Clinical features and management of autoimmune hepatitis

Edward L Krawitt

Autoimmune hepatitis (AIH) is a chronic hepatitis of unknown etiology which can progress to cirrhosis. Its clinical manifestations are highly variable and sometimes follow a fluctuating course. Diagnosis is based on characteristic histologic, clinical, biochemical and serological findings. Anti-inflammatory/immunosuppressive treatment frequently induces remission but long-term maintenance therapy is often required. Liver transplantation is generally successful in patients with decompensated cirrhosis unresponsive to or intolerant of medical therapy.

HISTOLOGY

The histologic appearance of AIH is that of chronic hepatitis, and, although certain changes are characteristic, there are no findings specific to the disease. The histologic differential diagnosis of chronic hepatitis is shown in Table 1. Based on the advances in virologic studies and refinements of cholangiographic methods, exclusion of other entities has become easier, although co-existence of chronic viral hepatitis and AIH may make the diagnosis difficult.

The inflammatory component is characterized by a mononuclear cell infiltrate, which invades the sharply demarcated hepatocyte boundary (limiting plate) surrounding the portal triad and permeates the surrounding parenchyma (periportal infiltrate; piecemeal necrosis; interface hepatitis) and beyond (lobular hepatitis). It may include an abundance of plasma cells and/or eosinophils, but the portal lesion generally spares the biliary tree. In all but the mildest forms of AIH, fibrosis is present. In advanced disease, fibrosis is extensive (bridging fibrosis) and, with distortion of the hepatic lobule and appearance of regenerative nodules, cirrhosis occurs. On occasion, centrilobular disease may be present.

The histologic findings differ somewhat comparing patients with acute onset AIH to those with an insidious presentation. Patients presenting with fulminant hepatic failure have more interface and lobular hepatitis, lobular disarray, hepatocyte necrosis, central necrosis and submassive necrosis, but less fibrosis and cirrhosis compared to patients presenting with a more chronic course[1,2]. Steatosis occurs in a minority of patients, although, given the increasing prevalence of diabetes, dyslipidemia and obesity in many parts of the world, non-alcoholic fatty liver disease may be seen more often accompanying AIH. Whether the co-morbidity of steatosis and/or steatohepatitis accelerate progression of disease in AIH is unknown. The prevalence of cirrhosis in patients ≥ 60 years at presentation was found to be higher than that in patients ≤ 30 years; when comparing groups of patients ≥ 60 years with those < 60 years, however, no differences were found[2,3]. In patients with a spontaneous or pharmacologically-induced remission, histologic findings may revert to normal; inflammation
Table 1  Histologic differential diagnosis of chronic hepatitis

<table>
<thead>
<tr>
<th>Histologic differential diagnosis</th>
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<tbody>
<tr>
<td>Autoimmune liver disease</td>
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<tr>
<td>Autoimmune hepatitis</td>
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<tr>
<td>Primary biliary cirrhosis</td>
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<tr>
<td>Primary sclerosing cholangitis</td>
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<td>Variant syndromes</td>
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<tr>
<td>Chronic viral hepatitis</td>
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<tr>
<td>Chronic hepatitis B</td>
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<tr>
<td>Chronic hepatitis C</td>
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<tr>
<td>Chronic hepatitis delta</td>
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<tr>
<td>Chronic hepatitis due to other viruses</td>
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<tr>
<td>Chronic drug-induced hepatitis</td>
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<tr>
<td>Alpha-antitrypsin deficiency</td>
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<tr>
<td>Wilson’s disease</td>
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<tr>
<td>Granulomatous hepatitis</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Graft-versus-host disease</td>
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<tr>
<td>Alcoholic steatohepatitis</td>
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<tr>
<td>Nonalcoholic steatohepatitis</td>
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may be confined to portal areas; cirrhosis may become inactive; and fibrosis may regress or disappear[16].

CLASSIFICATION

The most commonly accepted classification of AIH is based on patterns of circulating antibodies, although there is little evidence to support a role for these antibodies in pathogenesis (Table 2).

Type 1 AIH is most frequently characterized by antinuclear antibody (ANA), smooth muscle antibody (SMA) and antiatin antibody (AAA). Titters of significance vary depending on the autoantibody in question and assays employed[9]. Antititin (IgG anti F actin) antibodies measured by ELISA appear to be more sensitive than SMA measured by immunofluorescence[6,7].

The identification of other circulating autoantibodies, in particular anti-soluble liver antigen/liver-pancreas antigen (anti-SLA/LP) and atypical perinuclear anticytoplasmic antibody (pANCA) are sometimes helpful in diagnosing type 1 disease. Anti-SLA/LP is the most specific autoantibody detected in type 1 AIH but is found in only 10%-30% of type 1 AIH. Atypical pANCA is non-specific, but commonly present. Antimitochondrial antibodies (AMA) occur infrequently in type 1 AIH. At times AMA may be the sole antibody present and identify an entity sometimes referred to as AMA-positive AIH or the overlap syndrome[7].

Anti-liver/kidney microsome -1 (ALKM-1) and anti-liver cytosol-1 (ALC-1) antibodies occurring alone or together characterize type 2 AIH. Anti-liver cytosol-1 generally occurs in conjunction with anti-liver/kidney microsome-1, but may be the sole autoantibody[7].

Type 1 AIH in Caucasians is associated with the HLA-DR3 serotype, which is found in linkage disequilibrium with HLA-B8 and HLA-A1 in and HLA-DR3-negative patients with HLA-DR4. HLA-DR3-associated disease is more commonly found in patients ≤ 40 years at presentation[2]. In Japan, where HLA-DR3 is rare, the primary association is with HLA-DR4. Polymerase chain reaction studies genotyping for HLA-DRB, DQA and DQB have confirmed the serologic findings. In children, type 1 AIH is commonly associated with the HLA-DRB1*03 and HLA-DRB1*13 alleles. Type 2 AIH has been associated with HLA-DRB1 as well as HLA-DQB1 alleles[18].

Table 2  Classification of autoimmune hepatitis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Characteristic autoantibodies</th>
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<tbody>
<tr>
<td>Type 1</td>
<td>ANA (antinuclear antibody)</td>
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<tr>
<td></td>
<td>SMA (smooth muscle antibody)</td>
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<tr>
<td></td>
<td>AAA (antiatin antibody)</td>
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<tr>
<td></td>
<td>Anti-SLA/LP (anti-soluble liver antigen/liver-pancreas antigen)</td>
</tr>
<tr>
<td></td>
<td>pANCA (atypical perinuclear antineutrophil cytoplasmic antibody)</td>
</tr>
<tr>
<td></td>
<td>AMA (antimitochondrial antibody)</td>
</tr>
<tr>
<td>Type 2</td>
<td>ALKM-1 (anti-liver/kidney microsome-1)</td>
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<tr>
<td></td>
<td>ALC-1 (anti-liver cytosol-1)</td>
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</table>

'Occurs infrequently in association with other characteristic autoantibodies. It may be the sole antibody present in AMA-negative autoimmune hepatitis, also referred to as the overlap syndrome.

CLINICAL FEATURES

Although there is a female predominance, AIH occurs in children and adults of both sexes in diverse ethnic groups worldwide. Type 2 disease, which is seen predominantly in children and young women, is rare in North America[10]. Although AIH was thought previously to be primarily a disease of the young or middle aged, it is now clear that it also occurs in the elderly (generally defined as ≥ 60 years of age)[2,11].

The heterogeneous, sometimes fluctuating nature of AIH, leads to marked variability in clinical manifestations. Presentation may be asymptomatic or insidious, with mild non-specific symptoms only or may mimic acute viral hepatitis. Rarely, AIH presents as fulminant hepatic failure[1,12]. Patients with occult disease may have undetected cirrhosis and present only when decompensation occurs. The group of patients now labeled as cryptogenic cirrhosis, includes some patients with seronegative AIH, underscoring the possibility of the absence of circulating autoantibodies in AIH[13].

Many patients with an acute presentation have histological evidence of chronic disease in the liver biopsy, indicating that they have had antecedent subclinical disease, although the duration of the subclinical anicteric course is generally difficult to ascertain. In retrospect, a fluctuating course, which had been thought to reflect some other diseases, can be identified occasionally. Long periods of subclinical disease may also ensue after presentation. Recent surveys of pregnancy in AIH have indicated that the initial presentations of AIH may not only occur during pregnancy but in the early post-partum period[13]. AIH may occur in conjunction with a variety of autoimmune disorders, including celiac disease[16,17]. Arthralgia involving small joints is common, and inflammatory arthritis may be particularly troublesome.

One presentation of AIH is in the setting of medications, or herbal agents, used for other diseases. It is not
clear if they unmask and/or induce AIH or simply result in a drug-induced hepatitis with histological findings that mimic AIH. Minocycline and, more recently, statins [18], both of which induce other autoimmune syndromes, have been considered as drugs capable of “triggering” AIH.

Complications of AIH are those seen in any progressive liver disease and primary hepatocellular carcinoma is an expected, although uncommon, consequence [2, 19, 20]. There are no established guidelines for hepatocellular carcinoma screening in cirrhosis associated with AIH. A reasonable approach would be surveillance with an ultrasound and alpha feta-protein every 6-12 mo.

**DIAGNOSIS**

In the presence of a compatible histologic picture, the diagnosis of AIH is based on characteristic clinical and biochemical findings, circulating autoantibodies and abnormalities of serum globulins. A scoring system, proposed and subsequently revised by the International AIH Group for experimental purposes to standardize diagnosis for clinical trials and population studies, has been adopted by clinicians, but found to be problematic when applied to individual patients, especially children. Thus attempts were undertaken by the International AIH Group to devise a less complicated and more accurate system for wider application in clinical practice. A scoring system, using autoantibodies, gamma globulins, absence of viral hepatitis and histologic findings from patients form a wide geographic distribution, has been proposed as a sufficiently sensitive and specific scoring system [21].

**TREATMENT OF ADULTS WITH AIH**

Appropriate management of AIH can mitigate inflammation, slow progression of disease, prolong survival, improve quality of life and delay or avoid liver transplantation. However, depending on a variety of definitions of response, success rates only range from 65% to 80%, which leaves a significant number of patients in need of other than standard treatment. Considerable challenges still exist in the areas of initial and maintenance regimens, management of relapse, non-response, drug toxicity and intolerance, and non-compliance [8, 22].

Standard medications for initial and maintenance regimens are still receiving therapy, are not necessarily predictive when drug treatment is withdrawn, the majority requires long-term maintenance therapy. In general, the response is better with milder disease. Adults with cirrhosis at the time of initial biopsy and children, particularly those with type 2 disease, rarely stay in remission when treatment is withdrawn and will almost require life-long maintenance therapy.

No firm guidelines exist for decisions regarding withdrawal of medications because histologic changes may lag biochemical responses and a quiescent histologic appearance and normal biochemical findings while patients are still receiving therapy, are not necessarily predictive of continued remission once therapy is withdrawn. Although, in the past, aminotransferase levels ≤ 2 x normal were proposed as a guideline to reducing medications, relapse has been shown to be less likely in patients who achieve normal transaminase and gamma globulin (or IgG) levels [27].

Progress in non-standard treatment for patients with inadequate responses or intolerance to therapy with glucocorticosteroids alone or in combination with azathioprine or 6-mercaptopurine (including mycophenolate mofetil, methotrexate, cyclophosphamide, tacrolimus, budesonide and ursodeoxycholic acid) has been slow. In view of the paucity of trials with non-standard forms of therapy most decisions must be based on data obtained from case reports and series of small numbers of patients. Cyclosporine, which has been used successfully in children to induce remission [28], and tacrolimus are used occasionally to treat adults [29, 30]. Off-label use of mycophenolate mofetil has become more frequently employed in intolerant or non-responsive patients [31, 32]. The roles of cyclosporine, tacrolimus, mycophenolate mofetil,

<table>
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<tr>
<th>Regimen</th>
<th>Single-drug therapy</th>
<th>Combination therapy</th>
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<tr>
<td>Initial</td>
<td>Prednisone 20-60 mg/d</td>
<td>Prednisone 15-30 mg/d and azathioprine 50-100 mg/d</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Prednisone 5-15 mg/d or azathioprine 50-200 mg/d</td>
<td>Prednisone 5-10 mg/d and azathioprine 50-150 mg/d</td>
</tr>
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</table>

Homozygosity and heterozygosity for mutations in TPMT genes occur in Caucasian and other populations, and these patients may accumulate high levels of thioguanine nucleotides in bone marrow cells. Patients who are homozygous for a mutation of TPMT are at high risk for severe toxicity, including death. Patients, who are heterozygous for the TMPT mutation, probably have an intermediate risk of toxicity. These findings have led to the suggestion that prior to placing patients on azathioprine or 6-mercaptopturine, TPMT genotyping may be appropriate. Despite reliable methods for TMPT genotyping and measurement of levels of 6-mercaptopturine metabolites, their assessment in the clinical management of AIH is not established, and must be evaluated in the context of severity of disease, as well, as advanced fibrosis has been shown to predict azathioprine toxicity [24-26].
methotrexate, cyclophosphamide, ursodeoxycholic acid, budesonide[35,36] and other immunosuppressive medications have not been established.

AIH patients who develop decompensated cirrhosis may require liver transplantation. Five-year patient and graft survivals range from 80% to 90%. As in other autoimmune liver diseases, recurrence and cirrhosis may occur after transplantation[35,36] and mandate modifications of the post-transplantation therapeutic regimens. So-called de novo AIH, also referred to as post-transplantation immune hepatitis or graft dysfunction mimicking AIH, occurs after liver transplantation for diseases other than AIH in adults and children, and may require changes in post-transplantation therapy as well[37,38].

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