



Review Article

# Autoimmune Hepatitis: A Review with emphasis on its histomorphology

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## ABSTRACT

Autoimmune hepatitis is a chronic inflammatory disorder characterized by periportal inflammation, hypergammaglobulinemia with elevated autoantibodies, and a dramatic response to immunosuppression. Various environmental and genetic influences can trigger the immune mediated destruction of the liver. A plethora of clinical presentations can be seen ranging from chronic indolent disease to fulminant hepatic failure. Autoimmune hepatitis does not have a pathognomonic feature, and its laboratory, serologic, and histologic manifestations are found in acute and chronic liver disease of diverse causes. Difficulties in distinguishing toxic, drug-related, virus-induced, and autoimmune causes of severe acute liver injury can result in misclassification.

Our paper discusses autoimmune hepatitis, giving a detailed overview of its clinical presentation, immunopathogenesis, emphasis on histomorphological changes and the diagnostic criteria.

## INTRODUCTION

Autoimmune hepatitis (AIH) is an inflammatory disease of the liver characterized by circulating autoantibodies, hypergammaglobulinemia, inflammation and necrosis of the liver.<sup>1</sup>

The disease entity was first described by Leber in 1950 and has been given various terminologies since then. It is known as hypergammaglobulinemic chronic hepatitis active chronic hepatitis, chronic active hepatitis or autoimmune chronic active hepatitis and by other names such as chronic aggressive hepatitis, lupoid hepatitis and plasma cell hepatitis. The International Autoimmune Hepatitis Group designated "Autoimmune Hepatitis" as the most accurate and suitable term for the condition.<sup>2,3</sup>

## Epidemiology

Autoimmune Hepatitis is a relatively uncommon disease occurring in all races and in all geographical areas. According to different studies the prevalence of AIH in North America and western Europe is estimated to vary from 11-23 %.<sup>1,3</sup> The incidence of AIH among white in Northern Europe was 1.9 /100000.<sup>2</sup> There are large groups of patients reported from South America, Alaska, Scandinavia and Australia.<sup>4</sup> In Asia most report come from Japan with prevalence as high as 1:10000 cases.<sup>5</sup> AIH is now frequently reported in china<sup>6,7</sup> few cases in Singapore (2 cases).<sup>7</sup> Rafeey et al reported AIH to be 5.6 % of all childhood liver disease in Iran.<sup>8</sup>

Studies from India date back to 1998 where 10 cases were reported by Gohar et al. subsequently there are reports of AIH from different centers quoting the prevalence to be 1.5-6.4% of all liver disease.<sup>9-11</sup>

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There are no documented data regarding AIH in Nepal. But according to a report by KC et al, 12% of all chronic liver disease associated with hepatitis E is AIH.<sup>12</sup> The low prevalence of AIH in India and Nepal may be due to genetic or geographical makeup or an underestimation of prevalence of AIH as antibody studies are not accessible.

### Etiology and Pathogenesis

#### Infectious trigger/viruses

The development of AIH is associated with viral Hepatitis A, Hepatitis B, Hepatitis C. AIH has developed after vaccination for Hepatitis A and B. Other virus implicated to trigger the autoimmune process include human herpes virus, HIV, Measles virus, EBV, CMV. Molecular mimicry in B cells level between a structural motif of CYP2D and HCV protein could explain the production of anti LKMI antibodies in HCV infected patients.<sup>13,14</sup>

#### Drugs

Nitrofurantoin, methylphenidate and atomoxetine, propylthiouracil, resperidone, rifampicin, pyrazinamide; betainterferon, doxycycline, minocycline, methyl dopa.<sup>14,15</sup> The AIH may be related to hepatotoxic effects of these chemical, upregulation of p450 immunoregulatory proteins or related to drug acting as hapten modifying the hepatic protein and making them immunogenic. The drug induced AIH reverts after the drug is stopped.<sup>16,17</sup>

#### Genetic Association

AIH is a complex polygenic disease affected by various genetic and environmental triggers. HLA genes appear to play the dominant role in predisposing to AIH. HLA DR3 is common in early onset, severe form of autoimmune disease, which often occurs in girls and young women. They are resistant to corticosteroid treatment and require liver transplantation. HLA DR4 is more common in adults and associated with increased incidence of extrahepatic manifestation, milder disease and better response to corticosteroid treatment.<sup>1,2,18</sup> Other HLA association are given in the Table 1.<sup>19</sup>

Twenty percent of AIH is associated with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED) which follows Mendelian inheritance and prenatal genetic counseling is advised.

#### Immunopathogenesis

Liver is a part of lymphoid system with normal lymphocyte population residing in portal tracts. Various exogenous agents described above can upregulate expression of HLA I & II in hepatocytes. The antigens activate the T helper cells initiating the cascade of immune response

leading to activation of cytotoxic T cells. The cytotoxic T lymphocytes recognize the antigen presented by Class I molecules and also transform B lymphocytes to plasma cells. The autoantibodies release damages liver by release of interferon, complement or antibody dependent cytotoxic reaction (ADCC). CYP2D6 cytoplasmic enzyme is targeted by anti LKMI antibodies which damages the liver as shown in fig.1.<sup>20-22</sup>

There is reduction in regulatory T cells responsible for dampening the immune response stopping the proliferation and effector function of autoreactive T cells. The T reg are defective in number and functions and their level is inversely proportional to the levels of anti SLA and anti LKMI autoantibody titres.

#### Classification

The marked heterogeneity of AIH in regard to its variable presenting features, spectrum of disease severity, and presence of characteristic auto antibodies as well as response to therapy has led to several proposals for classification of the disease. The most approved classification includes type 1 and type 2 depending upon the antibodies present shown in Table 2.<sup>19</sup>

Type 1 AIH constitutes 80% of total AIH and is characterized by the presence of antibodies to nuclei (ANA), smooth muscle (SMA) and Soluble Liver Antigen/Liver Pancreas antigen (SLA/LP). About 25% of these patients present with cirrhosis. These are associated with other autoimmune diseases like celiac disease, ulcerative colitis and autoimmune thyroid disease.

Type II AIH is characterized by presence of antibodies against a particular epitope on cytochrome P450 (IID6) enzyme located in liver and kidney microsomes (ALKM-1) and antibodies to liver cytosol antigen (ALC-1 or LC1).<sup>1,2</sup> Most patients are children. Acute presentation can occur and progress to cirrhosis.

#### Clinical manifestation

The clinical presentation is heterogeneous. The spectrum of presentation range from no symptoms to debilitating symptoms and even fulminant hepatic failure. The patients are predominantly women >70% of cases and 50% are younger than 40 years. The age at onset varies from infancy to elderly. Presenting feature may include, lethargy, fatigue, arthralgia, myalgia, anorexia, abdominal pain, nausea and dark urine. Children and elderly present with cirrhosis.<sup>1-3,18,19</sup>

Physical examination may be normal, but may reveal hepatomegaly, splenomegaly, jaundice, stigmata of liver disease. Rarely hirsutism, acne, obesity and amenorrhoea are seen. There is associated other autoimmune disorder like Hashimoto's thyroiditis, type 1 DM, rheumatoid arthritis,

**Table 1: HLA Association in Autoimmune Hepatitis<sup>19</sup>**

HLA Association	Ethnicity	AIH type	No. of patient studied
HLA- DRB180401	i. European and north American. Increased susceptibility to type I in Caucasian ii. HLA DR3 in younger and severe forms than HLA DR4	I	119
HLA DRB3*0101	European and north America	I	119
HLA DRB1*0404	Mexican	I	30
HLA DRB1*0405	Japanese	-	49
HLA DRB1*07	Brazil	II	28
HLA B14	Germany	II	19

**Table 2: Classification of autoimmune hepatitis<sup>19</sup>**

Variable	Type I AIH	Type 2 AIH
Characteristic autoantibodies	ANA SMA AAA Antibody to SLA/LP antigen Atypical pANCA	Antibody against LKM Antibody against liver cytosol
Geographic variation	Worldwide	Worldwide, rare in North America
Age at presentation	Any age	Predominantly childhood and young adulthood
Sex	Female in 75% of cases	Female in approximately 95% of cases
Association with other autoimmune disorder	Common	Common
Clinical severity	Broad range	Generally severe
Histopathologic feature	Broad range	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long term maintenance	Variable	Approximately 100%

SLE, Ulcerative colitis and celiac disease in 20% of the patients.

### Laboratory Findings

#### Biochemical investigation

There is marked increase in AST and ALT, but levels are generally <500 u/l rarely reaching up to 1000 u/L. Some patients may have elevated conjugated bilirubin and alkaline phosphatase necessitating workup for primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), viral hepatitis, biliary obstruction. Alkaline phosphatase rarely exceeds 4x the normal. AIH is associated with high hypergammaglobulinemia with selective increase in IgG 1.2-3.0 times.<sup>1-3,18,19,23</sup>

#### Serology

Type 1 AIH is characterized by the presence of antibodies to nuclei (ANA), smooth muscle (SMA) and Soluble Liver Antigen/Liver Pancreas antigen (SLA/LP).<sup>3</sup> Type II

AIH is characterized by presence of antibodies against a particular epitope on cytochrome P450 enzyme located in liver and kidney microsomes and antibodies to liver cytosol antigen.<sup>1,19</sup>

#### Seronegative AIH

Approximately 10% to 15% of AIH is marker negative.<sup>23,24</sup> Data suggest that seronegative AIHs similar to seropositive AIH with respect to demographics, aminotransferase levels at diagnosis or after treatment, response to therapy, and histologic parameters, including portal and lobular inflammation, interface activity, and centrilobular necrosis.<sup>25</sup>

#### Liver Biopsy

The diagnosis of AIH cannot be made without Liver biopsy in all cases whether acute or subclinical. Interface hepatitis is a pathologic hallmark of active AIH. It is especially prominent during disease flares.<sup>26-28</sup> Interface hepatitis in AIH is characterized by a prominent lymphohistiocytic infiltrate at the portal tract mesenchymal-parenchymal

**Table 3: Simplified diagnostic criteria**

		Points
1. Autoantibodies	ANA or SMA or LKM > 1:40	1
	ANA or SMA or LKM > 1:80	2
	SLA/LP Positive (>20 units)	2
2. IgG (or gamma-globulins)	Upper normal limit	1
	>1.10 times normal limit	2
3. Liver histology	Compatible with AIH	1
	Typical for AIH	2
4. Absence of viral hepatitis	Yes	2
	No	0

**Table 4: Histologic component of the simplified criteria for the diagnosis of AIH<sup>37</sup>**

Histology category	Description	Points
Typical	Includes interface hepatitis, lymphocytic or lymphoplasmacytic infiltrates in portal tracts extending into the lobule, emperipolesis, and hepatocyte rosette formation	2
Compatible	Chronic hepatitis with lymphocytic infiltration without all the features considered typical	1
Atypical	Atypical Includes evidence of another diagnosis	0

junction with accompanying histologic evidence of liver cell damage. CD8-positive T cells are a dominant subset of lymphocytes within areas of interface hepatitis, and CD4-positive T cells predominate within the portal tracts.<sup>18</sup>

Histologically, AIH has many faces depending on the course of the disease, the form of its initial presentation, its evolution, and effects of treatment.<sup>1,19,29</sup>

### ACUTE AUTOIMMUNE HEPATITIS

Acute and fulminant forms of AIH were recognized by the IAIHG in 1992 when the diagnostic criteria waived the requirement for 6 months of disease activity to establish the diagnosis.<sup>30</sup> In acute AIH, histology showed brisk, recent, ongoing immune-mediated hepatitis activity overlapping with evidence of chronicity including septal fibrosis and overt cirrhosis despite the lack of correlating clinical chronicity.<sup>30</sup>

The histology shows extensive interface hepatitis may be extensive with portal inflammation and diffuse lobular necroinflammation (fig. 2A) sparing the biliary tree. Hepatitis activity may show zone 3 accentuation (fig. 2B). Plasma cells typically predominate at the interface and throughout the lobules and portal areas, hence the name plasma cell hepatitis, eosinophils are also frequently seen. Evidence of hepatocellular injury and necrosis (ballooning

degeneration, spotty hepatocyte necrosis, and apoptotic bodies) are common but not specific. Lobular disarray is present and bridging necrosis may occur. Injury may be followed by regeneration in the form of thickened hepatic plates and hepatic rosette formation. Most of these patients probably have a lobular “flare” in disease activity, which likely precipitated the clinical presentation as an acute hepatitis.

### FULMINANT AUTOIMMUNE HEPATITIS

The features are more severe than acute AIH. There is bridging, zonal, and multilobular necrosis. Massive hepatocyte necrosis and drop out, parenchymal extinction, and stromal collapse may be present.<sup>31</sup> Regenerative foci of hepatocytes may be present and mimicking cirrhosis.

### CHRONIC HEPATITIS

AIH can assume a chronic hepatitis pattern of injury, with portal and periportal lymphoplasmacytic infiltrates and interface hepatitis. Plasma cells are often, but not always, prominent, and are sometimes seen singly and in clusters in the lobule. The severity of necroinflammatory activity is quite variable. Ballooning degeneration, spotty hepatocyte necrosis, and apoptotic bodies are common but not specific.<sup>29</sup> Hepatocytes may form regenerating rosette-like structures.

### Pitfall in the diagnosis of AIH

#### A. Zone 3 necrosis with or without portal inflammation

- » not a specific finding of AIH
- » Can also occur in viral and drug-induced hepatitis

#### B. Sparsity or absence of plasma cells in the inflammatory infiltrate

- » Predominance of plasma cell infiltration is not specific for AIH
- » Its presence supports the diagnosis and the finding is more common in this condition (66%) than in chronic hepatitis B (40%) or chronic hepatitis C (21%).<sup>32,33</sup>
- » does not occur in all patients with the disease (34%), not present in seronegative cases
- » The absence of plasma cells does not preclude the diagnosis.<sup>32</sup>

#### C. Giant syncytial multinucleated hepatocytes

- » Giant syncytial multinucleated hepatocytes may be a dominant feature in AIH -“syncytial giant cell hepatitis”;
- » Also associated with drug toxicity and viral infection, especially with the paramyxovirus.

#### D. Duct injury in AIHs

- » Bile duct destruction is generally not prominent in AIH,
- » 12% of biopsies may show duct destruction.
- » Lymphocytic infiltration of bile duct epithelium (see fig. 3) without duct loss can be seen in another 12%.<sup>34</sup>

### AUTOIMMUNE HEPATITIS AS PART OF AN OVERLAP SYNDROME

PBC is a chronic cholestatic liver disease that is characterized by gradual destruction of the interlobular bile ducts that leads to damage of the hepatocytes. Approximately 10% of patients who have all the features of PBC—positive antimicrobial antibodies and cholestatic biochemical findings—present with additional features of AIH. These features include other autoantibodies such as smooth muscle antibodies, hypergammaglobulinemia with a fivefold elevation of AST or ALT, or a 10-fold elevation of the AST. Histologically, these patients may have lymphoplasmacytic interface hepatitis in addition to the typical florid duct lesions present in PBC. In addition to AIH-PBC overlap that is present at the time of diagnosis, a “sequential” overlap syndrome of AIH with PBC can occur.<sup>35</sup>

### AUTOIMMUNE HEPATITIS - POST TREATMENT

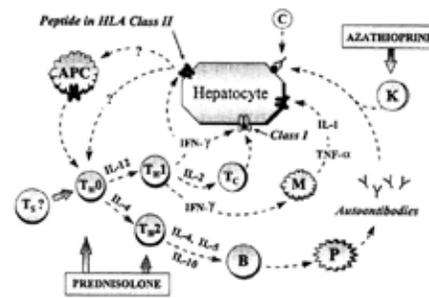
In inactive, or subclinical AIH with raised transaminases biopsy show fibrosis, without or with mild lobular, portal, or interface necroinflammatory activity or a combination of these. Histologic improvement lags behind clinical and laboratory improvement by 3 to 6 months. In 55% of cases, liver biopsy examination at the time of clinical and laboratory normality discloses residual interface hepatitis

The goals of corticosteroid therapy are to resolve symptoms, normalize laboratory tests, and improve histologic findings to normal, quiescent portal hepatitis, or inactive cirrhosis. Liver biopsy is the only means of confirming remission and it should be performed before drug withdrawal.<sup>34</sup>

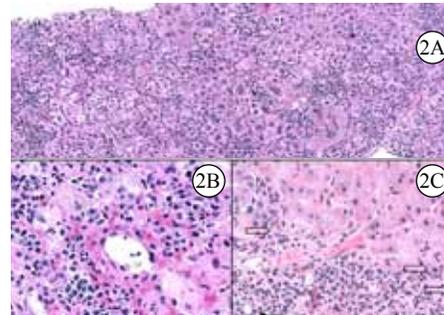
Restoration of normal hepatic architecture during treatment is associated with a 20% frequency of relapse after drug withdrawal; the presence of portal hepatitis is associated with a 50% frequency of relapse; and the presence of interface hepatitis of any degree or progression to 20% frequency of relapse after drug withdrawal; the presence of portal hepatitis is associated with a 50% frequency of relapse; and the presence of interface hepatitis of any degree or progression to cirrhosis is associated with an 87% to 100% frequency of relapse.<sup>17,32</sup>

### AUTOIMMUNE HEPATITIS - DIAGNOSTIC SCORING SYSTEMS

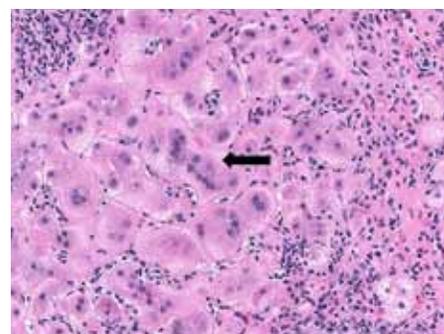
The clinical spectrum of autoimmune hepatitis is very wide. Diagnosis is usually made by a combination of clinical, laboratory and histological features. Diagnostic scores can help both in the daily diagnostic work-up of patients, and in allowing comparability of clinical scientific studies. In 1992 the international autoimmune hepatitis group (IAIHG) devised a diagnostic scoring system with the aim to categorize patients in groups of definite AIH and probable AIH. This was revised in 1999. This criteria allowed comparison of studies from different centers. Because these criteria are complex, insufficiently validated, and include a variety of parameters of questionable value, the IAIHG



**Figure 1:** Pathogenesis of Autoimmune Hepatitis



**Figure 2:** Autoimmune Hepatitis A. Diffuse parenchymal and portal inflammation (HE Stain, X50) B. Predominantly zone 3 involvement with plasma cell rich infiltrate and hepatocyte drop out and necrosis (HE Stain, X200) .C Interface activity(hollow arrows with minimal involvement of bile duct)(HE Stain, X200).



**Figure 3:** Liver parenchyma showing lymphoplasmacytic inflammation and several large multinucleated hepatocytes in the center of the field (HE Stain, X400).

decided to devise a simplified scoring system for wider applicability in routine clinical practice based on the data of patients with well-established diagnoses.<sup>30,36,37</sup>

ANA, antinuclear antibody; SLA, soluble liver antigen; IgG, immunoglobulin G;

The new system condenses the liver histology criteria into three categories (Table 4). In this new system by Hennes and colleagues<sup>37</sup>, the presence of histologic evidence of hepatitis is a necessary finding to categorize patients as having either “definite” or “probable” AIH in an objective manner. A positive weighting was given to female gender,

hepatocellular rather than cholestatic damage, and the presence of autoantibodies. The diagnosis of definite AIH required a liver biopsy.

However, all diagnostic scores have limitations in individual cases. The simplified score cannot detect for example; patients with coexistence of AIH and HCV. The latter could be a problem for areas with high endemicity of HCV infections. Twenty to forty percent of patients with chronic HBV or HCV are persistently positive for various autoantibodies, usually at low titers (B1:20 or 1:40).<sup>3</sup> Conversely, patients with AIH sometimes have a false-positive test for anti-HCV antibodies but will have undetectable HCV-RNA. Three categories of patients with potential concurrent AIH/hepatitis C may be identified:

- » patients with true AIH and false-positive anti-HCV antibodies (undetectable HCV-RNA);
- » patients with true HCV and autoantibodies at low titers, but no other signs of AIH;
- » patients with true HCV and features of AIH including young age, female gender, high
- » autoantibody titers (41:320), hypergammaglobulinemia, and history of extrahepatic autoimmune disorders.

Distinction of chronic viral hepatitis from AIH is important, because interferon therapy can exacerbate autoimmune conditions, and corticosteroids can enhance viral replication. In a study of the IAIHG, the simplified score was found 97% specific and 88% sensitive.<sup>37</sup>

The revised scoring system might be useful in the evaluation of “difficult” cases with few or atypical features of AIH after exclusion of other diagnoses, while the simplified scoring system – simpler in its determination – can be used in aetiologically distinctive cases with concurrent immune trappings in order to exclude AIH. The various studies strongly shows that as there is no single test for AIH, histology is very important where there is any doubt about the diagnosis, and in patients where there may appear to be more than one disease, histology is the best guide of treatment.<sup>30,36-38</sup>

## CONCLUSION

Early diagnosis and treatment of AIH shows a dramatic recovery of the patients. But the diagnosis of AIH is challenging because clinical picture is heterogeneous and there is no specific test applicable for all patients. The liver biopsy should be mandatory in patients with liver disorders in whom there is evidence of autoimmunity and absence of evidence of HBV or HCV markers. The cooperation between clinicians and pathologists seems mandatory.

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