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CASE STUDY

Autoimmune Hepatitis

Robert E. Frank, MD

Autoimmune hepatitis is an uncommon disease causing chronic inflammation of the liver and associated with various circulating autoantibodies. It shares some characteristics with other autoimmune liver diseases, such as primary biliary cirrhosis and sclerosing cholangitis. There has been confusion in past years regarding this entity, but there are now recognized diagnostic criteria by which to make a proper diagnosis. The disease is usually treatable with steroids. Certain proportions of treated patients become cured, although relapse is a problem often requiring chronic administration of steroid therapy. The expected mortality is close to normal in individuals who are cured or have only mild disease.

Address: Union Central Life Insurance Company, PO Box 40888, Cincinnati, OH 45240–0888.

Correspondent: Robert E. Frank, MD.

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CASE STUDY

A 47-year-old single female applied for $1.25 million worth of whole life insurance. She was president of a local bank, and there were business reasons for the insurance application. On the application, she admitted to being a smoker (1 pack per day). She also admitted in 1993 as having gastritis. She also stated that in 1994, 7 years prior to the application, she developed autoimmune hepatitis. She listed her medication as being ursodiol (twice daily).

A paramed examination was performed. This showed her height 5′ 2″, weight 118 pounds and stable, blood pressure 110/62. An EKG was normal. The blood chemistry profile was entirely normal, including AST, ALT, alkaline phosphatase, and GGT. The protein was 7.3 g/dL, with the albumin being 4.5 g/dL. The cholesterol was 230 mg/dL with the HDL fraction of 83 mg/dL (slightly elevated). The urine specimen was positive for cotinine, but otherwise was normal. Because of her admitted history regarding autoimmune hepatitis, an attending physician's statement (APS) was obtained.

The APS records showed that she had presented in 1994 with jaundice, fatigue and abdominal swelling. She was hospitalized. In addition to jaundice, the examination disclosed an enlarged liver with mild ascites. Her liver enzymes showed mild elevations of AST and ALT, a prolonged prothrombin time, and markedly elevated alkaline phosphatase and bilirubin levels. Her antimitochondrial antibody (AMA) was negative, but her antinuclear antibody (ANA) was mildly positive. An upper endoscopy revealed no esophageal varices. An attempted ERCP was unsuccessful. A liver biopsy was performed.

The pathology report stated that the specimen demonstrated mild to moderate portal fibrosis with extensive bile duct proliferation and mild to moderate fatty changes. There was also ductile proliferation, bile plugs, and chronic lymphocytic portal inflammation. The pathologist felt that the histologic picture

was nonspecific, but did raise the possibility of a drug induced or autoimmune etiology.

The other history noted in the APS was that of excessive alcohol intake for several years. She admitted to drinking 12 beers per night. Evaluation for other types of chronic liver disease, including hepatitis B and C was all negative. At this time, the working diagnosis was possible biliary cirrhosis, and she was placed on treatment with ursodiol, as well as furosemide and spironolactone because of her ascites.

Over the next 1-year period, she was maintained on these medications, with resolution of her ascites and overall decrease in her symptoms. The elevated liver enzymes became lower, although they still remained mildly elevated. At this time, approximately 1 year later, she was referred to a liver specialist at a local university hospital. A repeat liver biopsy was done. The repeat biopsy report was not available for review, but there were notations in the APS stating that this biopsy was more consistent with autoimmune hepatitis. Therefore, she was placed on prednisone, 15 mg daily. During the next 1-year period on prednisone, her liver function tests completely normalized. She was maintained on prednisone for approximately 2 years, and then it was gradually tapered and finally discontinued in 1998.

From 1998 forward, she was seen every 6 months by the gastroenterologist. It was noted she felt fine and was having no ongoing symptoms. The furosemide and spironolactone were gradually discontinued by 1999. Her only medication continued to be ursodiol. Liver enzymes were monitored at the time of each visit and were completely normal. Her most recent visit was May 2001, and she was noted to have a normal examination and normal liver enzymes. Her prothrombin time was normal. The listed diagnosis by the physician was that of autoimmune hepatitis with cholestasis.

DISCUSSION

Autoimmune hepatitis (AIH) is a chronic liver disease characterized by inflammation of unknown causation, which is associated with various circulating autoantibodies. It was first described in the 1950s and has been known by various names over the years. There has been much confusion between AIH and other types of chronic hepatitis over the years, especially chronic viral hepatitis. The term, autoimmune hepatitis, was recommended in 1992 by the International Autoimmune Hepatitis Group.[1] AIH is only 1 type of autoimmune liver disease, the other types being primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune polyendocrine syndrome type 1. There are also so called overlap syndromes, in which AIH overlaps with the serologic findings of primary biliary cirrhosis, and a type in which there are clinical features of primary biliary cirrhosis or sclerosing cholangitis in the absence of antimitchondrial antibodies. There is also an association between primary biliary cirrhosis and primary sclerosing cholangitis with various other types of autoimmune disease, including scleroderma, siccasyndrome, rheumatoid arthritis, lupus erythematosis, ulcerative colitis, autoimmune thyroiditis, Crohn's disease, diabetes mellitus, and others.

AIH is felt to have a genetic predisposition in the host. When the predisposed individual is exposed to certain environmental triggers, an autoimmune process develops that is directed at certain liver antigens, thus causing the inflammatory process. The relevant antigens and the pathophysiology of the inflammation remain largely undefined. The currently measured autoantibodies probably serve only as markers of the disease, rather than actually causing the inflammation. There are definitely associations between AIH and certain HLA histocompatibility antigens. It is also known that there is an increased prevalence of circulating autoantibodies in first-degree relatives of persons with AIH. The environmental triggers are unknown, although there has been some evidence to suggest various viral infections may be a part, including the hepatitis viruses and the E-B virus.[2]

AIH has been divided into 2 distinct types

Table 1. Types of Autoimmune Hepatitis

Type	ANA	ASMA	Anti-LKM1	Anti-SLA	Anti-HCV
Type 1	+	+	−	−	−
Type 2	−	−	+	−	±
Type 3*	−	±	−	+	−

* Not formally recognized and least well established
ANA—antinuclear antibody
Anti-LKM1—autoantibody to liver/kidney microsome type 1
Anti-SLA—antibody to soluble liver antigen
Anti-HCV—antibody to HCV

depending on the presence or absence of certain antibodies.[3] (Table 1) Type 1 or classic AIH is the most common in this country. It is much more common in females, usually presents as a chronic form of hepatitis, has 2 age peaks for onset (adolescence and middle age) and has high titers of antinuclear (ANA) and anti-smooth muscle antibody (ASMA) levels. There is usually moderate elevations of the liver enzymes, as well as an elevation of the gamma globulin level.

There is another type of AIH referred to as type 2. This is less common than type 1, and has been found primarily in Europe. The hepatitis usually has an acute onset, and both males and females are affected to a similar degree. In type 2, there are differences in the presence or absence of the various autoantibodies, and type 2 has been subdivided into subtypes 2a and 2b based upon some of these differences. There may also be a type 3, but this is not well established and has not been formally recognized.

Therefore, AIH can present as either an acute or chronic hepatitis like illness, is more likely to be present in females, and may have a wide variety of abnormal autoantibodies depending on the type. Although the diagnosis can be suspected in the typical clinical setting along with the confirmatory laboratory studies, the histologic appearance of a liver biopsy is of paramount importance not only in making the diagnosis but also in determining the severity of the disease and determining whether treatment is indicated.[4] Histologically, the biopsy will show mononuclear cell infiltrate in the portal areas that often invades the limiting plate, surrounding the portal triad, and often extending out into the lobular area, the so-called periportal infiltrate. The periportal infiltrate usually spares the biliary tree, often giving the appearance of the so-called piecemeal necrosis. Except those with the mildest disease, some degree of fibrosis is usually present. In more severe cases, bridging fibrosis connects the portal and central areas.

However, while the histologic appearance is characteristic, it is not specific to this disease. Similar findings can be found in a number of chronic liver diseases, including chronic viral hepatitis, drug-induced hepatitis, and even including the early stages of primary biliary cirrhosis and primary sclerosing cholangitis. In the early stages of sclerosing cholangitis, the histologic changes may be so similar that cholangiography may be necessary to distinguish between the two.

While the liver biopsy is helpful in making the diagnosis, the International Autoimmune Hepatitis Group also established a scoring system based on various parameters to help establish the correct diagnosis.[1] Since AIH is a heterogeneous disease, the hallmarks of the scoring system are defined by clinical and laboratory parameters, the biopsy histology, and response to treatment. Although the presence of autoantibodies represents the foundation for the diagnosis, there is no one autoantibody that is completely specific for the disease. The scoring system gives points for female gender, elevated gamma globulin levels, raised autoantibody titers of various types, the absence of viral hepatitis markers, and the absence of drug or alcohol effects on the liver. Obviously, other causes for chronic hepatitis must also be excluded.

Once the diagnosis is established, the majority of people will require treatment. Only in the very mildest cases, by biopsy and in which there are minimal symptoms, should treatment be withheld. Once an individual

has significant symptoms or has more than mild changes on biopsy, treatment is recommended.[5] The mainstay of treatment is prednisone alone, or in some cases low dose prednisone combined with azathioprine. Azathioprine alone does not induce remission. The initial response rate is between 65% to 80%. The 10-year life expectancy of treated patients is greater than 90%, and is similar to that of an age and sex matched normal population. However, even in some of the people who show response, there can be progression of the underlying liver disease, the partial responders. Untreated patients, especially if they have moderate to severe disease on biopsy, have a very poor prognosis, with 1 study showing a 3-year survival of only 50%.[6]

One of the major problems with treatment of this disease is the frequency of relapse.[5] Remission with treatment usually occurs within 6 to 12 months, but sometimes can take up to 2 years. It is unclear how long one should stay on prednisone, but usually the treatment is continued for a period of several more years, at which time the medication is tapered and then discontinued. The relapse rate during this tapering or discontinuing of medication is quite high, ranging anywhere from 20% to 87% within 1 year.[7] Only approximately 1 in 5 treated patients will experience an ongoing remission of their disease once treatment is stopped, the ones that could be considered ''cured.''[5] If an individual relapses, then treatment must be restarted. The majority of individuals will require long-term maintenance therapy. The ongoing chronic use of steroids usually results in the numerous known complications of this class of drugs. The more severe the disease on initial biopsy, the less likely one is to stay in remission without treatment.

Overall, the prognosis for sustained remission decreases as the severity of the liver biopsy increases. As such, these individuals need to be followed for prolonged periods of time, watching for a relapse characterized by a return of symptoms, elevation of liver enzymes, and the return of the autoantibody markers. Among non-responders and incomplete responders, approximately half will progress to histological cirrhosis within 10 years. Liver transplants have been performed for this disease process, and well-matched transplants usually show a disappearance of the autoantibodies with recurrent disease being rare.[8]

How can we apply all of this information to our proposed insured? Her presentation was somewhat consistent with AIH, although not completely typical. Her AMA was negative and the ANA was only mildly positive. Her gamma globulin level was only minimally elevated at 1.8g/dL. There seemed to be a significant cholestatic component, and the initial working diagnosis was biliary cirrhosis. There may have been a significant contribution to her hepatitis from her excessive alcohol intake. It was not until 1 year after the initial diagnosis and a repeat liver biopsy was done that the diagnosis of AIH was finally made. She did respond well to steroids, and 3 years after cessation of prednisone she remains disease free, although still on ursodiol. She had no other apparent autoimmune disorder.

It is possible she could have one of the overlap syndromes. Many of her features also fit autoimmune cholangitis, a term used to characterize persons with features of AIH and primary biliary cirrhosis. This overlap group usually responds favorably to treatment with steroids. Regarding the ongoing treatment with ursodiol, there is some evidence that this medication may preserve liver cell membrane stability, but its precise role in the treatment of AIH is unknown.

The most important question to ask is whether she is cured or not? As noted previously, the relapse rate is quite high when treatment is finally discontinued, but the majority of relapses occur within the first year. It is now 3 years since she has been on steroids. She remains on ursodiol, but it seems unlikely that this drug alone would prevent a relapse. Is this AIH alone or the overlap autoimmune cholangitis? I don't believe this can be answered with a high degree of certainty. I feel it is reasonable to conclude that

she most likely is cured of her disease process, whatever it was. Her liver biopsies did not show cirrhosis. As such, her life expectancy should approach normal. Some concern should be given to her prior alcohol abuse and the potential for relapse of this problem.

What would be the mortality expectations in a person with AIH who is not cured? The severity of the disease on biopsy would have to be considered. The greater the severity, the more likely one would be to have a worse outcome. Serial biopsies should be examined for any progression of disease. If an individual was a complete responder but still on treatment (no symptoms and normal liver enzymes), they may be insurable taking into account their age, the severity of the liver biopsy, and the potential long-term complications of the steroid therapy. A partial or nonresponder would be expected to have a worse prognosis and their expected mortality ratios may make them uninsurable.

AIH, although an uncommon disease, is treatable and at times curable. A liver biopsy is essential for proper evaluation. The treatment requires experience in this area and is best given by someone knowledgeable about this chronic disease and all of its nuances.

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