Autoimmune liver disease

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SUMMARY

Autoimmunity is regarded as the main mechanism involved in the pathogenesis of various liver diseases, such as autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), autoimmune cholangitis, overlap syndromes AIH-PBC and AIH-PSC and liver dysfunction due to connective tissue diseases1. Autoimmune hepatitis is an immune-mediated, auto-destructive liver disease with hepatocytes being the target cells of the human immune system.2,8 Primary biliary cirrhosis and primary sclerosing cholangitis are also regarded as autoimmune liver diseases with bile duct epithelia being the target cells, resulting in a continuous loss of bile ducts.3 These diseases may occur simultaneously in their full manifestations in about 10-20% of cases, thus constituting an overlap syndrome AIH-PBC or AIH-PSC.4

Key Words: Primary biliary cirrhosis, autoimmune hepatitis, primary sclerosing cirrhosis, overlap syndromes.

INTRODUCTION

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) represent acute and chronic inflammatory liver diseases in which immune reactions against host antigens are found to be the major pathological mechanism.3 Conditions in which the histologic findings suggest the overlap of two of these disorders or are insufficient for designation as classic disease constitute the variant syndromes.4 These diseases are characterized by abnormal liver function tests and a large number of serologic markers, some of which are specific to each one of them. The patients often suffer from fatigue, weight loss, anorexia, abdominal pain. Common clinical findings include hepatomegaly, jaundice and those of hepatic failure such as ascites. The diagnosis is often established by liver biopsy although sometimes the findings are not specific for one disease. Treatment mainly includes immunosuppressive drugs and ursodeoxycholic acid.5

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is a chronic progressive liver disease which was described for the first time in 1950 by Waldestrom6. It primarily affects women at a ratio men to women 1/4, in early ages, between 10-30, or adults above 40. It is often associated with extrahepatic immune-mediated syndromes such as Sjogren syndrome, thyroiditis Hashimoto, autoimmune haemolytic anemia, ulcerative colitis and rheumatoid arthritis.7, 27 It reveals with many clinical forms mild, acute and asymptomatic. Clinical findings of AIH often include hepatomegaly (50%), splenomegaly (30%), ascites (20%), jaundice (80%). Laboratory findings are moderate increase of SGOT and SGPT (up to 15 times normal), mild increase in serum bilirubin, hypoalbuminemia, mild increase of cholestatic enzymes, high level of serum gammaglobulin.6, 7, 27 By diverse autoantibodies (antinuclear autoantibodies-`˝`, antimitochondrial antibodies-`Ì`, antismooth muscle antibodies-SÌ`, against asialoglycoprotein receptor-ASGP-R 10, liver kidney microsomal antibodies LKM41,47, against Hepatitis C virus10,28, against liver specific antigen-LSP, soluble liver antibodies/liver and pancreas SLA/LP11,23, against extrahepatic targets such as thyroid cells10,27, liver membrane antibodies LMA11, 24), several subgroups of AIH can be distinguished9, 16 (Table 1). A very important
Primary biliary cirrhosis is a chronic cholestatic liver disease characterized by inflammation and progressive destruction of interlobular bile ducts, ultimately leading to biliary cirrhosis. The aetiopathogenesis of PBC remains unknown, although dysregulation of the immune system, genetic susceptibility and infection from mycobacteria seem important. Affected patients are typically middle-aged women (90% of all patients). The ratio of affected women to men is 9:1. PBC is often associated with other autoimmune diseases such as autoimmune thyroid disease, rheumatoid arthritis, systemic sclerosis, Sjogren syndrome, CREST syndrome. Most of signs and symptoms are results of chronic cholestasis, with major symptom the unexplained pruritus. It is often complicated by xanthelesma, xanthomata, osteoporosis (25%), osteomalacia due to malabsorption of fat soluble vitamins (A, K, D), higher frequency of gallstone disease (39%), upper abdominal pain (17%), portal hypertantion, steatorrhoea. Pruritus may occur and can precede jaundice by months to years. Laboratory tests shows elevated immunoglobulin M (IgM), hyperlipidaemia, high levels of ALP and gamma-GT. Antimitochondrial antibodies `Ì` and especially `Ì2 fraction are positive in 95% of patients. The `Ì` are divided in to several types (Ì1-Ì9). In PBC the dominant subtype is M2, while in overlap syndrome PBC-AIH the dominant subtypes are M2-M4. The antigenic target of `Ì2 are a complex of 2-oxo-acid dehydrogonase. The major autoantigens are ì2 and protein ×. Antinuclear antibodies `˝` are positive against protein Sp100,gp210. Anti-smooth muscle antibodies SMA are...
positive in 30% of patients. Also anti-LSP antibodies are usually positive, while anti-ASGP-R are positive in 50% of patients. There are 4 pathologoanatomic stages in relation to the hepatocellular and bile duct damage. (Ludwig’s classification)³¹

- Stage 1 inflammation within the portal space, focused on the bile duct.
- Stage 2 inflammation extending into the hepatic parenchyma.
- Stage 3 fibrosis.
- Stage 4 cirrhosis with regenerative nodules.

The survival of the symptomatic patients ranges between 7-11 years.³³ Ascites and portal hypertension indicate poor prognosis.³⁵,⁴５ Treatment of pruritus includes cholestyramine (12gr/day), antihistamines and phenobarbital (with poor results), rifampicin (150-600mg/d), hydrochloric colestipole, naloxone, stanozolol and flumenicol.³⁵,³⁴ Pruritus may be so annoying as to become a major indication for liver transplantation.³⁵,⁴⁶ Symptomatic support therapy includes: UVB, methyltestosterone, cholestyramine and simethidine for the jaundice.

### Table 2. Modified Scoring System for the diagnosis of AIH ¹³

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>FACTOR</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>+2</td>
</tr>
<tr>
<td>Alkaline phosphatase: AST ratio</td>
<td>&gt;3</td>
<td>-2</td>
</tr>
<tr>
<td></td>
<td>&lt;3</td>
<td>+2</td>
</tr>
<tr>
<td>Gamma-globulin or IgG levels above normal</td>
<td>&gt;2</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>1.5-2</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>1-1.5</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>ANA, SMA or anti-LKM 1 titers</td>
<td>&gt;1/80</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>1/80</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>1/40</td>
<td>+1</td>
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<tr>
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<tr>
<td>AMA</td>
<td>positive</td>
<td>-2</td>
</tr>
<tr>
<td>Viral markers</td>
<td>HbsAg</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td>IgM anti-HAV</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td>HCV RNA</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td>other viruses</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td>anti-HCV</td>
<td>-2</td>
</tr>
<tr>
<td></td>
<td>all negative</td>
<td>+3</td>
</tr>
<tr>
<td>HLA</td>
<td>DR3 or DR4</td>
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</tr>
<tr>
<td>Alcohol</td>
<td>&lt;25g/d</td>
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</tr>
<tr>
<td></td>
<td>&gt;40g/d</td>
<td>-2</td>
</tr>
<tr>
<td>Immune disease</td>
<td>patient or relative</td>
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</tr>
<tr>
<td>Histologic features</td>
<td>interface and acinar hepatitis with bridging</td>
<td>+3</td>
</tr>
<tr>
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<td></td>
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<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>other features</td>
<td>-3</td>
</tr>
<tr>
<td>Exposure to blood and/or drugs</td>
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<td>-2</td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>+1</td>
</tr>
<tr>
<td>Treatment response</td>
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<td>+2</td>
</tr>
<tr>
<td></td>
<td>remission with relapse</td>
<td>+3</td>
</tr>
</tbody>
</table>
fat-soluble vitamin supplements ` (retinol 100 000u/month), K (10mg/month), D (calciferol 250μg-4μg/d), calcium (1000-1500mg/day) and calcitonine (100u/2days for 2 months) for osteoporosis,35,41 diet with low fat for steatorrhoea. Treatment of PBC includes ursodeoxycholic acid (UDCA) as the first choice therapy35,40,42,44 and sometimes colchicine,35,38 and methotrexate35 (Table 3). Immunosuppressive therapy with azathioprine, cyclosporine and corticosteroids have poor results.37,39 Final treatment of PBC is liver transplantation. Indications for transplantation are the development of major complications of portal hypertension and liver failure, an unacceptable quality of life or anticipated death in less than 1 year.46

**PRIMARY SCLEROSING CHOLANGITIS**

Primary sclerosing cholangitis is an uncommon disease characterized by a diffuse inflammation of the biliary tract leading to fibrosis and strictures of the biliary system.48 It progresses to cirrhosis and chronic hepatic failure.49 It affects mainly young men in a ratio to women of 2/1.50 The disease is most common in men aged 20-40, and is closely associated with ulcerative colitis which is present in approximately 2/3 of patients with PSC.51 Clinically, the disease presents as progressively obstructive jaundice frequently associated with malaise, pruritus, anorexia, fatigue and indigestion. Very rarely, PSC appears at first with features similar to those of septic cholangitis.52 Cholangiocarcinoma may implicate the course of PSC in 10% of cases.50,58 Laboratory findings are high levels of cholestatic enzymes, increased SGOT, SGPT, increase of serum bilirubin, hypergammaglobulinemia (IgM 40-50%) in 1/3 of the patients.50,55 It is characterized by ANA(+), SMA(+) in 1/3 of the patients, p-ANCA(+) against catalase, a-enolase, lactoferrine53,60 and bactericidal permeability-increasing protein, BPI-ANCA.50,59 Immunological mechanisms are implicated. HLA associations include B8, DR3, DR2. The diagnosis of PSC is made by endoscopic retrograde cholangiography. The disease may be confined to small intrahepatic bile ducts, in which ERCP is normal and the diagnosis is suggested by liver biopsy.39,57 Treatment with corticosteroids and broad-spectrum antimicrobial agents has been employed with inconsistent and unpredictable results.50,56 Ursodeoxycholic acid may improve liver function test results but does not appear to alter the natural history of the disease. Careful endoscopic evaluation of the biliary tree may permit ballon dilation of localized strictures. If there is a major stricture, stenting is a possibility. For patients with cirrhosis and clinical decompensation, liver transplantation is the procedure of choice. Failure to identify patients who will benefit from non-transplantation therapeutic interventions or in whom a cancer will develop, and the risk associated with previous abdominal surgery, suggest that liver transplantation should be indicated early after onset of symptoms. Survival rates after liver transplantation for this disease are as high as 85% at 3 years.36

**OVERLAP SYNDROMES**

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) represent acute and chronic inflammatory liver diseases in which immune reactions against host antigens are found to be the major pathological mechanism. Conditions in which the histologic findings suggest the overlap of two disorders or are insufficient for designation as classic disease constitute the variant syndromes.61 The diagnosis of overlap syndromes requires a constellation of clinical, laboratory and histologic features of AIH, PSC, PBC and the treatment depends on the combination of these diseases (Table 4). Disorders which are regarded

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical improvement</th>
<th>Biochemical improvement</th>
<th>Histological improvement</th>
<th>Survival</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>D-penicillamine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Chlorambucile</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+?</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+?</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>+?</td>
</tr>
<tr>
<td>Colchicine</td>
<td>-</td>
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<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>UDCA</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>-</td>
</tr>
</tbody>
</table>
as overlap syndromes are autoimmune cholangitis, overlap syndrome AIH-PBC and overlap syndrome AIH-PSC.62,63

**Overlap syndrome AIH-PSC**

The overlap syndrome between autoimmune hepatitis and primary sclerosing cholangitis is a rare condition which includes patients that combine features from both diseases. Patients have elevated serum levels of alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase and immunoglobulin G, ANA (+), and/or SMA (+). Liver biopsy simultaneously shows criteria of both autoimmune hepatitis and primary sclerosing cholangitis.64,65 Endoscopic retrograde cholangiography pancreatography (ERCP) demonstrate features of PSC. The diagnosis of these 2 diseases may take place simultaneously, but in most cases the diagnosis of AIH precedes. It is often associated with ulcerative colitis and not with Crohn’s disease, but the absence of it doesn’t exclude the existence of PSC. The presence of this syndrome should be considered certain and should be verified with ERCP in patients with AIH who have some of these (non-typical for the diagnosis of AIH) features:66, 69

- High levels of ALP or ratio increase of ALP/increase of AST >1.5, especially when histologic injuries in bile ducts co-exist
- Not so good response to corticosteroid treatment
- Co-existence with ulcerative colitis

Corticosteroid treatment seems to decrease the level of SGOT and SGPT but fails to control cholestasis.67, 68

**Overlap syndrome AIH-PBC**

It refers to patients who display characteristics of both AIH (high levels of ALT, AST, gammaglobulin, gamma-glutamyl transpeptidase, high titers of ANA and/or ASMA and damaged hepatocytes in liver biopsy) and PBC (cholestasis, damaged intrahepatic bile ducts, (+) anti-M2 antibodies).70 The characteristics of these two diseases may appear simultaneously or at different time. Also, during the progress of the syndrome, the features of one disease may dominate over the other. The time difference between the appearance of these 2 diseases may be up to 7 years.71 Response to ursodeoxycholic acid treatment in patients with overlap syndrome was comparable with that obtained in PBC. Therefore it should be the first-line of treatment.72 Non-responsive patients may benefit from the use of ursodeoxycholic acid plus prednisone combination.73

**Autoimmune cholangitis**

Autoimmune cholangitis is an idiopathic disorder with mixed hepatocellular and cholestatic findings, laboratory and histologic features similar to those of PBC but typically with negative anti-M2 fraction of AMA antibodies and positive antinuclear antibodies in titer more than 1/640.74, 75 It affects mainly middle-aged women (90% of all patients). Half of the patients are asymptomatic while others suffer from weight loss, pruritus and abdominal pain. It is very often associated with other autoimmune diseases such as Sicca syndrome (50%), CREST syndrome and hypothyroism. The natural history of this disease is characterized by a slow progression to cirrhosis. Laboratory tests show high levels of ALP and gamma-GT, hypergammaglobulinemia with high levels of IgM and IgG, while ERCP is always normal. SMA are
positive in 50% of patients. Antibodies against the cytoplasm of neutrophils p-ANCA and against lactoferrine are always present. Taking into consideration recent data, autoimmune cholagitis should be regarded as AMA (-) PBC.

CONNECTIVE TISSUE DISEASES AND LIVER

Connective tissue diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjogren's syndrome and scleroderma, are systemic disorders that may have an autoimmune basis. Liver involvement in patients with connective tissue diseases has been well documented but is generally considered rare. Although advanced liver disease with cirrhosis and liver failure is rare in patients with connective tissue diseases, clinical and biochemical evidence of associated liver abnormalities is common. Previous treatment with potentially hepatotoxic drugs or coincident viral hepatitis has usually been implicated as the main causes of liver dysfunction in patients with connective tissue diseases. Although hepatic steatosis and abnormal results on biochemical liver function tests are the most common hepatic abnormalities associated with connective tissue diseases, other less frequent abnormalities have been noted, such as nodular regenerative hyperplasia, portal vein obliteration and portal hypertension and rarely portal fibrosis with abnormal lobular architecture. Vascular disorders of the liver have also been described, such as Budd-Chiari syndrome.

CONCLUSIONS

Autoimmune liver diseases are chronic, serious disorders which affects the quality of life of patients as they often lead to hepatic failure and, if not, the patients have to be under medication for a long period of time even for life. Taking under consideration that there is no prevention for these diseases, treatment is becoming more significant than ever. Apart from immunosuppressive therapy and liver transplantation, novel therapeutic approaches are under investigation, such as T cell vaccination, gene therapy, cytokine manipulations, blocking peptides, soluble cytotoxic T lymphocyte antigen-4, monoclonal antibodies.

REFERENCES


23. Manns MP. Antibodies to soluble liver antigen, specific marker of autoimmune hepatitis. J Hepatol 2000; 33:326-328


35. Levy C, Lindor KD. Current management of primary biliary cirrhosis and primary sclerosing cholangitis. J Hepatol 2003; 38:24-37


44. Poupon RE, Bonnand AM, Chtetien Y, Poupon R, UDCA-PBC STUDY GROUP. Ten-year survival in ursodeoxycholic acid-treatment patients with primary biliary cirrhosis. 1999; 29:1668-1671


58. Rosen CB, Nagomey DM. Cholangiocarcinoma complicating
64. Talwalkar JA, Keach JC, Angulo P, Lindor KD. Overlap of autoimmune hepatitis and primary biliary cirrhosis, an evaluation of a modified scoring system. Am J Gastroenterol 2002 May; 97:1191-1197
69. Podymova SD. Syndrome of cross-over between primary biliary cirrhosis and autoimmune hepatitis. Ter Arkh 2002; 74:41-44
70. Criga T, Tromm A, Muller KM, May B. Overlap syndrome between autoimmune hepatitis and primary sclerosing cholangitis in two cases. Eur J Gastroenterol Hepatol 2000 May; 12: 559-564