Review

Autoimmune liver disease

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SUMMARY

Autoimmunity is regarded as the main mechanism involved in 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 diseases[1]. 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 cirrrhosis 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 ursode-oxycholic acid.[5]

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AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is a chronic progressive liver disease which was described for the first time in 1950 by Waldestrom[6]. It primarily affects women at a ratio men to women 1/4, in early ages, beween 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, accute and asymptotic. 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 gamma-globulin.[6, 7, 27] By diverse autoantibodies (antinuc-lear autoantibodies-ANA, antimitochondrial antibodies-AMA, antismooth muscle antibodies-SMA, against asialoglycoprotein receptor-ASGP-R[10], liver kidney microsomal antibodies LKM[11,47], against Hepatitis C virus[10,28], against liver specific antigen-LSP, soluble liver antibodies/liver and pancreas SLA/LP[11,23], against extrahepatic targets such as thyroid cells[10,27], liver membrane antibodies LMA[11, 24]), several subgroups of AIH can be distinquished [9, 16] (Table 1). A very important

Table 1. Types of Autoimmune Hepatitis[14,16,25]

Type 1

- It affects young women with clinical features of acute or chronic hepatitis.
- ANA(+), SMA(+)Anti-LSP(+), anti-ASGP-R(+), p-ANCA(+).
- It is often associated to other immune-mediated diseases.
- Good response to corticosteroids treatment.
- 50% relapse after recess of treatment, leads to cirrhosis in 43% of patients after 3 years.

Type 2

- It affects mainly young people. It is related with other autoimmune diseases.
- It leads very soon to cirrhosis (83% of patients).
- LKM(+), anti-LC1(+).

  Uridine Diphosphate Glucuronosyltransferase (UGT) was identified as an antigenic target in a subgpoup of liver-kidney microsomal autoantibodies and was termed LKM-3.
- ANA(-), SMA(-), mild increase in gamma-globulin.
- Good response to immunosuppressive therapy.
- Sometimes antibodies against hepatitis virus C.

disease-promoting factor seems to be the genetically determined background for autoimmunity characterized by the HLA haplotype A1, B8, DR3, DR4, A11.[12] The liver tissue examination, after liver biopsy, shows chronic inflammation, portal plasma cell infiltration, mainly by CD4+ lemphocytes and plasmatocytes, creation of rosettes from hepatocytes, while bile ducts are normal.[8, 9] The natural history of AIH shows a poor prognosis with frequent progression to cirrhosis and hepatic insufficiency in untreated patients. The occurrence of hepatocellular carcinoma is rare and is found only in long-standing cirrhosis.[7,17] The benefit from immunosuppressive therapy with prednisolone and azathioprine is well estamblished.[15] Remission can be achieved in 80% of patients within 3 years, and the 10 to 20-year survival rates exceed 80%. Histological cirrhosis does not affect response or longevity and all patients with severe disease should be treated, including children, elderly adults, postmenopausal women and those without conventional autoantibodies.[17,22,26] Treatment for AIH includes corticosteroids (15-30mg prednisone/d), until ANA become negative and SGOT, SGPT and gamma-globulin become normal,[17,26] and azathioprine (50-100mg/d) for 10 days. After 10 days we continue with 5-15mg/d prednisone and 50mg/d azathioprine for 2-3 years or for lifetime.[18,19,21] Other drugs that are under investigation are cyclophosphamide, ursodeoxycholic acid, 6-mercaptopurine, cyclosporin, methotrexate.[20] Recent treatment includes T cell vaccination, gene therapy, cytokine manipulations, blocking peptides, soluble cytotoxic T lymphocyte antigen-4, monoclonal antibodies.[15] Liver transplantation is indicated for patients in the final stage of cirrhosis and for patients refractory to or intolerant of immunosuppressive therapy.[17,26] A scoring system has been proposed by the International Autoimmune Hepatitis Group and the validity of a modification of this system for the diagnosis of autoimmune hepatitis has been demonstrated (Table 2). By grading each manifestation of the disease in accordance with its diagnostic importance, a numerical score is generated that reflects the net strength of the diagnosis.[13] (pretreatment score: definite diagnosis score >15, probable diagnosis 10-15, nondiagnostic <10, posttreatment score: definite diagnosis score >17, probable diagnosis 12-17, nondiagnostic <12).

PRIMARY BILLIARY CIRRHOSIS

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.[29] Affected patients are typically middle-aged women (90% of all patients). The ratio of affected women to men is 9/1.[30] PBC is often associated which other autoimmune diseases such as autoimmune thyroid disease, rheumatoid arthritis, systemic sclerosis, Sjogren syndrome, CREST syndrome.[29] Most of signs and symptoms are results of chronic cholestasis, with major symptom the unexplained pruritus.[30] 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 AMA and especially M2 fraction are positive in 95% of patients. The AMA are divided in to several types (M1-M9). In PBC the dominant subtype is M2, while in overlap syndrome PBC-AIH the dominant subtypes are M2-M4. The antigenic target of M2 are a complex of 2-oxo-acid dehydrogonase. The major autoantigens are E2 and protein X.[30,32,33] The antinuclear antibodies ANA are positive against protein Sp100,gp210.[30,34] Anti-smooth muscle antibodies SMA are

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

CATEGORY	FACTOR	SCORE
Gender	Female	+2
Alkaline phosphatase: AST ratio	>3	-2
	<3	+2
Gamma-globulin or IgG levels above normal	>2	+3
	1,5-2	+2
	1-1,5	+1
	<1	0
ANA, SMA or anti-LKM 1 titers	>1/80	+3
	1/80	+2
	1/40	+1
	<1/40	0
AMA	positive	-2
Viral markers	HbsAg	-3
	IgM anti-HAV	-3
	HCV RNA	-3
	other viruses	-3
	anti-HCV	-2
	all negative	+3
HLA	DR3 or DR4	+1
Alcohol	<25g/d	0
	>40g/d	-2
Immune disease	patient or relative	+1
Histologic features	interface and acinar hepatitis with bridging	+3
	interface hepatitis	+2
	rosettes	+1
	plasma cells	+1
	biliary changes	-1
	other features	-3
Exposure to blood and/or drugs	yes	-2
	no	+1
Treatment response	remission alone	+2
	remission with relapse	+3

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 hepatocecullar 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.[35] 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)[36], hydrochloric colestipole, naloxone, stanozolol and flumenicol.[35,54] Pruritus may be so annoying as to become a major indication for liver transplantation.[35,46] Symptomatic support therapy includes: UVB, methyltestosterone, colestyramine and simethidine for the jaundice,

fat-soluble vitamin supplements A (retinol 100000u/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 therapy [35,40,42,44] and sometimes colchicine,[35,38] and methotrexate[35] (Table 3). Immunosuppresive 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, prutitus, anorexia, fatigue and indigenstion. 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, lactoferrine[53,60] 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 retrogate cholangiography. The disease may be confined to small intrahepatic bile ducts, in which ERCP is normal and the diagnosis is suggested by liver biopsy.[49,57] Treatment with corticosteroids and broad-spectrum antimicrobial agents has been employed with incosistent 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.[56]

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 3. Treatment of PBC[35,37,39,40,42-44]

Drug	Clinical improvment	Biochemical improvment	Histological improvment	Survival	Side effects
Azathioprine	-	-	-	+	-
D-penicillamine	-	-	-	-	+
Chlorambucile	-	+	+	?	+
Methotrexate	+	+	+	?	+?
Prednisolone	+	+	+	?	+?
Cyclosporine	+	+	?	?	+?
Colhicine	-	+	-	+	-
UDCA	+	+	?	?	-

Table 4. Diagnostic criteria and treatment options for overlap syndromes[61-63]

TYPES	DIAGNOSIS	TREATMENT
AIH+PBC	Type 1 AIH with AMA or PBC with aggregate scores for AIH>10.	Prednisone alone (20mg/d) or lower dose (10mg/d) with azathioprine (50mg/d). Usodeoxycholic acid (13-15mg/d) alone or with prednisone if marked with features of cholestasis.
AIH+PSC	Cholangiographic changes of PSC and aggregate scores for AIH>10.	Prednisone trial (20mg/d) for 3-6 mo if mainly hepatocecullar ctivity. Prednisone (20mg/d) and ursodeoxycholic acid (13-15mg/Kg daily) for 3-6 mo if equally mixed features.
Autoimmune cholangitis	AMA(-) PBC	Prednisone trial (20mg/d) for 3-6 mo if mainly hepatocecullar activity. Ursodeoxycholic acid trial (13-15mg/kg/d) for 3-6 mo if mainly cholestatic features. Prednisone (20mg/d) and ursodeoxycholic acid (13-15mg/Kg daily) for 3-6 mo if equally mixed features

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 immunoglobuline 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 abscense of it doesn't exclude the existance of PSC. The presense 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-existance 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 appearence 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 prednisolone combination.[73]

Autoimmune cholangitis

Autoimmune cholangitis is an idiopathic disorder with mixed hepatocecullar 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 weigth 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 και IgG, while ERCP is always normal. SMA are

positive in 50% of patients.[76] Antibodies against the cytoplasm of neutrophils p-ANCA and against lactoferrine are always present.[59,60] Taking into consideration recent data, autoimmune cholagitis should be regarded as AMA (-) PBC.[77]

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.[78] 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.[78]

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 immuno-suppressive 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.[63]

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