Review

Autoimmune Hepatitis: Clinical Overview and Pathological Findings

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Autoimmune hepatitis (AIH) is an uncommon cause of severe chronic hepatitis with a female predilection and affecting all ages and ethnic groups. Although its pathogenesis is still not completely clear, the condition has been linked to dysimmunoregulation of T lymphocytes, which attack and damage the hepatic parenchyma. Characteristic autoantibodies are produced against hepatocytes leading to cell injury and necrosis, eventually progressing to cirrhosis in a subset of patients. The goal of treatment is to prevent or halt disease progression by immunosuppressive therapy. Liver transplantation is the choice of treatment in selected patients with end stage liver disease, acute liver failure or hepatocellular carcinoma. Up to a third of post-transplanted patients have AIH recurrence in the allograft. The overall prognosis is good with high mortality in untreated cases.

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INTRODUCTION

Autoimmune liver diseases are disorders in which the body develops autoantibodies against hepatic tissue resulting in destruction and loss of function. These disease entities include autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC) and autoimmune cholangitis (AIC). The clinical, histologic and serological findings in each of these are distinct. They can coexist or overlap creating clinical and histologic diagnostic difficulties.[1]

AIH is a chronic liver disease of unknown etiology. As with other types of autoimmune diseases, the condition can be triggered by environmental factors, dysregulation of the immune system and shows a genetic predilection. It is therefore not unusual that patients with AIH have or will develop other autoimmune disorders during their lifetime.[1,2]

Waldenstrom introduced AIH (initially known as chronic active hepatitis) as a new entity in 1951 while increasing levels of gamma globulins were detected in cases of cirrhosis as far back as the 1940s. Prior to that era, all chronic active hepatitis was thought to be primarily due to viral infections.[3] The term lupoid hepatitis was introduced in 1956 when antinuclear antibodies and LE cells were identified in young female patients with chronic hepatitis. By 1965, the association with young females, lymphoplasmacytic infiltration, autoantibodies and response to immune-suppressive therapy led to the establishment of the term "autoimmune hepatitis".[3,4]

The genetic predisposition to AIH has been established with the strongest association found in the human leukocyte antigen region (HLA), which plays a role in adaptive immunity. The HLA alleles are situated on chromosome 6p. The genes in this region can trigger adaptive immune response to an antigen which leads to self-destruction.[5] Type 1 (adult) AIH shows a strong association with HLA-A1, B8, DR3 and DR4 molecules. HLA DR3 and DR4 have been considered to be included in the revised diagnostic scoring system proposed by the International autoimmune hepatitis group.[36] AIH type 2 (pediatric) is associated with HLA DR7 and DR3. HLA DR7 is associated with worse prognosis and aggressive disease course.[6]

The precise worldwide prevalence of AIH is not known.[1] The prevalence of AIH is higher in North America and Europe with Alaska having the highest rate at 42.9 per 100,000 people and Denmark at 23.9 per 100,000 people. HLA DR3 and DR4 are the dominant genes in North America and Europe while DR3 is more common than DR4 in Asia. There are varied genetic predispositions in the different ethnic groups even within the United States. In general, the prevalence of AIH is lower than most of the other more common liver diseases.[7]

The diagnosis is based upon a combination of clinical, serological and histological findings. Other causes of chronic liver disease including alcohol, medications, viral infections, etc have to be excluded before establishing the diagnosis of

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AIH. A response to immunosuppressive therapy helps affirm the diagnosis.[8]

CLINICAL PRESENTATION AND WORKUP

AIH usually occurs in young women but can present at any age and in all ethnic groups. The clinical presentation of type 1 and type 2 is indistinguishable. AIH type 1 usually presents in adults while type 2 is more common in children. More than 20% of adults greater than 60 years old develop the disease over time.[9] In developing countries, younger patients develop AIH and they frequently develop cirrhosis.[4-10]

The clinical presentation is variable and can range from asymptomatic cases to acute liver failure. The onset is often insidious especially in older patients in which case the elevated liver enzymes are detected when the patient is worked up for other symptoms or disorders. They can have non-specific symptoms such as fatigue, jaundice, arthralgias and abdominal pain. A quarter of patients present with acute hepatitis.[11] Patients who are asymptomatic as initial presentation have a good prognosis as opposed to those who present with cirrhosis on the initial biopsy.[12] AIH is often seen in association with other autoimmune disorders such as thyroiditis, diabetes mellitus type 1, ulcerative colitis, gluten sensitive enteropathy and rheumatoid arthritis. Physical examination may be normal or hepatomegaly may be detected.[13]

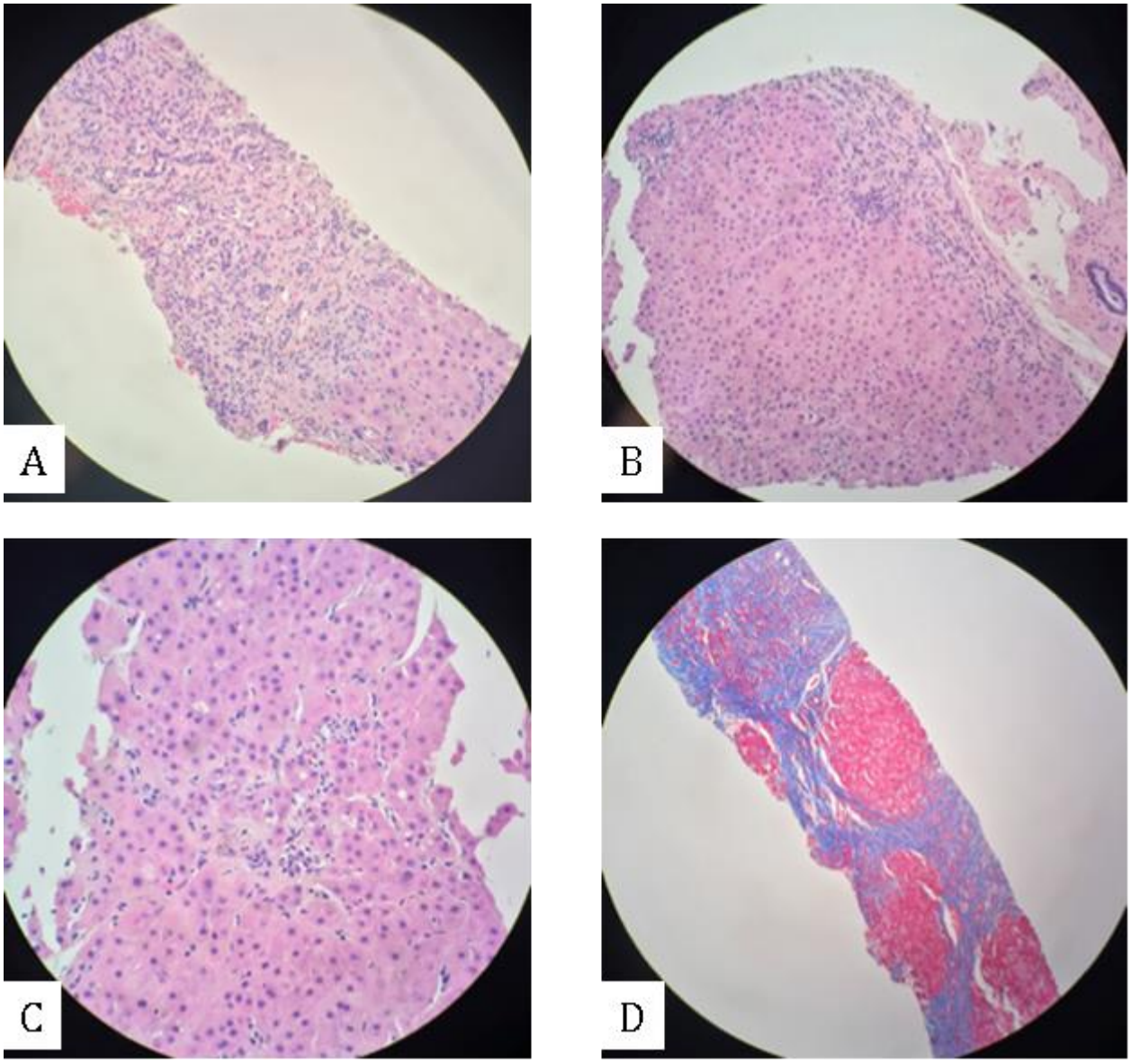

Figure 1. Histologic findings in autoimmune hepatitis. The portal tracts show fibrous expansion and bile ductular proliferation (**A**). Lymphocytes and plasma cells are seen within the portal areas. There is mild interphase activity with rare hepatocyte necrosis (**B**). Widespread mild lobular activity is present (**C**). Trichrome special stain shows bridging fibrosis, sinusoidal fibrosis, portal fibrous expansion, and small nodular formation, compatible with cirrhosis (**D**).

The levels of serum biochemical markers vary with stage and grade of the disease. Laboratory evaluation includes determination of liver enzymes (alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (AP)), bilirubin, albumin and gamma globulins. AST and ALT may be normal in quiescent (inactive) disease. These enzymes increase considerably during flare-ups and so does bilirubin. Lower ALT levels are often seen in asymptomatic men. AP levels are often normal but may be minimally elevated. Gamma glutamyl transferase (GGT) levels are better indicators of biliary damage for especially primary biliary sclerosis (PBC) than alkaline phosphatase that is elevated in growing children. Neither GGT nor AP normal levels can exclude bile duct damage in children with AIH. Serum levels of total globulin, gamma globulins or IgG are often elevated in all patients. In the cirrhosis stage, there are biochemical alterations of cirrhosis and increased bilirubin levels.[1,9,14]

PATHOGENESIS

AIH is similar to other autoimmune conditions in that it is also triggered by defective suppressor T cell immune response. The trigger can be unknown (most common) or secondary, commonly following viral infections such as hepatitis A, Epstein Barr virus or certain drug use.[2,15] The defect results in disregulation of the immune system and production of autoantibodies, which react against hepatocytes. Bile ducts destruction is present in up to 12% of cases while intraepithelial lymphocytes are present in 12-29% of cases. The presence of bile duct injury does not exclude AIH or suggest overlap with PBC.[16,17]

While most autoantibodies produced in AIH are non-specific, they are still important for diagnosis. Clinically significant autoantibodies include anti-nuclear antibodies (ANA), which occur in up to 80% of affected patients and give a speckled or homogenous nuclear staining by immunofluorescence.[18] Another important antibody is the anti-smooth muscle antibody (ASMA), which occurs in 70% of patients. The titer of both of these antibodies should be greater than 1:40 to be considered as significant. AIH type 1 is the classic type that is associated with ANA and ASMA. The latter can be seen in low levels in non-AIH cases such as alcoholic and non-alcoholic fatty liver disease, Wilson disease and hepatitis C infection.[8]

Autoantibody to soluble liver antigen/liver pancreas is a recent diagnostic autoantibody seen in 15-20% of patients with type 1 AIH. Type 2 on the other hand is positive for anti-liver kidney microsomal antibody type 1 and 3 (anti-LKM 1/3) and/or anti-liver cytosol type 1 antibody (anti-LC1).[1] Type 2 AIH is usually negative for ANA and ASMA. It is not common and seen mostly in children. Anti-LKM can be seen in up to 10% of hepatitis C cases. Its presence is associated with unfavorable clinical outcome and rapid clinical decline. Less common autoantibodies include anti-liver pancreas antigen, anti-soluble liver antigen and anti-asialoglycoprotein receptor.[8,18-20]

PATHOLOGY

The pathological diagnosis of AIH is made in conjunction with the clinical and serological findings. Grossly the liver often shows no or little diagnostic change. The appearance of the liver may be entirely normal especially in early stage. When parenchymal collapse from hepatocyte necrosis occurs and later on as cirrhosis sets in, the liver may shrink giving rise to a nodular appearance.[8,9,21]

Liver biopsy provides valuable information for the diagnosis of AIH. Sometimes, the diagnosis cannot be made especially in patients that present with established cirrhosis, refuse to have a biopsy or have a bleeding disorder. In recent years, pathological specimens have included explanted livers and post transplant liver biopsies.[8,21,22]

The histologic findings of AIH include a spectrum of panlobular inflammatory involvement of the liver parenchyma varying from absent to minimal histopathologic change in quiescent phase to increased plasma cells admixed with chronic inflammatory cells in the portal and periportal areas during flare-ups (**Figure 1A-C**).[1,23] The quantity of inflammatory cells varies depending on the grade of the disease. While a few intraepithelial lymphocytes may be seen within the biliary epithelium, bile ductal destruction is usually absent. If it is present, the possibility of primary biliary cirrhosis or overlap syndrome should be considered.[8,23-25]

Severe cases usually present with marked lymphoplasmacytic inflammation involving the portal tracts and interface hepatitis with destruction of hepatocytes resulting in acidophil bodies. The latter is non-specific and can be seen in viral hepatitis, drug associated injury and other conditions (including PBS or PSC).[23] The necroinflammatory process usually extends into the lobules and causes single cell necrosis and acidophil bodies. Some balloon degeneration, rarely cholestasis and hepatocyte swelling can also be present. Lobular inflammation is usually worse in disease flare-ups and resolves with treatment. A pericentral lymphoplasmacytic inflammatory infiltrate may be seen in early phase of AIH lacking the more commonly seen portal and periportal inflammation. Severe lymphoplasmacytic inflammation and necrosis with parenchyma collapse is seen in rapid onset AIH.[23,25]

Cholestasis is not characteristic for AIH and mild levels can be seen in cases with severe lobular inflammation. Similarly steatosis is not a characteristic component of AIH. Progression of fibrosis is staged similar to that in viral hepatitis starting from portal expansion, periportal and bridging fibrosis to overt cirrhosis (**Figure 1D**). Interface hepatitis can persist in cirrhotic liver within the fibrous septa and regenerative nodules. Studies have shown that most cases of acute flare-ups occur in patients with occult chronic disease and both scenarios show similar clinical and serological findings.[26]

Several histologic scoring systems for AIH have been developed. The earliest formulated in 1981 is the Knodell scoring system that failed to distinguish between cirrhosis and necroinflammation.[27] This was corrected in the Ishak's modification in 1995, which graded the severity of the inflammation and staged the fibrosis of AIH.[28] A simplified Batts and Ludwig scoring system scores necroinflammation and fibrosis on a scale of 0-4.[29] The French METAVIR system used for chronic viral hepatitis is similar and grades the inflammation on scale of 0-3 and stages the fibrosis on scale of 0-4. The preferred scoring system depends on the pathologist and institutional preference of the clinicians.[30]

MANAGEMENT

The goal for the treatment of AIH is to achieve and maintain remission as well as prevent disease progression. Asymptomatic patients may not require immunosuppressive therapy but should be followed closely.[31] Initial management of AIH begins with immunosuppressive therapy when serum ALT and AST levels are greater than ten folds of upper limits, five folds upper limit with increased serum gamma globulins and/or necrosis on biopsy. Children are treated with immunosuppression regardless they are symptomatic or not.[2]

Treatment is either monotherapy with prednisolone or preferably combined with azathioprine. Azathioprine reduces corticosteroid-induced complications and is convenient for long-term use. Azathioprine is not indicated if patient has marked pancytopenia or deficiency of thiopurine methyltransferase.[2] Patients that develop tolerance to azathioprine or fail to respond to steroid therapy can be given alternate drugs such as cyclosporine, tacrolimus or mycophenolate mofetil.[2,31]

Histological improvement lags behind clinical and biochemical resolution by 3-8 months. Average duration of treatment ranges from 18 months to 2 years. A repeat liver biopsy provides evidence of complete response to treatment and cessation of therapy. Complete response does not exclude the possibility of relapse. Relapse is managed with steroids and azathioprine therapy followed by discontinuation of steroids following resolution and indefinite azathioprine maintenance therapy. Alternatively low dose prednisolone can be used.[31]

Patients with multiple relapses are more likely to progress to cirrhosis. For patients with established cirrhosis, liver transplant is a consideration but AIH can recur in the allograft liver in about 30% of cases. Transplant is also indicated in acute liver failure or if hepatocellular carcinoma meets transplant criteria. The success rate is high with the 10-year survival at 75%. However, if the patient is left untreated, the 10 year survival is less than 30%.[31,34]

Hepatocellular carcinoma occurs in 4% of AIH type 1 patients. High risk factors include male, portal hypertension, esophageal varices, low platelets, immunosuppression for at least 3 years and cirrhosis for at least 10 years. AIH patients with cirrhosis are supposed to undergo hepatic ultrasound studies at 6-month interval.[32,35]

SUMMARY

AIH is an uncommon chronic disease of the liver that demands prompt recognition and management. The clinical presentation varies from subclinical cases to fulminant hepatitis resulting in acute liver failure and death. The diagnosis is based on the presence of hypergammaglobulinemia, autoantibodies, and classic histological findings. Other causes of chronic hepatitis need to be excluded. A third of patients go on to develop cirrhosis. The goal of treatment is to prevent or halt liver damage and resolve symptoms by the use of immunosuppressive therapeutic agents. Some patients may not respond or only have incomplete response. Liver transplantation is indicated in up to 10% of patients.[2]

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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