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Bruce A. Luxon MD, PhD

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Autoimmune hepatitis

Making sense of all those antibodies

Bruce A. Luxon, MD, PhD

PREVIEW

In many patients with chronic hepatitis, no obvious cause can be found. Some of these patients have an overactive immune system reaction that is responsible for the chronic inflammation. Diagnosis can be difficult because autoantibodies and other typical features of autoimmunity are not present in all cases. In this article, Dr Luxon provides a roadmap through the maze of antibodies that are involved in autoimmune hepatitis and discusses current treatment options and evaluation of response to medical therapy.

Autoimmune hepatitis is an idiopathic hepatitis characterized by histologic evidence of chronic liver inflammation, autoantibodies, and increased serum levels of γ-globulins.[1] The clinical manifestations of the disease have been well characterized since its initial description by Waldenström in 1950. Surprisingly, the clinical presentation and understanding of this disease have remained essentially unchanged in the last 50 years. The purpose of this article is to provide a brief summary of the diagnostic criteria for autoimmune hepatitis, emphasizing new information about autoantibodies and autoantigens, and to provide an algorithmic approach to initial treatment.

Diagnostic considerations

Like many other autoimmune diseases, autoimmune hepatitis has no pathognomonic feature. The diagnosis requires the presence of typical features and the exclusion of other conditions (table 1).[2] The clinical features may be suggestive of autoimmune hepatitis or of another condition that can cause hepatitis. The conditions that are most likely to confuse diagnosis are Wilson's disease, chronic viral hepatitis (especially hepatitis C), and drug-induced hepatitis.

A scoring system for the quantitative diagnosis of autoimmune hepatitis has been proposed by the International Autoimmune Hepatitis Group (table 2).[3] In this system, a patient is evaluated on the basis of a number of biochemical, epidemiologic, and clinical markers before treatment, and a pretreatment score is calculated. The score can be modified by response to treatment and allows appropriate diagnosis in patients with discrepant features. High scores (>15) before corticosteroid treatment are consistent with a "definite" diagnosis of autoimmune hepatitis. A definite diagnosis after treatment requires a score higher than 17. Patients with a score of less than 10 are unlikely to have autoimmune hepatitis.

The scoring system was originally designed to aid in the selection of homogeneous groups of patients

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Table 1. Features of autoimmune hepatitis required or excluded for a definite diagnosis

Criteria	Diagnostic features		
	Clinical	Laboratory	Histologic
Inclusion	Female predominance	Predominant transaminase abnormality	Interface hepatitis with or without lobular hepatitis or bridging necrosis
	Acute, fulminant, or indolent onset	γ-Globulin and/or IgG level >1.5 × normal	
	Concurrent immune disease(s)	ANA and/or ASMA >1:80	
Exclusion	Blood transfusion or exposure	Active infection with hepatitis A, B, or C virus	Bile duct lesions
	Hepatotoxic medication	Epstein-Barr virus	Granulomas
	Excessive alcohol use (>35 g/day in men, >25 g/day in women)	Cytomegalovirus	Copper or iron accumulation
		α_1-Antitrypsin deficiency	Any lesions suggestive of another disease

ANA, antinuclear antibodies; ASMA, anti-smooth-muscle antibodies; IgG, immunoglobulin G.

for research purposes. However, it has also proved valuable in routine clinical practice, especially for atypical or overlapping cases. The system has been validated in several large patient populations in the United States, Europe, and Asia. Its sensitivity for probable or definite autoimmune hepatitis ranges from 97% to 100%, and its specificity for excluding autoimmune hepatitis in patients with chronic hepatitis C is 66% to 92%.[4] However, the ability of the scoring system to differentiate autoimmune hepatitis from a variety of cholestatic syndromes is not nearly as good. In one study,[5] patients with cholestatic features due to primary sclerosing cholangitis were especially likely to be erroneously categorized as having autoimmune hepatitis.

Liver biopsy remains essential to diagnosis and evaluation of disease severity in patients with autoimmune hepatitis. The degree of elevation of transaminase levels is not predictive of the histologic pattern of injury or the extent of fibrosis. Liver biopsy is also key in diagnosis and treatment of variant syndromes of autoimmune hepatitis and exclusion of concomitant liver diseases, such as nonalcoholic fatty liver disease, and drug toxicity.

A liver biopsy specimen showing the typical interface hepatitis is presented in figure 1. Interface hepatitis consists of a lymphoplasmacytic inflammatory infiltrate that may extend from the portal tract into the lobule. Plasma cells are classically thought to be a hallmark of the disease, although 34% of patients with autoimmune hepatitis have few or no plasma cells.[6] A rosette of hepatocytes (figure 2) is a collection of swollen hepatocytes separated from other damaged hepatocytes by inflammation and collapsed

Bruce A. Luxon, MD, PhD

Dr Luxon is associate professor, division of gastroenterology and hepatology, and director, GI fellowship training program, Saint Louis University, St Louis.

Correspondence: Bruce A. Luxon, MD, PhD, 3635 Vista at Grand, GI Division, 9S FDT, St Louis, MO 63110-0250. E-mail: luxonba@slu.edu.

Table 2. Diagnostic scoring system for atypical autoimmune hepatitis in adults

Category	Factor	Score
Sex	Female	+2
Ratio of ALP to AST or ALT	>3	−2
	<1.5	+2
γ-Globulin or immunoglobulin G level (times above upper limit of normal)	>2.0	+3
	1.5-2.0	+2
	1.0-1.5	+1
	<1.0	0
ANA, ASMA, or anti-LKM1 titers	>1:80	+3
	1:80	+2
	1:40	+1
	<1:40	0
Antimitochondrial antibodies	Positive	−4
Viral markers of active infection	Positive	−3
	Negative	+3
Hepatotoxic drugs	Yes	−4
	No	+1
Alcohol consumption	<25 g/day	+2
	>60 g/day	−2
Concurrent immune disease	Any nonhepatic disease of an immune nature	+2
Other autoantibodies*	Anti-SLA/LP, actin, LC1, pANCA	+2
Histologic features	Interface hepatitis	+3
	Plasma cells	+1
	Rosettes	+1
	None of the above	−5
	Biliary changes†	−3
	Atypical features‡	−3
Human leukocyte antigen	DR3 or DR4	+1
Treatment response	Remission alone	+2
	Remission with relapse	+3
Pretreatment score	Definite diagnosis	>15
	Probable diagnosis	10-15
Posttreatment score	Definite diagnosis	>17
	Probable diagnosis	12-17

ALP, alkaline phosphatase; ALT, alanine transaminase; ANA, antinuclear antibodies; anti-LKM1, antibodies to liver-kidney microsome type 1; anti-SLA/LP, antibodies to soluble liver antigen and liver-pancreas antigen; ASMA, anti-smooth-muscle antibodies; AST, aspartate transaminase; LC1, liver cytosol type 1; pANCA, perinuclear antineutrophil cytoplasmic antibodies.

*Unconventional or generally unavailable antibodies associated with liver disease include pANCA, anti-SLA/LP, and antibodies to actin, asialoglycoprotein receptor, and LC1.

†Includes destructive cholangitis, nondestructive cholangitis, and ductopenia.

‡Includes steatosis, iron overload consistent with genetic hemochromatosis, alcoholic hepatitis, viral features (eg, ground-glass hepatocytes), and inclusions (cytomegalovirus, herpes simplex).

Adapted from Alvarez et al.[3]

stroma. These rosettes are often found in conjunction with portal plasma cell infiltration.

Traditional autoantibodies

Autoimmune hepatitis is traditionally associated with three antibodies: antinuclear antibodies (ANA), anti-smooth-muscle antibodies (ASMA), and antibodies to liver-kidney microsomes (anti-LKM). These three antibodies are the main ones that define autoimmune hepatitis, and they also may serve as a means of serologic subclassification of autoimmune hepatitis. The presence of these antibodies should be determined in all patients in whom autoimmune hepatitis is suspected.

Antinuclear antibodies

ANA are common markers of immune-mediated disease in humans and are the traditional markers of autoimmune hepatitis. They are present in two thirds of patients with the disease. Most commonly, the determination of ANA is performed by indirect immunofluorescence. A homogeneous or speckled immunofluorescence pattern is typical. Despite intensive research, the particular nuclear targets of ANA in autoimmune hepatitis remain uncertain. Proposed targets include the centromere, ribonuclear proteins, and ribonucleoprotein complexes. None of these antigens are associated with a specific pattern on immunofluorescence.

In diagnosis of autoimmune hepatitis, the specific molecular targeting of the antibody does not connote

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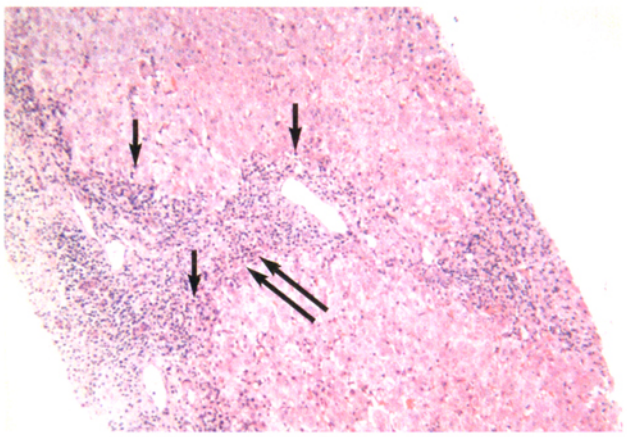

Figure 1. Photomicrograph of low-power view highlights marked portal inflammation characteristic of most cases of autoimmune hepatitis. The majority of cells in the infiltrate are plasma cells (single arrows); interface activity (double arrows) is severe.

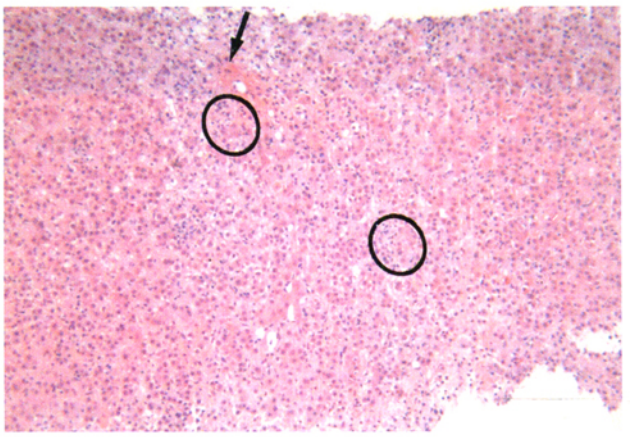

Figure 2. Photomicrograph shows abnormal hepatic cord architecture due to extensive hepatitic rosetting (ovals). Note focal central necrosis (arrow).

Figures 1 and 2 courtesy of E. M. Brunt, MD, Saint Louis University, St Louis.

additional information to increase diagnostic precision. ANA occur in high titers, usually exceeding 1:160. However, the titer does not correlate with disease stage, activity, or prognosis.[7] These antibodies can also be found in other hepatitic and cholestatic liver diseases, including primary biliary cirrhosis, primary sclerosing cholangitis, chronic viral hepatitis, drug-induced hepatitis, nonalcoholic steatohepatitis, and alcoholic liver disease.

Anti-smooth-muscle antibodies

These antibodies are traditionally found in autoimmune hepatitis and are directed against cytoskeletal proteins, including actin, troponin, tubulin, vimentin, desmin, and skeletin. ASMA are present in 87% of patients with the disease and are accompanied by ANA in 54% of patients.[7] They are not specific for autoimmune hepatitis; rather, they occur in other liver diseases as well as various infectious and rheumatologic disorders. ASMA are detected with immunofluorescence using murine stomach and kidney. Antibody titer does not correlate with disease course or prognosis, and titers can change dramatically over time in individual patients.[7]

Microsomal antibodies

Autoantibodies directed against the cytochrome enzymes are found in patients who typically do not have antibodies against smooth-muscle or nuclear antigens. These antibodies to liver-kidney microsomes (anti-LKM) are directed against specific members of the cytochrome P-450 system, including 2D6, 2C9, 2A6, and 1A2.[8] Anti-LKM are rare in the United States and are found in less than 1 in 25 adults with autoimmune hepatitis. In Europe, they are found in pediatric patients as well as in up to 20% of affected adults. Although the cause of these geographic differences is unknown, genetic differences in the immune response to a particular target antigen have been suggested.[9]

Anti-LKM also occur in patients who have drug-induced hepatitis. In such patients, drug-metabolizing

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enzymes may create reactive metabolites, which cause the immune system to form autoantibodies. Responsible agents include halothane (Fluothane), dihydralazine, and anticonvulsive agents.

Subtypes of autoimmune hepatitis

Different forms of autoimmune hepatitis are defined on the basis of the presence of specific antibodies. Type 1 (classic) autoimmune hepatitis is the most common and the predominant form in the United States. Patients with type 1 autoimmune hepatitis have either ANA or ASMA. The age distribution is bimodal: teenagers and adults aged 50 to 70 years are most commonly affected. In contrast, type 2 autoimmune hepatitis is rare in the United States and primarily affects young children. Patients with type 2 autoimmune hepatitis have anti-LKM; by definition, ANA and ASMA are absent. Type 3 autoimmune hepatitis is characterized by antibodies to soluble liver antigen (discussed later) or liver-pancreas antigen and has a bimodal age distribution similar to that of type 1 disease.

Nontraditional autoantibodies

A variety of nontraditional autoantibodies and autoantigens are involved in autoimmune hepatitis. Although specific laboratory tests are not currently universally available, several research laboratories are actively studying these factors in hopes of providing improved understanding of the origin of and potential therapies for autoimmune hepatitis. Antibodies against the asialoglycoprotein receptor (ASGPR), soluble liver and liver-pancreas antigens, and liver cytosol have been studied.

ASGPR antibodies

ASGPR is a glycoprotein that exists only on the cell membrane of hepatocytes. An antibody against ASGPR (anti-ASGPR) occurs in 88% of patients with autoimmune hepatitis.[10] However, this antibody is not specific and is also found in patients with chronic hepatitis B, alcoholic liver disease, and primary biliary cirrhosis. In contrast to other autoantibodies, the presence of antibodies to ASGPR seems to correlate with histologic activity and the response to corticosteroid treatment.

Soluble liver antigen antibodies

Autoantibodies against soluble liver antigen and liver-pancreas antigen (anti-SLA/LP) show a high specificity for autoimmune hepatitis. However, they are detectable in only 10% to 30% of patients with the disease. They appear to be directed against a 50-kd cytosolic protein involved in the selenocysteine pathway.[11] Anti-SLA/LP have been associated with HLA-DR3 antigen and a higher rate of relapse after corticosteroid therapy. Several studies have suggested that patients with anti-SLA/LP have a more severe course of autoimmune hepatitis, although the exact function and role of this autoantibody remain unclear.[11]

Antibodies to liver cytosol type 1

Antibodies to liver cytosol type 1 (anti-LC1) occur more frequently in younger patients and are rare in patients older than 40 years. Also, they are more common in patients who have anti-LKM antibodies. In addition to occurring in autoimmune hepatitis, they are seen in chronic hepatitis C and primary sclerosing cholangitis. As with anti-ASGPR, the presence of anti-LC1 autoantibodies appears to correlate with disease activity.[12]

Who should be treated?

As with many other chronic liver diseases, treatment is not mandated in every case of autoimmune hepatitis. Careful balancing between the benefits and risks of therapy is needed to help select patients who are most likely to benefit from treatment. In addition,

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knowledge of the natural history of autoimmune hepatitis can help predict which patients may progress to end-stage liver disease despite appropriate therapy.

As with many other chronic liver diseases, treatment is not mandated in every case of autoimmune hepatitis.

The natural history of autoimmune hepatitis has been characterized in several retrospective and prospective studies. A series of sentinel reports from the Mayo Clinic, Rochester, Minnesota,[13] showed that patients with aspartate transaminase levels greater than 10 times normal, or aspartate transaminase levels greater than five times normal with a twice-normal elevation of γ-globulin levels, had a 3-year mortality rate of 50% and a 10-year mortality rate of 90%. On the basis of these dismal survival rates, treatment is clearly indicated in patients with severe hepatitis. In addition, histologic evidence of bridging necrosis or multilobular necrosis on a pretreatment liver biopsy is associated with a rapid progression to cirrhosis within 5 years.

Patients with only mild or moderate elevation of transaminase levels, even in combination with γ-globulin abnormalities, have a 10-year life expectancy of higher than 80%. Similarly, patients with mild changes on liver biopsy (eg, mild interface hepatitis) have a normal 5-year survival rate and a 10-year progression to cirrhosis of less than 10%. In these patients, the decision to treat is more difficult and needs to include evaluation of subjective symptoms, such as myalgias and fatigue.

Patients with compensated cirrhosis may still benefit from therapy. A 3- to 6-month treatment trial may be beneficial in patients whose biopsy results show significant inflammatory activity. Such patients are more likely to have drug-related complications than those without cirrhosis.[14] Established fibrosis or cirrhosis is unlikely to resolve even with therapy. However, treatment may delay or obviate liver transplantation. In contrast, patients with decompensated liver disease due to autoimmune hepatitis do not usually benefit from corticosteroid therapy. These patients should be considered for orthotopic liver transplantation.

Table 3. Suggested doses for initial treatment of type 1 autoimmune hepatitis

Time	Combination therapy*		Steroids alone†
	Prednisone (mg/day)	Azathioprine (mg/day)	Prednisone (mg/day)
Week 1	30	50	60
Week 2	20	50	40
Week 3	15	50	30
Week 4	10	50	30
Until clinical end point reached	10	50	20

*Preferred initial therapy.

†Should be used in patients with severe cytopenia or a concurrent neoplasm, those who are pregnant or wish to become pregnant, and those who have known intolerance for azathioprine.

Medical therapy

Steroid-based treatment regimens are the mainstay of therapy and are successful in causing clinical, biochemical, and histologic remission. Three controlled clinical trials[13-15] have demonstrated that treatment with prednisone alone or in combination with azathioprine enhances immediate survival. Combination therapy is preferred because of a lower frequency of corticosteroid-induced side effects.[15] Nearly all of the controlled trials regarding autoimmune hepatitis

have been done in patients with type 1 disease.

A suggested treatment schedule is shown in table 3. Most experts agree that combination treatment is preferred initially for type 1 autoimmune hepatitis.[16] On the basis of theoretical considerations, some investigators have suggested that prednisolone should be used in place of prednisone in patients with advanced cirrhosis, because of the effect of impaired liver function on conversion of prednisone to prednisolone. However, even in advanced cirrhosis, conversion of prednisone to prednisolone is sufficient to achieve a good treatment response.[17] Other modifications of the regimen shown in table 3 that have been studied include administering prednisone on alternate days or modifying the dose on the basis of sex, age, or body weight. However, studies in treatment-naive persons have failed to document that such modifications are clinically significant.

Evaluation of treatment response

The response to immunosuppressive therapy is determined on the basis of clinical, biochemical, and histologic factors. Conventional wisdom suggests that failure to normalize serum transaminase or γ-globulin levels implies that autoimmune hepatitis may be refractory to therapy. However, the converse is not generally true. A substantial proportion of patients who normalize serum transaminase levels may continue to have ongoing active hepatitis involving inflammation and fibrosis. An important caveat is that histologic improvement may lag behind clinical and laboratory improvement by as much as 6 months. Therefore, a second liver biopsy should be considered only after that time to ensure adequate histologic resolution of the disease process. A proposed algorithm for treatment of type 1 autoimmune hepatitis is shown in figure 3.

Use of liver biopsy results to determine treatment end points on the basis of histologic features remains controversial. One end point that has been suggested

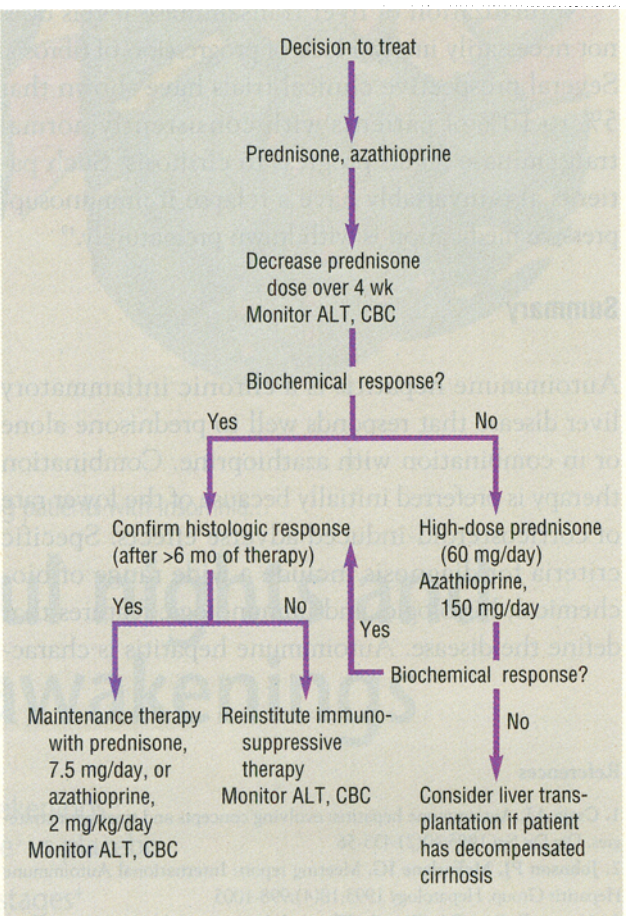

Figure 3. Treatment algorithm for autoimmune hepatitis type 1. ALT, alanine transaminase; CBC, complete blood cell count.

Adapted, with permission, from Luxon BA. Autoimmune hepatitis: a primer for clinicians. Clin Perspect Gastroenterol 2001;4(5):311.

is normal histologic findings on a subsequent liver biopsy. However, this scenario is relatively infrequent, even in patients who undergo liver biopsy 6 months after their transaminase levels returned to normal. Nevertheless, a second liver biopsy does have important prognostic value. Complete normalization of the hepatitis is associated with a relatively low risk of relapse (15% to 20%). In contrast, persistence of interface hepatitis portends a much higher frequency of relapse (90%).[18]

continued

Normalization of liver transaminase levels does not necessarily imply a lack of progression of fibrosis. Several prospective clinical trials have shown that 5% to 10% of patients with consistently normal transaminase levels progress to cirrhosis. Such patients also invariably have a relapse if immunosuppressive medication is withdrawn prematurely.[19]

Summary

Autoimmune hepatitis is a chronic inflammatory liver disease that responds well to prednisone alone or in combination with azathioprine. Combination therapy is preferred initially because of the lower rate of corticosteroid-induced adverse effects. Specific criteria for diagnosis include a wide range of biochemical, histologic, and immunologic features that define the disease. Autoimmune hepatitis is characterized by various autoantibodies, both traditional and nontraditional. Most of these autoantibodies are measured for diagnostic purposes and do not correlate with disease severity or activity. Sustained histologic remission is achievable in the majority of patients, although many patients require low-dose maintenance therapy. Drug therapy may be beneficial in patients with cirrhosis when considerable inflammation is noted on biospy. Orthotopic liver transplantation should be considered for patients with decompensated cirrhosis due to autoimmune hepatitis or those with severe hepatitis in whom initial therapy is not successful. **PGM**

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