) as a chronic, progressive inflammatory liver disorder, primarily affecting young women and marked by elevated gamma globulin levels.[1]Elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), immunoglobulin G (IgG) levels, and the detection of autoantibodies serve as serological markers of AIH, whereas interface hepatitis and lymphocytic infiltration in the liver represent its histological features.[2][3]AIH predominantly impacts women, though approximately 25–30% of those diagnosed are men.[3][4][5]. Autoimmune hepatitis (AIH) exhibits a bimodal pattern of onset, with a peak occurring in childhood as well as adolescence, and another peak typically appearing between the fourth and sixth decades of life. It can affect individuals of various ethnic backgrounds.[3][5][6] Autoimmune hepatitis (AIH) may initially present as an acute hepatitis episode or develop more gradually. In some instances, it can advance to cirrhosis, hepatocellular carcinoma, or even result in death.[3][7][8] Prevalence of autoimmune hepatitis (AIH) varies significantly across populations. In children in Canada, the rate is about 2.4 cases per 100,000 people, whereas among native Alaskans, it's much higher—around 42.9 cases per 100,000. Comparable prevalence rates have also been reported in several Asian countries, suggesting a global distribution with regional differences.[9]

Etiopathogenesis:

The exact cause of autoimmune hepatitis (AIH) remains unclear, but Its development is thought to be strongly influenced by a combination of genetic susceptibility and environmental factors.[3]Type 1 autoimmune hepatitis (AIH) is commonly linked to the presence of anti-smooth muscle antibodies and/or antinuclear antibodies, whereas type 2 AIH is characterized by the detection of anti–liver kidney microsomal antibodies and/or anti–liver cytosol type 1 (LC1) antibodies.[10][11][12] Several drugs have been linked to AIH-like liver injury, including diclofenac,

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methyldopa, hydralazine, nitrofurantoin, and minocycline. More recently, statins and anti–tumor necrosis factor-alpha (TNF-α) agents have also been implicated.[13] The underlying mechanism of autoimmune liver diseases is believed to involve T-lymphocyte-mediated destruction of liver cells, dysregulation of immune cell activity, and an impaired immune response to foreign antigens due to a loss of tolerance to immune triggers.[14][15][16][17][18]

Clinical features:

Autoimmune hepatitis (AIH) presents with a broad spectrum of clinical manifestations, ranging from asymptomatic elevations in liver enzymes to acute liver failure. The classic presentation includes nonspecific symptoms such as fatigue, malaise, anorexia, nausea, and abdominal discomfort, which may be accompanied by jaundice, pruritus, and hepatomegaly on physical examination. Arthralgia, particularly involving the small joints, and other extrahepatic manifestations such as thyroiditis, type 1 diabetes, and vitiligo may also be present due to the autoimmune nature of the disease.[19] While AIH is classically associated with young to middle-aged women, it can affect individuals of all ages and both sexes, and its presentation may vary accordingly.[20] In approximately 25–34% of patients, AIH is diagnosed incidentally during routine testing for unrelated conditions.[21] In more severe cases, patients may present acutely with symptoms mimicking viral hepatitis, including nausea, jaundice, dark urine, and right upper quadrant pain, and up to 25% of adults and 50% of children may present with acute hepatitis.[22] Longstanding disease may lead to consequences like cirrhosis, portal hypertension, and hepatocellular carcinoma, often identified at the time of diagnosis if AIH is not suspected early.[23]

Differential diagnosis:

Diagnosing autoimmune hepatitis (AIH) involves identifying specific clinical and laboratory findings while ruling out other potential causes of chronic hepatitis and cirrhosis. The clinical evaluation should assess alcohol intake and the use of medications associated with liver toxicity. Laboratory tests should measure serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), albumin, total or gamma globulin, immunoglobulin G (IgG), and both conjugated and unconjugated bilirubin.[24]

Table 1: Codified Diagnostic Criteria of the International Autoimmune Hepatitis Group.

Features	Definite	Probable
Liver histology	Moderate to severe interface hepatitis with or without lobular hepatitis or central-portal bridging necrosis, lacking biliary lesions, granulomas, or other indicative changes of alternate diseases.	Same as for ‘‘definite’.
Serum biochemistry	Elevated serum aminotransferases without a significant rise in alkaline phosphatase; normal levels of alpha-antitrypsin, copper, and ceruloplasmin.	Same as "Definite," although minor abnormalities in copper or ceruloplasmin are acceptable if Wilson disease is excluded.
Serum immunoglobulins	Levels of total serum globulin, gamma-globulin, or IgG that exceed 1.5 times the upper limit of normal.	Any increase above the upper limit is acceptable.
Serum autoantibodies	Positive ANA, SMA, or anti-LKM-1 at titers >1:80; lower titers may be significant in children. AMA should be negative.	Positive at titers ≥1:40; other seropositive findings may also be considered.
Viral markers	Absence of active hepatitis A, B, or C infection.	Same as for ‘‘definite’’
Other etiological factors	Alcohol intake below 25 g/day; no recent hepatotoxic drug use.	Alcohol intake below 50 g/day; recent hepatotoxic drug use

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Sex	Female	+2	**HLA**	DR3 or DR4	+1
AP:AST (or ALT) ratio	>3	−2	**Immune Disease**	Thyroiditis, colitis, others	+2
	<1.5	+2			
γ-globulin or IgG level above normal	>2.0	+3	**Other markers**	Anti-SLA, anti-actin, anti LC1, pANCA	+2
	1.5-2.0	+2			
	1.0-1.5	+1			
	<1.0	0			
ANA, SMA, or anti-LKM1 titers	>1:80	+3	**Histological features**	Interface hepatitis	+3
	1:80	+2		Plasmacytic	+1
	1:40	+1		Rosettes	+1
	<1:40	0		None of above	−5
				Biliary changes	−3
				Other features	−3
AMA	Positive	−4	**Treatment response**	Complete	+2
				Relapse	+3
Viral markers	Positive	−3			
	Negative	+3			
Drugs	Yes	−4	**Pretreatment aggregate score:**		
	No	+1	**Definite diagnosis >15**		
			Probable diagnosis 10-15		
Alcohol	<25 g/day	+2	**Posttreatment aggregate score:**		
	>60 g/day	−2	**Definite diagnosis >17**		
			Probable diagnosis 12-17		

Adapted from Alvarez F, Berg PA, Bianchi FB, et al. J Hepatol 1999;31:929-938.

AMA, antimitochondrial antibody; anti-LC1, antibody to liver cytosol type 1; anti-LKM1, antibody to liver/kidney microsomes type 1; anti-SLA, antibody to soluble liver antigen; ANA, antinuclear antibody; AP:AST (or ALT) ratio, ratio of alkaline phosphatase level to aspartate or alanine aminotransferase level; HLA, human leukocyte antigen; IgG, immunoglobulin G; pANCA, perinuclear anti-neutrophil cytoplasmic antibody; SMA, smooth muscle antibody.

Management:

Table 2: Immunosuppressive Treatment Regimens for Adults in Autoimmune Hepatitis

Treatment Regimen	Week 1	Week 2	Week 3	Week 4	Maintenance (until endpoint)
Monotherapy					
Prednisone*	60 mg/day	40 mg/day	30 mg/day	30 mg/day	20 mg/day or less
Combination Therapy					
Prednisone*	30 mg/day	20 mg/day	15 mg/day	15 mg/day	10 mg/day
Azathioprine	50 mg/day	50 mg/day	50 mg/day	50 mg/day	50 mg/day
Azathioprine	1–2 mg/kg/day	1–2 mg/kg/day	1–2 mg/kg/day	1–2 mg/kg/day	1–2 mg/kg/day

***Prednisolone may be substituted for prednisone in equivalent doses.**

Monotherapy is suited for patients with cytopenia, TPMT deficiency, pregnancy, or malignancy, typically used for less than six months. Combination therapy is preferred in individuals with osteoporosis, brittle diabetes, obesity, acne, emotional instability, or hypertension.The endpoints of immunosuppressive treatment in autoimmune hepatitis (AIH) are critical in guiding therapeutic decisions and assessing patient progress. These endpoints include remission, treatment failure, incomplete response, and drug toxicity—each characterized by specific clinical, biochemical, and

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histological criteria. For instance, remission involves normalization of liver function tests and hepatic histology, prompting gradual steroid tapering, whereas treatment failure or incomplete response may necessitate escalation or modification of therapy. Drug toxicity also plays a key role in determining long-term treatment suitability and may require dose adjustment or discontinuation. Understanding these endpoints allows for individualized, responsive management strategies in AIH patients.

Table 3: Outcomes of Initial Immunosuppressive Therapy and Management Strategies in Autoimmune Hepatitis.

Treatment Endpoint	Criteria	Courses of Action
Remission	Complete symptom resolution, normal aminotransferases, bilirubin, and γ-globulin levels, normal histology or inactive cirrhosis.	Gradual prednisone withdrawal over 6 weeks; monitor liver tests every 3 weeks initially, then every 6 months for the first year, and annually thereafter.
Treatment failure	Deterioration in clinical, laboratory, or histological parameters despite adherence to therapy; development of jaundice, ascites, or encephalopathy.	High-dose prednisone (60 mg/day) or prednisone 30 mg/day with azathioprine 150 mg/day for 1 month; adjust doses monthly with clinical improvement.
Incomplete response	Partial or no improvement after 2–3 years of compliant therapy; condition stable but not resolved.	Taper prednisone by 2.5 mg monthly to minimum effective dose (≤10 mg/day); long-term azathioprine (2 mg/kg/day) if steroid intolerance occurs.
Drug toxicity	Cosmetic concerns, osteopenia, emotional instability, hypertension, brittle diabetes, or cytopenias.	Reduce or stop the offending drug; adjust remaining medications accordingly.

II. CASE PRESENTATION

A 45-year-old female initially presented in May 2023 with symptoms of jaundice, fatigue, and malaise. Laboratory investigations revealed significantly elevated liver transaminases (AST: 390 U/L, ALT: 202 U/L) and total bilirubin of 11.9 mg/dL, with a predominantly direct component (9.4 mg/dL). Abdominal ultrasonography on May 29, 2023, showed mild hepatomegaly with gallbladder wall edema, suggestive of acute hepatitis. A basic autoimmune and viral hepatitis workup was performed during this admission. Serologic tests for hepatitis B surface antigen (HBsAg), anti-HCV, HAV IgM, and HCV IgM were negative. The autoimmune panel showed a weakly positive antinuclear antibody (ANA) with a titre of 1:100, while other antibodies—including smooth muscle antibody (ASMA), liver kidney microsomal antibody (LKM-1), and mitochondrial antibody (AMA-M2)—were negative. Despite the clinical and biochemical suspicion of underlying autoimmune etiology, the patient declined liver biopsy at that time. She was discharged with supportive management and was lost to follow-up.

In early 2025, nearly two years after the initial presentation, the patient returned with complaints of fatigue, dark urine, reduced appetite, and yellowing of the eyes—symptoms similar to those experienced in 2023. Repeat laboratory investigations in February and March 2025 revealed a recurrence and further escalation of hepatic dysfunction. AST and ALT levels were markedly elevated again (AST: 754 U/L on March 3; ALT: 549 U/L on March 8), and bilirubin levels had increased to 3.07 mg/dL. Importantly, a follow-up ultrasound performed on February 18, 2025, showed nodular liver contour, mild caudate lobe enlargement, and mild splenomegaly—imaging features concerning the early stages of chronic liver disease.

In light of the recurrent hepatic inflammation, abnormal liver function tests, and progression on imaging, autoimmune hepatitis (AIH) was strongly suspected. After detailed counseling, the patient agreed to undergo a liver biopsy, which was performed on March 11, 2025. The histopathological findings received on March 15, 2025, revealed moderate to marked portal

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inflammation with dense lymphoplasmacytic infiltrates, moderate interface hepatitis, focal hepatocellular necrosis, lobular inflammation, and rosette formation. Fibrosis was staged as F2 based on the METAVIR scoring system. These findings were consistent with a diagnosis of autoimmune hepatitis.

The diagnosis of AIH in this patient was challenging due to the absence of definitive autoimmune markers and her initial reluctance to invasive diagnostic procedures. However, the clinical course, histological pattern, and partial serological evidence (ANA positivity) all converged toward the diagnosis. This case exemplifies the diagnostic complexity of AIH, especially in cases presenting with incomplete or nonspecific serological profiles, and underscores the importance of tissue biopsy in uncertain or evolving hepatic conditions. The progression from elevated transaminases in 2023 to established fibrosis and chronic liver changes by 2025 also highlights the potentially insidious nature of AIH when left undiagnosed or untreated.

Despite incomplete autoimmune serological markers, the progressive clinical course, recurrent biochemical derangement, and histological features confirmed the diagnosis of AIH.

The patient was initiated on immunosuppressive therapy starting March 15, 2025, aimed at controlling hepatic inflammation and preventing disease progression. She was prescribed**OMNACORTIL** (Prednisolone) at a dose of 30 mg/day (administered as 20 mg in the morning and 10 mg at night) as the primary immunosuppressive agent to rapidly reduce inflammation and transaminase levels. **AZORAN** (Azathioprine) 25 mg once daily was added as a steroid-sparing agent to allow for earlier tapering of corticosteroids and maintain long-term remission. To counteract the potential side effects of corticosteroid therapy, especially bone demineralization, **SHELCAL** (Calcium Carbonate) 500 mg daily was prescribed.

At the 20-day follow-up, the patient showed clinical stability, and her treatment was adjusted: prednisolone was tapered to 10 mg twice daily to reduce the steroid burden, while Azathioprine was increased to 50 mg once daily for sustained immunosuppression. Additionally, **SUPRADYN** (a multivitamin supplement) was introduced to address possible micronutrient deficiencies, and **RBSON** (Rabeprazole 20 mg) was added to protect against steroid-induced gastric irritation or ulcers. This comprehensive approach reflects the standard therapeutic strategy in AIH, which balances effective immunosuppression with supportive measures to minimize adverse effects and promote patient adherence.

Table 4: Serial Laboratory Investigations

Date	Bilirubin (mg/dL)	AST (U/L)	ALT (U/L)	ALP (U/L)	Albumin (g/dL)	PT (sec)	Platelet (L/µL)
25-05-2023	11.9	390	202	—	—	—	2.24
29-05-2023	7.31	225.1	391.3	—	—	—	—
03-06-2023	5.91	203	240	162	—	—	—
14-07-2023	1.89	502	274	145	—	—	1.56
27-07-2023	1.8	547	302	—	3.10 / 2.39	—	—
10-08-2023	3.07	754	549	—	—	—	—
12-02-2025	2.20	960	537	—	—	17.70	1.31
03-03-2025	1.7	79.4	57.4	—	—	18.70	1.48

Table 5: Serologic and Imaging Investigations

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Test	Date	Result/Remarks
HBsAg	27-07-2023	Negative
Anti-HCV	27-07-2023	Negative
HAV IgM	27-07-2023	Negative
HCV IgM	27-07-2023	Negative
ANA	27-07-2023	Weak Positive (+, 1:100)
ASMA	27-07-2023	Negative
LKM-1	27-07-2023	Negative
AMA-M2	27-07-2023	Negative
USG Abdomen	29-05-2023	Mild hepatomegaly, GB wall edema
USG Abdomen	18-02-2025	Nodular liver, caudate lobe enlargement, mild splenomegaly
Liver Biopsy	11-03-2025	Portal inflammation, rosettes, Stage F2 AIH

III. DISCUSSION

Diagnostic difficulties:

Autoimmune hepatitis (AIH) can present with a diverse range of clinical features, from an initial asymptomatic state to severe cases culminating in acute liver failure.Its varied laboratory findings and histological patterns further contribute to the complexity of making an accurate diagnosis.[25] The diagnosis and management of autoimmune hepatitis (AIH) can become more challenging when it overlaps with or coexists alongside other liver diseases, potentially affecting both clinical assessment and treatment strategies.[26][27]Autoimmune liver diseases encompass autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis, each characterized by distinct clinical features; however, AIH can sometimes exhibit characteristics of PBC or primary sclerosing cholangitis, a scenario referred to as 'overlap syndrome.'[27]AIH-PBC overlap syndrome occurs in nearly 10% of adults diagnosed with either AIH or PBC, whereas AIH-primary sclerosing cholangitis is more commonly observed in children, adolescents, and young adults.[28]Certain cases of cryptogenic cirrhosis are believed to be end-stage or 'burnt-out' forms of autoimmune hepatitis (AIH).[29] Additionally, patients with autoimmune hepatitis (AIH) who also have coexisting metabolic dysfunction–associated steatotic liver disease (MASLD) — referred to as AIH-MASLD overlap — need careful management, as corticosteroids, the standard first-line treatment for AIH, may exacerbate MASLD.[30]Autoimmune hepatitis (AIH) has a wide and varied differential diagnosis, requiring a comprehensive assessment of clinical signs, laboratory findings, and liver histology to reach an accurate diagnosis.[25] Serological testing for autoantibodies is essential in diagnosing autoimmune hepatitis (AIH); however, approximately 10% of cases may be seronegative, lacking detectable autoantibodies, which increases the risk of underdiagnosis.[25][31]Moreover, performing a liver biopsy is essential both for confirming the diagnosis and for evaluating characteristic histological features.[32]

Current and future therapies:

The primary goals of autoimmune hepatitis (AIH) treatment are to relieve symptoms, stop liver inflammation, prevent the progression of hepatic fibrosis, and achieve as well as sustain long-term disease remission.[25]Complete biochemical remission in autoimmune hepatitis (AIH) is characterized by serum transaminase and immunoglobulin G (IgG) levels returning to normal within six months of initiating therapy.[33] An “insufficient response” refers to the failure to attain complete biochemical remission and is considered

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a potential indicator of poor prognosis in autoimmune hepatitis (AIH).[33]The conventional approach to treating AIH involves initiating therapy with corticosteroids, followed by long-term maintenance using nonsteroidal immunosuppressive agents.[32][34] According to the 2019 guidelines by the American Association for the Study of Liver Diseases, first-line treatment for autoimmune hepatitis (AIH) includes predniso(lo)ne or budesonide, either alone or in combination with the immunosuppressant azathioprine, which serves as a steroid-sparing agent.[35]

Various second- and third-line therapies are available for maintenance treatment, including tacrolimus, mycophenolatemofetil (MMF), and biologic agents.[35][36]Mycophenolatemofetil (MMF) can be used to treat autoimmune hepatitis (AIH) either as a first-line therapy or as a second-line option for patients who are intolerant to azathioprine. [37] Mycophenolatemofetil (MMF) has shown more favourable outcomes than azathioprine in patients newly diagnosed with autoimmune hepatitis (AIH),[38][39]a meta-analysis revealed that MMF achieved a pooled response rate of 58%.[40] However, mycophenolatemofetil (MMF) is known to have teratogenic effects and should be avoided or discontinued in patients who are planning to become pregnant.[32]In patients with autoimmune hepatitis (AIH) who are unresponsive to conventional therapy, a recent meta-analysis suggests that tacrolimus may serve as a safe and effective alternative treatment.[41] Additional salvage treatment options for autoimmune hepatitis (AIH) that is resistant to standard therapies include cyclosporine, rituximab, and infliximab—an anti–tumour necrosis factor-alpha (TNF-α) monoclonal antibody. [35][36][42] It is important to note that, although rare, TNF-α inhibitors have the potential to induce de novo autoimmune hepatitis (AIH).[43][44]

Although autoimmune hepatitis (AIH) has been recognized for a longer time than hepatitis C, advancements in its treatment have been relatively limited. The most recent notable progress was the inclusion of budesonide in the treatment regimen, following the study by Mann et al. in 2010.[32][45] Although budesonide is a corticosteroid with immunosuppressive properties, it tends to cause fewer steroid-related side effects compared to other corticosteroids. This is largely due to its extensive first-pass metabolism in the liver, with about 90% of the drug being inactivated before reaching systemic circulation.[45][46]

In recent years, treatment strategies for various autoimmune diseases have shifted from broad immunosuppression toward more targeted immunomodulation, focusing on specific inflammatory mediators involved in the disease process.[47]Current immunomodulatory therapies for other autoimmune conditions may justify their application in AIH patients and are often already administered to those with relevant autoimmune comorbidities. Among the emerging treatments, rituximab—a monoclonal antibody that targets CD20 and depletes B cells—has shown promise in improving outcomes for patients with difficult-to-treat autoimmune hepatitis (AIH).[48]Zetomipzomib (KZR-616), created by Kezar Life Sciences in San Francisco, CA, is a pioneering small-molecule drug that selectively inhibits the immunoproteasome. It is presently undergoing assessment in a randomized, double-blind, placebo-controlled phase 2a clinical trial (PORTOLA; NCT05569759) that includes patients with autoimmune hepatitis (AIH) who have either failed standard treatments or experienced a relapse.[49][50]

IV. CONCLUSION

This case highlights the critical need for both precise diagnosis and prompt initiation of treatment in autoimmune hepatitis (AIH).The initial diagnostic challenge stemmed from nonspecific symptoms, weakly positive autoimmune serology, and the patient's reluctance to undergo liver biopsy. However, the progression of clinical symptoms and biochemical markers prompted further investigation, with histopathology ultimately confirming AIH. Initiation of immunosuppressive therapy with prednisolone and azathioprine led to marked clinical stabilization and biochemical improvement. Supportive medications, including calcium supplements, multivitamins, and gastric protection, enhanced treatment tolerance and adherence. This case illustrates that even in atypical presentations with diagnostic delays, structured and responsive treatment can significantly alter the disease course and prevent further hepatic deterioration. Early biopsy, appropriate therapeutic escalation, and close follow-up are essential in managing AIH effectively.

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