

REVIEW ARTICLE

MEDICAL PROGRESS

Autoimmune Hepatitis

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AUTOIMMUNE HEPATITIS IS A GENERALLY PROGRESSIVE, CHRONIC HEPATITIS of unknown cause that occurs in children and adults of all ages. Occasionally, it has a fluctuating course, with periods of increased or decreased activity. The diagnosis is based on histologic abnormalities, characteristic clinical and biochemical findings, and abnormal levels of serum globulins, including autoantibodies. Since the first descriptions of this disorder more than 50 years ago,¹ many labels have been applied, but “autoimmune hepatitis” has been accepted as the most appropriate and least redundant term.^{2,3} Variant, overlapping, or mixed forms of autoimmune hepatitis that share features with other putative autoimmune liver diseases, primary biliary cirrhosis, and primary sclerosing cholangitis occur as well. The distinctions among these disorders at present are necessarily descriptive.

It remains important to distinguish autoimmune hepatitis from other forms of chronic hepatitis, because a high percentage of cases respond to antiinflammatory or immunosuppressive therapy, or both. Although appropriate management can prolong survival, improve the quality of life, and avoid the need for liver transplantation, considerable therapeutic challenges remain in the treatment of this disorder.⁴

PATHOGENESIS

A conceptual framework for the pathogenesis of autoimmune hepatitis postulates an environmental agent that triggers a cascade of T-cell-mediated events directed at liver antigens in a host genetically predisposed to this disease, leading to a progressive necroinflammatory and fibrotic process in the liver.

POTENTIAL TRIGGERS

The environmental agents assumed to induce autoimmune hepatitis have not been delineated but include viruses. The finding of molecular mimicry by cross-reactivity between epitopes of viruses and certain liver antigens adds credence to a hypothesis of virally triggered disease. Because the trigger or triggers of autoimmune hepatitis may be part of a so-called hit-and-run phenomenon, in which induction occurs many years before overt autoimmune disease, identifying an infectious agent may prove impossible. There has been evidence implicating measles virus, hepatitis viruses, cytomegalovirus, and Epstein-Barr virus as initiators of the disease; the most convincing evidence is related to hepatitis viruses.⁵⁻⁷

Certain drugs, including oxyphenisatin, methyldopa, nitrofurantoin, diclofenac, interferon, pemoline, minocycline, and atorvastatin, can induce hepatocellular injury that mimics autoimmune hepatitis.⁸⁻¹² It has also been suggested that herbal agents such as black cohosh and dai-saiko-to might trigger autoimmune hepatitis. Whether drugs and herbs unmask or induce autoimmune hepatitis or simply cause a drug-induced hepatitis with accompanying autoimmune features is unclear. Minocycline^{10,11}

and atorvastatin, which induce other autoimmune syndromes, have been implicated most recently as potential triggering agents of this disease.

GENETIC SUSCEPTIBILITY

Most knowledge concerning the genetics of autoimmune hepatitis comes from studies of the HLA genes that reside in the major histocompatibility complex (MHC), located on the short arm of chromosome 6. The MHC is a genetic system with extensive polymorphism. Although multiple genes are probably involved, HLA genes appear to play the dominant role in a predisposition to autoimmune hepatitis.^{13,14}

Type 1 autoimmune hepatitis, characterized by circulating antinuclear antibodies (ANA), smooth-muscle antibodies, antiactin antibodies, atypical perinuclear antineutrophilic cytoplasmic antibodies (pANCA), and autoantibodies against soluble liver antigen and liver–pancreas antigen (SLA/LP), is associated with the HLA-DR3 serotype (found in linkage disequilibrium with HLA-B8 and HLA-A1), particularly among white patients. There is an association with HLA-DR4 among patients who are HLA-DR3–negative. HLA-DR3–associated disease is more common in the early-onset, severe form of autoimmune hepatitis, which often occurs in girls and young women. In comparison, the association with HLA-DR4 is more common in adults and may be associated with an increased incidence of extrahepatic manifestations, milder disease, and a better response to corticosteroid therapy. In Japan, where HLA-DR3 is rare, the most common associated HLA locus is HLA-DR4.

The results of serotyping studies have been confirmed with the use of genotyping for HLA-DRB, DQA, and DQB with polymerase-chain-reaction techniques. A high frequency of the HLA-DRB1*0301DRB3*0101DQA1*0501DQB1*0201 haplotype (the first two elements correspond to the serologic determinants DR3 and DR52) and the HLA-DRB1*0401 allele have been observed in association with autoimmune hepatitis. In South American populations, an increased frequency of the HLA-DRB1*1301 allele was reported,^{15,16} whereas in Japan, autoimmune hepatitis has been associated with the DRB1*0405DQB1*0401 haplotype.¹⁷ In children, type 1 autoimmune hepatitis is commonly associated with the HLA-DRB1*03 and HLA-DRB1*13 alleles.

Type 2 autoimmune hepatitis, a rare disorder characterized by antibodies against liver–kidney

microsome 1 (LKM-1) and liver cytosol 1 (ALC-1), has been associated with the HLA-DRB1 and HLA-DQB1 alleles.¹⁸ HLA-DR2 appears to be protective in white northern Europeans, and a study of white Argentineans suggested that the HLA-DRB1*1302 allele is protective.^{14,15}

Susceptibility to autoimmune hepatitis has been reported to be associated with tumor necrosis factor (TNF) genes, the loci of which are in the class III region of the MHC, although this finding has been disputed.^{19,20} A polymorphism at position 308 of the TNF- α gene has been associated with susceptibility to type 1 autoimmune hepatitis in both European and North American patients, but it may simply represent linkage disequilibrium with HLA-DRB1*0301. There were no significant differences in the response to therapy between those with and those without the 308 polymorphism.¹⁹ Furthermore, this association was not present in Japanese or Brazilian patients with autoimmune hepatitis.^{17,20} Similar associations of susceptibility with polymorphisms of cytotoxic T-lymphocyte antigen 4 observed in northern European patients were not seen in Brazilian patients.^{21,22} Potential associations with loci in other chromosomes are under investigation.^{23,24}

MECHANISMS OF ABERRANT AUTOREACTIVITY

Knowledge concerning autoantigens responsible for initiating the cascades of events in autoimmune hepatitis is still rudimentary. A leading candidate for many years has been the asialoglycoprotein receptor, a liver-specific membrane protein with high levels of expression in periportal hepatocytes. Information based on the identification of SLA/LP autoantibodies and the cloning and characterization of the SLA/LP antigen, which shares some amino acid sequences with the asialoglycoprotein receptor, suggests that this 50-kD cytosolic protein may represent a relevant antigen in at least some patients with type 1 autoimmune hepatitis.^{25,26}

Evidence of an autoimmune process in the type 2 form of the disease is more compelling. The presence of immunodominant B-cell epitopes of cytochrome P-450 2D6 (CYP2D6) and evidence of cross-reactivity with homologues of different viruses suggest that relevant antigens exist within CYP2D6.²⁷

The identification of CD4+ regulatory T cells has reinvoked the concept that failure of or escape

from normal suppression of reactivity against the self has an essential role in the development of autoimmune disease. The hypothesis that this escape phenomenon occurs in autoimmune hepatitis has remained attractive and is based on early studies of immune regulation.²⁸⁻³¹ Recent experimental evidence suggests that immunoregulatory dysfunction characterized by decreased numbers of CD4+CD25+ regulatory T cells and decreased levels of scurfin, the protein product of the *FOXP3* gene that is a member of the forkhead family of transcription factors, may occur in autoimmune hepatitis.³² Such observations suggest that a decrease in the number of regulatory T cells and their ability to expand may lead to autoimmune liver disease.

CLINICAL CHARACTERISTICS

Autoimmune hepatitis is more common among women than men, but it occurs globally in children and adults of both sexes in diverse ethnic groups.^{16-18,33-41} Since chronic viral hepatitis appears to be very common, the prevalence of autoimmune hepatitis may be higher than reported because of concomitant chronic hepatitis C or B or both.³⁸

PRESENTATION

The presentation of autoimmune hepatitis is heterogeneous, and the clinical course may be characterized by periods of decreased or increased activity; thus, clinical manifestations are variable. The spectrum of presentation ranges from no symptoms to debilitating symptoms and even fulminant hepatic failure.

Patients may present with nonspecific symptoms of varying severity, such as fatigue, lethargy, malaise, anorexia, nausea, abdominal pain, and itching. Arthralgia involving small joints is common. Physical examination may reveal no abnormalities, but it may also reveal hepatomegaly, splenomegaly, jaundice, and signs and symptoms of chronic liver disease.

Patients with severe or fulminant symptoms accompanied by profound jaundice and a prolonged prothrombin time may have aminotransferase levels in the thousands.⁴² Many patients with an acute presentation have histologic evidence of chronic disease on liver biopsy, indicating that they probably have had subclinical dis-

ease for a long time. Long periods of subclinical disease may also occur after presentation.

Autoimmune hepatitis may first become evident during pregnancy or in the early postpartum period. Furthermore, postpartum exacerbations may occur in patients whose condition improved during pregnancy.⁴³⁻⁴⁵

One clue to diagnosing autoimmune hepatitis is the presence of other diseases with autoimmune features, commonly thyroiditis, ulcerative colitis, type 1 diabetes, rheumatoid arthritis, and celiac disease.^{46,47} Occasionally, circulating anti-endomysial antibodies, antiglutin antibodies, and anti-tissue transglutaminase antibodies may be found in patients with autoimmune hepatitis; this finding generally reflects the coexistence of celiac sprue and autoimmune hepatitis.

LABORATORY ABNORMALITIES

In general, aminotransferase elevations are more striking than abnormalities in bilirubin and alkaline phosphatase levels in patients with autoimmune hepatitis. Some cases, however, are characterized by cholestasis, with high levels of conjugated bilirubin and alkaline phosphatase. In such circumstances, extrahepatic obstruction and cholestatic forms of viral hepatitis, drug-induced disease, primary biliary cirrhosis, primary sclerosing cholangitis, and variant syndromes must be considered.

One characteristic laboratory feature of autoimmune hepatitis, although not invariant, is a generalized elevation of serum globulins, in particular, gamma globulin and IgG, which are generally 1.2 to 3.0 times normal. The characteristic circulating autoantibodies seen in autoimmune hepatitis include ANA, smooth-muscle antibody, antiactin antibody, SLA/LP autoantibodies, pANCA, anti-LKM-1, and anti-LC-1. Antimitochondrial antibodies are sometimes present in patients with autoimmune hepatitis. It should be noted, however, that autoantibodies are found in various liver diseases, and their presence, by itself, is not diagnostic of autoimmune hepatitis. There is little evidence that autoantibodies play a part in its pathogenesis.

CLASSIFICATION AND AUTOANTIBODIES

Classification of autoimmune hepatitis on the basis of autoantibody patterns has been helpful to clinicians (Table 1). Although the distinction was

initially based on circulating antibodies alone, other differences have become apparent. The main serologic markers of type 1 autoimmune hepatitis are ANA and smooth-muscle antibody. Titers of at least 1:80 are generally accepted as positive,³ but results vary, depending on the assays used; lower titers may signify a positive response in children. Antiactin antibodies are more specific for type 1 autoimmune hepatitis.⁴⁸ Anti-LKM-1 and anti-LC-1 characterize type 2 disease.^{18,33,34}

The identification of other circulating autoantibodies, in particular SLA/LP autoantibodies^{25,26,49} and atypical pANCA,⁵⁰⁻⁵² are sometimes helpful in diagnosing type 1 disease. SLA/LP autoantibodies are the most specific autoantibody identified in type 1 autoimmune hepatitis but is found in only 10 to 30 percent of cases. Atypical pANCA is frequently present, and on rare occasions, it occurs as an isolated autoantibody.⁵²

Anti-LKM-1 and anti-LC-1 can occur alone or together in type 2 autoimmune hepatitis.^{18,33,34,53} Anti-LKM-1, which is directed at CYP2D6, can occur in chronic hepatitis C, though the antibody response to immunodominant epitopes differs.²⁷ Anti-LC-1 generally occurs in conjunc-

tion with anti-LKM-1, but it may be the sole autoantibody.³⁴ It recognizes formiminotransferase cyclodeaminase, a liver-specific 58-kD metabolic enzyme.⁵⁴

COMPLICATIONS

The complications of autoimmune hepatitis are the same as in any progressive liver disease. Primary hepatocellular carcinoma is a known consequence of autoimmune hepatitis; in some patients, chronic hepatitis progresses to cirrhosis and, ultimately, to carcinoma. However, carcinoma occurs in association with autoimmune hepatitis less frequently than does chronic viral hepatitis.

HISTOLOGIC APPEARANCE

The histologic appearance of autoimmune hepatitis is the same as that of chronic hepatitis, and although certain changes are characteristic, no findings are specific for autoimmune hepatitis.⁵⁵ The histologic differential diagnosis of chronic hepatitis is provided in Table 2. Advances in virologic studies and refinements in cholangiographic methods have made it easier to rule out other clinical entities.

Table 1. Classification of Autoimmune Hepatitis.

Variable	Type 1 Autoimmune Hepatitis	Type 2 Autoimmune Hepatitis
Characteristic autoantibodies	Antinuclear antibody* Smooth-muscle antibody* Antiactin antibody† Autoantibodies against soluble liver antigen and liver-pancreas antigen‡ Atypical perinuclear antineutrophil cytoplasmic antibody	Antibody against liver-kidney microsome 1* Antibody against liver cytosol 1*
Geographic variation	Worldwide	Worldwide; rare in North America
Age at presentation	Any age	Predominantly childhood and young adulthood
Sex of patients	Female in approximately 75% of cases	Female in approximately 95% of cases
Association with other autoimmune diseases	Common	Common§
Clinical severity	Broad range	Generally severe
Histopathologic features at presentation	Broad range	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	Approximately 100%

* The conventional method of detection is immunofluorescence.

† Tests for this antibody are rarely available in commercial laboratories.

‡ This antibody is detected by enzyme-linked immunosorbent assay.

§ Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is seen only in patients with type 2 disease.⁴⁷

Table 2. Histologic Differential Diagnosis of Chronic Hepatitis.

Disease	Distinguishing Features*
Autoimmune hepatitis	Conspicuous plasma-cell infiltrates
Primary biliary cirrhosis	Lymphocytic and granulomatous infiltrates of bile ducts; ductopenia
Primary sclerosing cholangitis	Fibrous obliterative cholangitis; ductopenia
Autoimmune cholangitis†	Lymphocytic and granulomatous infiltrates of bile ducts; ductopenia
Chronic viral hepatitis	Ground-glass hepatocytes; immunoperoxidase staining for hepatitis B surface and core antigens in patients with chronic hepatitis B; nodular-appearing infiltrates characteristic in patients with chronic hepatitis C; steatosis possible in patients infected with hepatitis C virus genotype 3
Chronic drug-induced hepatitis	No helpful distinguishing histologic features
Alpha ₁ -antitrypsin deficiency	Intracytoplasmic globules
Wilson's disease	Heavy copper deposition
Granulomatous hepatitis	Conspicuous and frequent granulomas
Graft-versus-host disease	Lymphocytic and granulomatous infiltrates of bile ducts; ductopenia
Alcoholic steatohepatitis	Steatosis; central inflammation and fibrosis; Mallory bodies
Nonalcoholic steatohepatitis	Glycogenated nuclei; steatosis; central inflammation and fibrosis; Mallory bodies

* These histologic features may be helpful in distinguishing among the causes of chronic hepatitis. Differences in histopathological findings among the diseases may be more apparent depending on the grade and stage of disease.⁵⁵

† There is still debate as to whether this entity is antimitochondrial-antibody-negative primary biliary cirrhosis.⁵⁶

Autoimmune hepatitis is generally characterized by a mononuclear-cell infiltrate invading the limiting plate — that is, the sharply demarcated hepatocyte boundary that surrounds the portal triad and permeates the surrounding parenchyma (periportal infiltrate, also called piecemeal necrosis or interface hepatitis that progresses to lobular hepatitis). There may be an abundance of plasma cells, a finding that in the past led to the use of the term “plasma-cell hepatitis.” Eosinophils are frequently present. The portal lesion generally spares the biliary tree. Fibrosis is present in all but the mildest forms of autoimmune hepatitis. In advanced disease, the fibrosis is extensive, and with the distortion of the hepatic lobule and the appearance of regenerative nodules, it results in cirrhosis.⁵⁵ Occasionally, centrilobular lesions occur.^{42,57}

The findings in patients with acute-onset autoimmune hepatitis differ somewhat from those with an insidious presentation. Patients presenting with fulminant hepatic failure tend to have interface and lobular hepatitis, lobular disarray, and hepatocyte, central, and submassive necro-

sis. However, they have less fibrosis than patients who present with a more chronic course.⁴² Steatosis occurs in a minority of patients,⁵⁵ although nonalcoholic fatty liver disease may occur in conjunction with autoimmune hepatitis. The various histologic appearances are depicted in Figure 1.

In patients who have a spontaneous or pharmacologically induced remission, the histologic findings may revert to normal or inflammation may be confined to portal areas. In this setting, cirrhosis may become inactive and fibrosis may diminish or disappear.^{55,59-61}

DIAGNOSIS

In the presence of a compatible histologic picture, the diagnosis of autoimmune hepatitis is based on characteristic clinical and biochemical findings, circulating autoantibodies, and abnormal levels of serum globulins. Circulating antibodies are absent in about 10 percent of patients. A scoring system proposed and subsequently revised by the International Autoimmune Hepatitis Group³ to standardize the diagnosis for clinical trials and population studies has had limited

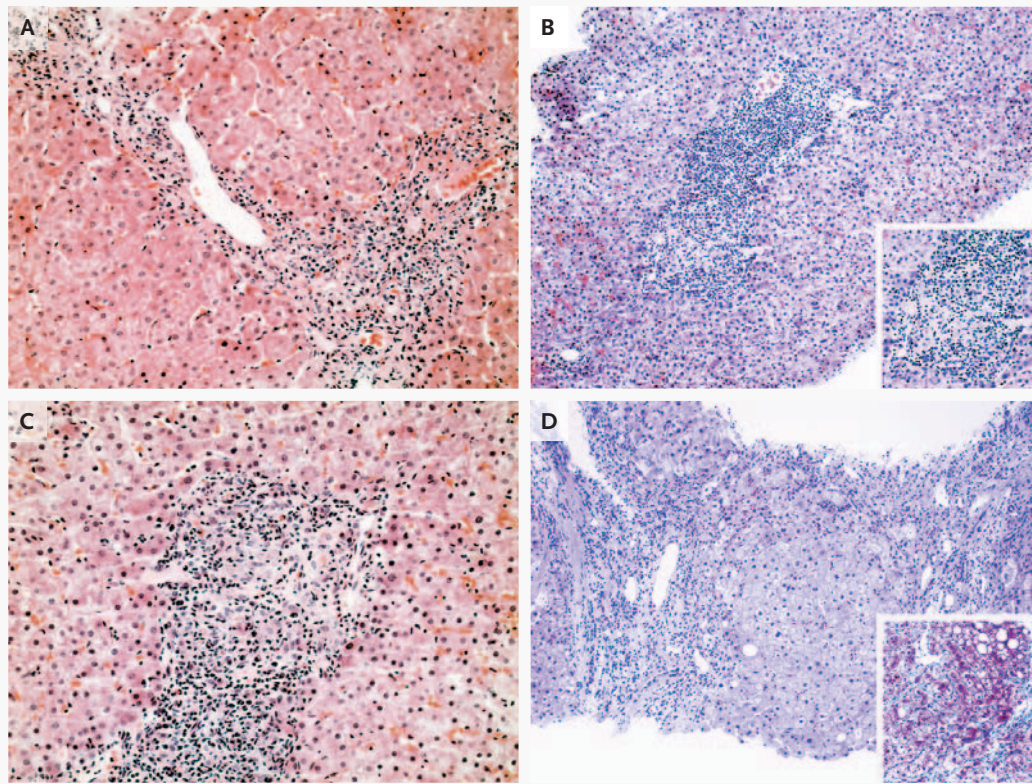


Figure 1. Photomicrographs of Liver-Biopsy Specimens from Four Patients with Autoimmune Hepatitis.

Panel A shows portal and interface hepatitis, with a mixed inflammatory infiltrate composed of lymphocytes, plasma cells, and eosinophils (hematoxylin and eosin). This specimen was obtained from a 16-year-old girl in whom autoimmune hepatitis developed while she was taking minocycline for acne. A test for antinuclear antibody was positive; tests for smooth-muscle antibody and antibodies against liver–kidney microsome 1 (LKM-1) were negative, and the IgG level was 2180 mg per deciliter. After treatment with prednisone for only two months, her aminotransferase levels became normal and prednisone was discontinued. A subsequent exacerbation was treated with prednisone for nine months. The patient completed the therapy and has remained in remission for 15 months. Panel B shows interface hepatitis, with a mixed inflammatory infiltrate composed of lymphocytes and plasma cells (hematoxylin and eosin). A granuloma, which is commonly seen in primary biliary cirrhosis but occurs occasionally in autoimmune hepatitis, is present (inset, hematoxylin and eosin). This specimen was obtained from a 44-year-old woman, who weighed 95.3 kg, with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 36. A test for smooth-muscle antibody was positive; tests for antinuclear antibody and antimitochondrial antibody were negative; the gamma globulin level was 3.2 g per deciliter. No steatosis was present in the biopsy specimen, although diabetes mellitus subsequently developed during treatment with prednisone. Panel C shows interface hepatitis with a mixed inflammatory infiltrate composed of lymphocytes, plasma cells, and eosinophils, as well as diffuse ballooning degeneration of the hepatocytes (hematoxylin and eosin). The bile ducts were heterochromatic but normal in number and not infiltrated. No granulomas were present. This specimen was obtained from a 50-year-old woman with autoimmune hepatitis of acute onset. A test for antimitochondrial antibody was positive; tests for antinuclear antibody, smooth-muscle antibody, and anti–LKM-1 were negative. The IgG level was 2580 mg per deciliter, and the peak bilirubin level was 11.3 mg per deciliter (193.2 μ mol per liter). The alkaline phosphatase level was 224 U per liter, the alanine aminotransferase level was 3400 U per liter, and the aspartate aminotransferase level was 2200 U per liter. The patient’s response to prednisone and subsequently to azathioprine therapy was typical of that seen in patients with autoimmune hepatitis. Now called “antimitochondrial-antibody–positive autoimmune hepatitis,” it is also known as the “overlap syndrome.”⁵⁸ Panel D shows cirrhosis with interface hepatitis characteristic of autoimmune hepatitis (hematoxylin and eosin). Steatosis and “chickenwire” pericentral fibrosis (inset, trichrome stain) are characteristic of nonalcoholic steatohepatitis. This specimen was obtained from a 78-year-old woman with hyperlipidemia who weighed 56.7 kg and had a body-mass index of 28. Tests for antinuclear antibody and antimitochondrial antibody were negative; a test for smooth-muscle antibody was positive. The total globulin level was 4.7 g per milliliter, and the gamma globulin level was 1.7 g per milliliter.

value and may be inaccurate when applied to individual patients, especially children. Attempts are under way to devise a less complicated and more accurate system.⁶²

VARIANT SYNDROMES

Although we have long known that the clinical, histologic, and serologic profiles of so-called overlap, mixed, or variant syndromes differ from the classic features of autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis, no consensus regarding categorization has been reached. Terms such as “overlap syndrome,” “antimitochondrial-antibody-negative primary biliary cirrhosis,” “the hepatic form of primary biliary cirrhosis,” “autoimmune cholangitis,” “autoimmune cholangiopathy,” “chronic autoimmune cholestasis,” “immunocholangitis,” “immune cholangiopathy,” and “combined hepatitic/cholestatic syndrome” have all been used to describe patients with features of both autoimmune hepatitis and primary biliary cirrhosis. The presentation of putative coincidental diseases, consecutive diseases, and evolution from one disease to another have highlighted the complexity of this issue.^{56,58,63-66}

One approach is to consider the variant syndromes of autoimmune hepatitis and primary biliary cirrhosis as part of a continuum that extends from classic autoimmune hepatitis to classic primary biliary cirrhosis. Examination of a biopsy specimen with histologic features of autoimmune hepatitis but serologic findings characteristic of primary biliary cirrhosis, such as an isolated antimitochondrial antibody directed toward enzymes in the 2-oxo acid dehydrogenase family, would

be indicative of the overlap syndrome,⁵⁸ or antimitochondrial-antibody-positive autoimmune hepatitis (Table 3). The clinical course and response to therapy in this syndrome appear to be identical to those in classic autoimmune hepatitis.

There is disagreement as to whether the variant most commonly called autoimmune cholangitis^{56,58} merely represents antimitochondrial-antibody-negative primary biliary cirrhosis (Table 3). Immunoblotting and enzyme-linked immunosorbent assays for antimitochondrial antibodies and primary biliary cirrhosis-specific antinuclear antibodies (anti-Sp100 and anti-gp210) have yielded different autoantibody profiles for the two conditions, underscoring the heterogeneity of these syndromes.⁶⁶

Identifying and classifying autoimmune hepatitis–primary sclerosing cholangitis overlap syndromes is also difficult, particularly in children.^{53,67-72} “Autoimmune sclerosing cholangitis” is the term applied to this disease in affected children and could arguably be applied to that in adults as well. Although primary sclerosing cholangitis can evolve to autoimmune hepatitis, autoimmune hepatitis more commonly evolves to autoimmune sclerosing cholangitis.⁷² Autoimmune sclerosing cholangitis cannot be diagnosed in the absence of cholangiographic abnormalities. Patients suspected of having autoimmune hepatitis who also have histologic bile-duct abnormalities, cholestatic laboratory changes (e.g., elevations of alkaline phosphatase, γ -glutamyltransferase, or both), pruritus, inflammatory bowel disease, or loss of response to antiinflammatory or immunosuppressive therapy may have autoimmune sclerosing cholangitis.

Table 3. Characteristics of Autoimmune Hepatitis–Primary Biliary Cirrhosis Variant Syndromes.

Characteristic	Overlap Syndrome*	Autoimmune Cholangitis†
Antinuclear antibody	Absent	Generally present
Smooth-muscle antibody	Absent	Generally present
Antimitochondrial antibody	Present	Absent
Biochemical cholestasis†	Absent	Present
Histologic evidence of bile-duct abnormalities	Absent	Present
Cholangiographic abnormalities	Absent	Absent
Responsiveness to immunosuppression	Present	Variable

* This syndrome is also called antimitochondrial-antibody-positive autoimmune hepatitis.⁵⁸ There is debate as to whether autoimmune cholangitis and antimitochondrial-antibody-negative primary biliary cirrhosis represent different entities.^{56,63-66}

† This condition is characterized by elevated levels of serum alkaline phosphatase, γ -glutamyltransferase, or both.

TREATMENT

In the 1970s, evidence that mercaptopurine and azathioprine were effective in treating autoimmune diseases, together with controlled studies of corticosteroids, led to the opinion that autoimmune hepatitis is a treatable disease. Antiinflammatory or immunosuppressive therapy has been a mainstay in the treatment of both type 1 and type 2 disease. Depending on the definition of a response, therapy is reported to be successful in 65 to 80 percent of cases, which indicates that a substantial percentage of patients require therapy beyond standard treatment. Current response rates appear better than those in early trials, presumably because earlier trials involved more patients with severe disease and antedated the present ability to test for chronic viral hepatitis B and C. Ten-year survival rates (with the end point being death or transplantation) among treated patients are now considered to exceed 90 percent; but the 20-year survival rate may be less than 80 percent among patients without cirrhosis and less than 40 percent among those with cirrhosis at presentation.⁷³ Once the disease is in remission, maintenance therapy with azathioprine alone is successful in approximately 80 percent of patients.⁷⁴

Response to treatment is helpful in establishing the diagnosis of autoimmune hepatitis, but the response rate to standard therapy is not 100 percent. Thus, a lack of response cannot rule out this diagnosis. Moreover, not all patients receive treatment, and the prescribed doses of prednisone and azathioprine or mercaptopurine vary. In addition, other diseases, including some variant syndromes, may respond to corticosteroids.

Progress in the medical management of autoimmune hepatitis has been slow. Considerable challenges still exist in the areas of initial and maintenance regimens, management of relapse, management of a lack of response to therapy, drug toxicity and intolerance, noncompliance, and treatment during pregnancy. Although guidelines for the treatment of autoimmune hepatitis have been published by the American Association for the Study of Liver Diseases, these are meant to be flexible.⁷⁵ The heterogeneity of autoimmune hepatitis underscores the need for individualized therapy in adults and children.^{4,75,76}

STANDARD TREATMENT

Initial treatment with prednisone (or prednisolone) alone or in combination with azathioprine

should be instituted in nearly all patients in whom the histologic findings include interface hepatitis, with or without fibrosis or cirrhosis. The magnitude of aminotransferase and gamma globulin elevations does not necessarily correlate with the histologic extent of injury and provides little help with respect to the initiation of treatment. In patients with only portal inflammation, the decision to treat is often determined on the basis of the levels of aminotransferase, gamma globulin, or both; the symptoms; or the combination of levels and symptoms. Asymptomatic patients and those with portal inflammation without fibrosis may be followed without treatment, but their clinical status, including the findings on liver biopsy, should be monitored carefully for evidence of progression of disease, since the activity of autoimmune hepatitis sometimes fluctuates. Initial treatment consists of combination therapy in order to avoid or mitigate the side effects of corticosteroid treatment. An alternative approach is to wait until remission is achieved before corticosteroid-sparing treatment with azathioprine or mercaptopurine is initiated (Table 4).

Adverse effects or intolerance of azathioprine, mercaptopurine, or both is an issue of particular concern.^{79,80} Azathioprine is a prodrug of mercaptopurine. The methylation of mercaptopurine and 6-thioguanosine 5'-monophosphate is catalyzed by thiopurine methyltransferase, which is encoded by highly polymorphic genes. Patients who are homozygous for a mutation of thiopurine methyltransferase associated with low enzyme activity are at high risk for severe complications, including death. Patients who are heterozygous for a mutation of thiopurine methyltransferase probably are at intermediate risk. Given these findings, some investigators have suggested performing thiopurine methyltransferase genotyping before prescribing azathioprine or mercaptopurine. However, some patients who cannot tolerate azathioprine appear to be able to tolerate mercaptopurine without side effects, indicating that azathioprine-induced toxicity is not simply due to a deficiency of thiopurine methyltransferase.⁸¹ Despite the availability of reliable methods for genotyping thiopurine methyltransferase and determining levels of mercaptopurine metabolites, their use in the clinical management of autoimmune hepatitis is not established.^{79,80}

In general, a patient's progress is followed by monitoring levels of serum aminotransferases

Table 4. Drugs Used in the Treatment of Autoimmune Hepatitis in Adults and Children.

Drug	Initial Therapy	Maintenance Therapy	Comments
Prednisone or prednisolone	Used as monotherapy in adults (20–60 mg/day) and children (1–2 mg per kilogram of body weight/day); also used in combination therapy in adults (15–30 mg/day) and children (1–2 mg/kg/day) with azathioprine or mercaptopurine	Used as monotherapy in adults (5–15 mg/day) and children (1 mg/kg/day); also used in combination therapy in adults (5–10 mg/day) and children (0.5–1.0 mg/kg/day) with azathioprine or mercaptopurine	Relatively contraindicated in patients with osteoporosis, diabetes mellitus, glaucoma, cataracts, arterial hypertension, major depression, and femoral avascular necrosis; reduced doses may work; use of budesonide under investigation ⁷⁷
Azathioprine	Used in combination with prednisone or prednisolone in adults (50–100 mg/day) and children (1.5–2.0 mg/kg/day)	Used as monotherapy in adults (50–200 mg/day) and children (1.5–2.0 mg/kg/day); also used in combination therapy in adults (50–150 mg/day) and children (1.5–2.0 mg/kg/day)	Contraindicated in patients with homozygous thiopurine methyltransferase deficiency; relatively contraindicated in patients with heterozygous thiopurine methyltransferase deficiency, cancer, or cytopenia, and pregnant patients
6-Mercaptopurine	May be substituted for azathioprine in combination therapy in adults (25–100 mg/day) and children (0.75–1.0 mg/kg/day)	Used as monotherapy in adults (25–100 mg/day) and children (0.75–1.0 mg/kg/day); also used in combination therapy in adults (25–100 mg/day) and children (0.5–1.0 mg/kg/day)	Contraindicated in patients with homozygous thiopurine methyltransferase deficiency; relatively contraindicated in patients with heterozygous thiopurine methyltransferase deficiency, cancer, or cytopenia, and pregnant patients
Cyclosporine	Sometimes used as monotherapy in children ⁷⁸ ; sometimes used as an alternative drug in adults with treatment-refractory disease	Sometimes used as an alternative drug in adults with treatment-refractory disease	Once remission achieved in children, maintenance therapy initiated with a combination of prednisone and azathioprine ⁷⁸ ; role of tacrolimus in place of cyclosporine not established
Mycophenolate mofetil	Sometimes used in patients with treatment-refractory disease or in patients with adverse drug reactions to or intolerance of azathioprine, mercaptopurine, or both	Sometimes used in patients with treatment-refractory disease or in patients with adverse drug reactions to or intolerance of azathioprine, mercaptopurine, or both	Role of mycophenolate mofetil, methotrexate, and cyclophosphamide not established
Ursodiol	Sometimes used in combination with prednisone, azathioprine, or both	Sometimes used in combination with prednisone, azathioprine, or both	Role of ursodiol not established

and circulating globulins (total or gamma globulin, or both, with or without IgG). The histologic response typically lags behind the biochemical response, and a clinical remission does not necessarily mean that there is histologic evidence of resolution. Reasonable intervals for repeated liver biopsy appear to be one year after levels of aspartate aminotransferase and alanine aminotransferase have become normal or approximately two years after presentation.

Although some patients remain in remission after drug treatment is withdrawn, most require long-term maintenance therapy. In general, pa-

tients with milder disease have a better response. Adults and children with cirrhosis at the time of the initial biopsy, particularly children with type 2 disease, rarely stay in remission when treatment is withdrawn. Thus, lifelong maintenance therapy is generally indicated in such cases. The wisdom of the administration of azathioprine alone or as a corticosteroid-sparing agent should be approached by weighing the side effects of long-term corticosteroid use against those of long-term azathioprine use; patients treated with azathioprine alone frequently have arthralgia.⁷⁴

In the presence of severe side effects from the

use of corticosteroids, partial control of the autoimmune hepatitis in patients who have multiple relapses may be preferable and can be achieved with doses of prednisone lower than conventional doses.⁸² Some patients remain in remission for months or years before the disease flares. These patients may not need antiinflammatory therapy for long periods, but their condition should still be monitored every three to six months, so that therapy can be reinstated if the disease becomes active.

OTHER THERAPY

Decisions regarding the use of other medications must be based on meager data obtained from case reports and series of small numbers of patients. Cyclosporine appeared effective in a group of adult patients who were corticosteroid-resistant.⁸³ A regimen of cyclosporine for six months followed by the administration of prednisone and azathioprine was reported as successful in inducing remission in children.⁷⁸ Limited data are available concerning the use of tacrolimus,⁸⁴ methotrexate,^{85,86} cyclophosphamide,⁸⁷ ursodiol,⁸⁸ budesonide,⁷⁷ and mycophenolate mofetil⁸⁹ (Table 4).

TREATMENT OF VARIANT SYNDROMES

No trials have been performed that could provide a basis for the treatment of variant syndromes. The treatment for antimitochondrial-antibody-positive autoimmune hepatitis is identical to that outlined for classic autoimmune hepatitis. Reports concerning the effectiveness of corticosteroid therapy in other autoimmune hepatitis—primary biliary cirrhosis variant syndromes have been conflicting. Although ursodiol, the mainstay of treatment for primary biliary cirrhosis,⁹⁰ may reduce levels of liver enzymes, it is not known whether the drug mitigates the necroinflammatory process or retards the progression of disease in these variant syndromes.^{63,65} A therapeutic trial of corticosteroids with or without ursodiol, especially in patients with few cholestatic features, no or minimal bile-duct changes on biopsy, or both, may be required before a long-term regimen can be devised.

Limited success has been achieved with variant forms of autoimmune hepatitis—primary sclerosing cholangitis in adults with use of a regimen combining corticosteroids, azathioprine, and ursodiol.⁶⁹ Present therapeutic options include

immunosuppression, ursodiol, or both, but data regarding efficacy are conflicting.⁶⁷⁻⁶⁹

LIVER TRANSPLANTATION

Liver transplantation is required in patients who are refractory to or intolerant of immunosuppressive therapy and in whom end-stage liver disease develops. The survival rate among patients and grafts 5 years after liver transplantation is approximately 80 to 90 percent, the 10-year survival rate is approximately 75 percent, and the recurrence rate has been reported to be as high as 42 percent.⁹¹⁻⁹⁵ Histologic evidence of recurrence may precede clinical and biochemical evidence of recurrence.⁹⁵ Recurrence may be related to the immunosuppressive regimen used after transplantation.

Autoimmune hepatitis has been reported after liver transplantation for other diseases in adults and children,⁹⁶⁻¹⁰⁰ although the use of the term in this setting has been questioned. It has been suggested that alternative nomenclature such as “post-transplant immune hepatitis” or “graft dysfunction mimicking autoimmune hepatitis” may be more appropriate.⁹⁷ This entity, however, appears to respond well to corticosteroid treatment, thus avoiding graft rejection and the need for another transplantation and improving long-term survival.⁹⁹

SUMMARY

Autoimmune hepatitis is a generally progressive, chronic disease with occasionally fluctuating activity that occurs worldwide in children and adults. Although the cause of autoimmune hepatitis is unknown, aberrant autoreactivity is thought to have a role in its pathogenesis. The diagnosis is based on histologic changes, characteristic clinical and biochemical findings, circulating autoantibodies, and abnormal levels of serum globulins. Variant forms of autoimmune hepatitis share features with other putative autoimmune liver diseases, primary biliary cirrhosis, and primary sclerosing cholangitis. Despite its clinical heterogeneity, autoimmune hepatitis generally responds to antiinflammatory or immunosuppressive treatment, or both. Lifetime maintenance therapy may be required, especially for patients with type 2 autoimmune hepatitis and those who have cirrhosis at presentation. Liver transplantation has been

successful in patients who have no response to medical management.

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