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Original Research Article | **Hepato-Gastroenterology and Proctology**

Diagnostic Challenges in Autoimmune Hepatitis

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Abstract

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by heterogeneous clinical, biochemical, immunological, and histological features, which may make its diagnosis challenging in clinical practice. This study aimed to analyze the diagnostic difficulties encountered in patients with suspected AIH and to highlight the role of a comprehensive diagnostic approach. We conducted a retrospective descriptive study over a five-year period from January 2019 to July 2025 in the Department of Hepato-Gastroenterology and Proctology at Ibn Sina University Hospital in Rabat. Clinical records of patients evaluated for suspected AIH were reviewed, and demographic, clinical, biochemical, immunological, and histological data were analyzed. A total of 24 patients were included, with a mean age at diagnosis of 45.5 years and a marked female predominance (83.3%). Cholestatic jaundice was the most common presenting manifestation (45.8%), followed by portal hypertension syndrome (29.2%) and chronic cytolysis (16.7%). Elevated serum IgG levels were observed in 79.2% of patients. Antinuclear antibodies and anti–smooth muscle antibodies were positive in 75% and 70.8% of cases, respectively. According to the simplified International Autoimmune Hepatitis Group (IAIHG) criteria, definite AIH was diagnosed in 11 patients (45.8%) and probable AIH in 3 patients (12.5%). In the remaining cases, alternative diagnoses were established, including primary biliary cholangitis, chronic hepatitis C, metabolic dysfunction–associated steatohepatitis, hepatic sarcoidosis, drug-induced hepatitis, and cryptogenic cirrhosis. Histopathological examination played a crucial role in confirming the diagnosis and identifying overlap syndromes or alternative etiologies. Patients with confirmed or probable AIH were treated with corticosteroids in combination with azathioprine, with favorable clinical outcomes in most cases. These findings underline the diagnostic complexity of AIH and emphasize the importance of integrating clinical, biological, immunological, and histological data to establish an accurate diagnosis and guide appropriate management.

Keywords: Autoimmune hepatitis, Liver biopsy, Immunoglobulin G, Antinuclear antibodies, Anti–smooth muscle antibodies, Corticosteroid therapy, Azathioprine, Chronic liver disease.

INTRODUCTION

Autoimmune hepatitis (AIH) is a severe chronic inflammatory liver disease affecting genetically predisposed individuals, predominantly women. Although the precise immunopathological mechanisms underlying AIH remain incompletely understood, accumulating evidence suggests that molecular mimicry, along with an imbalance between effector and regulatory immune responses, plays a central role in disease pathogenesis.

While the diagnosis of classical AIH is usually straightforward, several diagnostic pitfalls persist due to the marked heterogeneity of clinical presentations. Indeed, AIH encompasses a broad clinical spectrum, making the recognition of atypical forms particularly

challenging and potentially leading to delays in appropriate diagnosis and optimal management.

The aim of this study is to explore the diagnostic challenges encountered in routine clinical practice among patients with suspected AIH by integrating clinical, biochemical, immunological, and histological data.

MATERIALS AND METHODS

We conducted a retrospective descriptive study over a five-year period, from January 2019 to July 2025, in the Department of Hepato-Gastroenterology and Proctology (Medical Unit B) at Ibn Sina University Hospital, Rabat. The study involved a review of medical records of patients followed in a specialized hepatology outpatient clinic for suspected autoimmune hepatitis (AIH).

RESULTS

A total of 24 patients with suspected autoimmune hepatitis (AIH) were identified.

The mean age at diagnosis was 45.5 years (range: 28–73 years). The female-to-male ratio was 5, with 20 women (83.3%) and 4 men (16.7%). Eight patients (33.3%) had a history of autoimmune diseases, including ankylosing spondylitis (1 case, 12.5%), ulcerative colitis (2 cases, 25%), psoriasis (2 cases, 25%), and autoimmune thyroiditis (3 cases, 25%). A history of duloxetine use for depressive syndrome was identified in one patient (4.2%).

Table 1: Baseline demographic and clinical characteristics of the study population

Characteristic	Value
Total number of patients	**24**
Sex, n (%)	
Female	20 (83.3)
Male	4 (16.7)
Female-to-male ratio	5
Age at diagnosis (years)	
Mean age	45.5
Range	28–73
History of autoimmune diseases, n (%)	8 (33.3)
Ankylosing spondylitis	1 (12.5)
Ulcerative colitis	2 (25)
Psoriasis	2 (25)
Autoimmune thyroiditis	3 (37.5)
Medication history, n (%)	
Duloxetine	1 (4.2)

Cholestatic jaundice was the most frequent mode of presentation, observed in 11 patients (45.8%). Other clinical presentations included portal hypertension syndrome in 7 cases (29.2%), chronic cytolysis in 4 cases (16.7%), severe acute hepatitis in 2 cases (8.3%), and right upper quadrant abdominal pain in 1 case (4.2%).

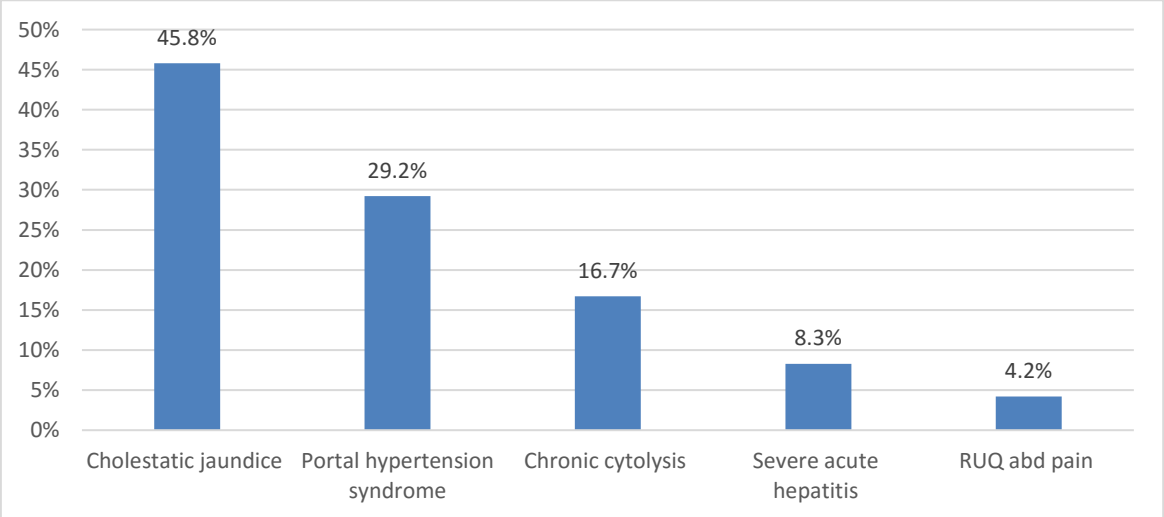

Figure 1: Initial clinical features in suspected AIH

From a biochemical perspective, mean laboratory values were 113 IU/L for aspartate aminotransferase (AST), 117 IU/L for alanine aminotransferase (ALT), 31 mg/L for total bilirubin, 103 IU/L for alkaline phosphatase, and 116 IU/L for gamma-glutamyl transferase (GGT). Elevated serum IgG levels were observed in 19 patients (79.2%), with a mean value of 29 g/L. Antinuclear antibodies (ANA) were positive in 18 cases (75%), smooth muscle antibodies (SMA) in 17 cases (70.8%), anti–soluble liver antigen (anti-SLA) antibodies in 3 cases (12.5%), and anti–liver cytosol type 1 (anti-LC1) antibodies in 4 cases (16.7%). Anti-mitochondrial M2 antibodies were detected in 1 patient (10%). Chronic hepatitis C virus infection was identified in 1 patient (10%).

Table 2: Biological and immunological data of the study population

Liver tests (mean)	
AST (U/L)	113
ALT (U/L)	117
Total bilirubin (mg/L)	31
Alkaline phosphatase (U/L)	103
GGT (U/L)	116
Elevated IgG, n (%)	19 (79.2)
Mean IgG (g/L)	29
Autoantibodies positive, n (%)	
ANA	18 (75)
SMA	17 (70.8)
Anti–SLA	3 (12.5)
Anti–LC1	4 (16.7)
Anti–mitochondrial M2	1 (4.2)
Viral serology, n (%)	
HCV positive	1 (4.2)

Eleven patients (45.8%) fulfilled criteria for definite AIH, with a simplified IAIHG score ≥ 7; among them, 2 patients (19%) were diagnosed with AIH–primary biliary cholangitis (PBC) overlap syndrome based on the Paris II criteria. Liver biopsy was performed in all 11 cases. Histological analysis revealed interface hepatitis in 9 patients (82%) and lymphoplasmacytic infiltrates in 5 patients (45.5%), consistent with typical features of AIH. All patients received corticosteroid therapy followed by azathioprine initiation. Therapeutic escalation to tacrolimus was required in 1 patient (9%) due to failure of previous treatment lines. A favorable outcome was observed in 8 patients (72.7%), with normalization of transaminases and IgG levels after 12 months of treatment, while progression to cirrhosis occurred in 3 patients (27.3%).

Three patients (12.5%) were classified as having probable AIH, with a simplified IAIHG score ≥ 6. Histological examination showed typical AIH features in 1 case (33.3%), compatible findings in 1 case (33.3%) characterized by mild portal inflammation with hepatocellular injury, and portal fibrosis with multiple septa without necroinflammatory activity in 1 case (33.3%). All three patients were treated with corticosteroids followed by azathioprine. Due to lack of response in one patient (33.3%), treatment escalation to mycophenolate mofetil (MMF) and subsequently infliximab was implemented. A favorable outcome was achieved in 2 patients (66.7%), whereas one patient (33.3%) died due to hepatic encephalopathy.

In 10 patients (42%), the diagnosis of AIH was not retained due to incomplete diagnostic criteria or alternative etiologies. Anti-mitochondrial M2 antibodies were positive in 1 case (10%), supporting a diagnosis of primary biliary cholangitis. Chronic hepatitis C infection was identified in 1 patient (10%), with clinical and biochemical improvement following antiviral therapy. Histological findings were consistent with metabolic dysfunction–associated steatohepatitis (MASH) in 2 cases (20%), sarcoidosis in 1 case (10%), drug-induced hepatitis in 1 case (10%), and cirrhosis without identifiable etiology in 4 cases (40%).

Table 3: Diagnostic, treatment, and evolution of patients according to final diagnosis

Characteristic	**Definite AIH**	**Probable AIH**	**AIH not confirmed**
Effective, n (%)	11 (45.8)	3 (12.5)	10 (42)
Liver biopsy, n(%)	11 (100)	3 (100)	10 (100)
Interface hepatitis	9 (82)	1 (33)	—
Other diagnoses	—	—	-MASH: 2 cases (20) -Sarcoidosis: 1 case (10) -Drug-induced hepatitis: 1 case (10%) -Cryptogenic cirrhosis: 4 cases (40)

Characteristic	Definite AIH	Probable AIH	AIH not confirmed
Treatment, n(%)			
Initial immunosuppressive therapy	CTC + AZA: 11 (100)	CTC + AZA: 3 (100)	—
Therapy escalation	Tacrolimus: 1 (9)	MMF/ IFX: 1 (33)	—
Outcome			
Favorable	8 (73)	2 (67)	—
Progression to cirrhosis	3 (27)	—	—
Death	—	1 (33)	—

Overall, among the 24 patients initially suspected of having AIH, the diagnosis was confirmed in only 11 cases (45.8%) and remained probable in 3 cases (12.5%), while the remaining patients were reclassified to alternative diagnoses, including chronic hepatitis C (1 patient), PBC (1 patient), MASH (2 patients), sarcoidosis (1 patient), and drug-induced hepatitis (1 patient). In four patients, a definitive diagnosis could not be established due to liver biopsy findings revealing established cirrhosis.

Table 4: Diagnostic breakdown in patients with suspected AIH

Final diagnosis	n (%)
Definite AIH	11 (45.8)
Probable AIH	3 (12.5)
AIH not confirmed	10 (42)
└ Hepatitis C virus (HCV)	1 (4.2)
└ Primary biliary cholangitis (PBC)	1 (4.2)
└ metabolic dysfunction–associated steatohepatitis (MASH)	2 (8.3)
└ Hepatic sarcoidosis	1 (4.2)
└ Drug-induced hepatitis	1 (4.2)
└ Cryptogenic cirrhosis	4 (16.7)

DISCUSSION

Autoimmune hepatitis (AIH) is a rare chronic liver disease, with an estimated worldwide incidence ranging from 0.4 to 2.4 cases per 100,000 inhabitants per year and a prevalence varying between 5 and 40 per 100,000 inhabitants depending on geographic regions. AIH predominantly affects women, accounting for approximately 70–80% of cases, but it may occur at any age, including in elderly patients [1].

From a pathophysiological standpoint, AIH results from a complex interplay between genetic susceptibility and environmental or drug-related triggers capable of initiating the disease in predisposed individuals. These mechanisms lead to an autoimmune response directed against hepatocytes, characterized by lymphoplasmacytic infiltration and the production of characteristic autoantibodies [2].

The diagnosis of AIH remains a major clinical challenge due to its heterogeneous presentation and the absence of a single pathognomonic marker. Recent EASL 2025 recommendations emphasize the importance of an integrated and individualized diagnostic approach, combining clinical, biochemical, immunological, and histological data [2].

AIH diagnosis relies on composite criteria integrating clinical features, laboratory findings, and histology, yet it may remain difficult, particularly in atypical or overlap forms. The simplified International Autoimmune Hepatitis Group (IAIHG) score has been widely used to standardize diagnostic assessment and demonstrates excellent specificity; however, its sensitivity varies depending on patient populations and clinical presentations [3,4]. Several studies have shown that this score may underestimate AIH in patients with low-titer autoantibodies or atypical histological findings, and that a substantial proportion of patients meet only the criteria for probable AIH [4,5].

Cholestatic jaundice is recognized as a frequent presenting feature of AIH, particularly in patients with overlap syndromes involving autoimmune cholangitis, with some series reporting frequencies as high as 60–70% [5,6]. Nevertheless, the literature highlights the marked heterogeneity of clinical presentations, ranging from flu-like symptoms and severe acute hepatitis to isolated chronic cytolysis, all of which may complicate initial diagnostic orientation and delay disease recognition [4,7,8].

Elevated serum IgG levels and the presence of autoantibodies represent key biological elements guiding the diagnosis of AIH [2,6]. Antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) are the most frequently detected serological markers in adults, with variable sensitivity across studies, whereas anti–soluble liver antigen (anti-SLA) antibodies, though less common, exhibit high specificity [2,8]. However, these biological abnormalities are not pathognomonic and may

also be observed in other chronic liver diseases, thereby complicating diagnostic interpretation [2,5,8].

Accordingly, while serological markers and IgG elevation are essential tools for suspecting AIH, their interpretation must be carefully integrated with clinical and histological findings to avoid diagnostic errors, particularly in atypical or overlap forms [2,5].

Histological evaluation remains a cornerstone in the diagnosis of AIH, especially in atypical or overlap presentations. Typical histological features include interface hepatitis, dense lymphoplasmacytic infiltrates, plasma cells, and occasionally lobular necrosis [2,6]. Fibrosis is frequently present at diagnosis, particularly in patients with chronic or delayed disease presentation. Liver biopsy also allows identification of features suggestive of overlap syndromes or alternative diagnoses such as primary biliary cholangitis (PBC), metabolic dysfunction–associated steatohepatitis (MASH), or drug-induced liver injury [2,5].

In our series, histological analysis played a decisive role in confirming or excluding the diagnosis of AIH, particularly in cases with atypical or incomplete clinical and immunological features. It enabled the identification of cryptogenic cirrhosis, MASH, hepatic sarcoidosis, drug-induced hepatitis, and PBC. Beyond its value in excluding alternative etiologies, histology also contributed to confirming AIH in several patients. These findings underscore the critical role of liver biopsy in differentiating AIH from its main differential diagnoses and in strengthening diagnostic certainty when biological markers are only partially suggestive [2,4,8].

Thus, clinico-biological-histological correlation remains essential for accurate diagnosis and appropriate classification of AIH, particularly in atypical, overlap, or advanced cirrhotic forms [2].

Therapeutic management of AIH is based on corticosteroid therapy, often combined with an immunosuppressive agent such as azathioprine to maintain remission [2,5]. Corticosteroids usually induce rapid improvement in transaminase levels and hepatic inflammation, while azathioprine allows steroid dose reduction and relapse prevention [5,6]. In cases of treatment failure, intolerance, or severe disease, alternative therapies such as mycophenolate mofetil (MMF), tacrolimus, or even biological agents may be considered, although available evidence remains limited and is largely derived from case series [4,6].

The prognosis of AIH largely depends on the timeliness of diagnosis, initial disease severity, and response to immunosuppressive therapy. Most studies report clinical and biochemical improvement under corticosteroids and azathioprine, with complete remission achieved in approximately 60–80% of patients [2,5]. However, a variable proportion of patients may progress to advanced fibrosis or cirrhosis, particularly in cases of delayed diagnosis or severe initial presentation [2,3]. Mortality remains low but may occur in the context of severe liver disease, decompensated cirrhosis, or infectious complications [2,6].

CONCLUSION

Autoimmune hepatitis remains a complex disease from both diagnostic and prognostic perspectives. Our series highlights the clinical, biological, and histological heterogeneity of AIH, which may mimic other liver diseases and complicate diagnosis, even in the presence of suggestive serological markers. Liver biopsy retains a central role in confirming the diagnosis and guiding patient management. Standard treatment based on corticosteroids and azathioprine is generally effective, with favorable outcomes under appropriate medical follow-up.

These findings emphasize the necessity of an integrated diagnostic approach combining clinical, biological, and histological data to ensure optimal management and prevent long-term complications.

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