

Liver and pancreatic disorders

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LIVER DISEASES

Liver diseases have been found in about a quarter of patients with Sjögren's syndrome.^{2,3,9,10} These are both chronic infections with hepatitis C virus (HCV) in regions with a high prevalence of HCV infection, such as the Mediterranean area (13%), and autoimmune liver diseases (table 10.1). Primary biliary cirrhosis (PBC) is the most frequent (4-10%) autoimmune liver disease in Sjögren's patients. Less frequent are autoimmune hepatitis (2-4%) and primary sclerosing cholangitis.

A. Autoimmune liver diseases

Autoimmune liver diseases include a spectrum of diseases which comprises both cholestatic and hepatitic forms:

1. autoimmune hepatitis
2. primary biliary cirrhosis and autoimmune cholangitis
3. primary sclerosing cholangitis
4. overlap syndromes

In the overlap syndromes, hepatitic and cholestatic damage coexist. The autoimmune liver diseases are characterized by an extremely high heterogeneity of presentation, varying from asymptomatic, acute (as in a subset of autoimmune hepatitis) or chronic (with aspecific symptoms such as fatigue and myalgia in autoimmune hepatitis or fatigue and pruritus in primary biliary cirrhosis and primary sclerosing cholangitis).¹

1. Autoimmune hepatitis

Two types (1 and 2) of autoimmune hepatitis are distinguished (table 10.2). Antinuclear antibodies (ANA) and anti-smooth muscle antibodies (SMA) mark type 1 AIH, while liver kidney microsomal antibody type 1 (LKM1) and liver cytosol type 1 (LC1) are the serological markers of type 2 AIH.

Clinical manifestations

Patients may present with nonspecific symptoms of varying severity, such as fatigue, lethargy, malaise,

Table 10.1 Diseases of the liver and pancreas that occur more often in patients with Sjögren's syndrome than in the general population

- autoimmune hepatitis type 1
- granulomatous hepatitis
- hepatitis C
- primary biliary cirrhosis
- autoimmune cholangitis
- primary sclerosing cholangitis
- autoimmune pancreatitis

anorexia, nausea, abdominal pain, and itching. Arthralgia involving small joints is common. Physical examination may reveal no abnormalities, but it may also reveal hepatomegaly, splenomegaly, jaundice, and signs and symptoms of chronic liver disease.

Rarely, AIH presents as fulminant hepatic failure. Patients with occult disease may have undetected cirrhosis and present only when decompensation occurs.

Many patients with an acute presentation have histological evidence of chronic disease in the liver biopsy, indicating that they have had antecedent subclinical disease.^{4,5}

Histopathology

AIH is characterized by a lymphocytic infiltrate. There may be an abundance of plasma cells and eosinophils are frequently present. The portal lesion generally spares the biliary tree.

Fibrosis is present in all but the mildest forms of autoimmune hepatitis. In advanced disease, the fibrosis is extensive, and with the distortion of the hepatic lobule and the appearance of regenerative nodules, it results in cirrhosis.^{4,5}

Diagnosis

The detection and characterization of non-organ specific autoantibodies plays a major role in the diagnostic approach of autoimmune liver disease. In the presence of a compatible histologic picture, the diagnosis of AIH is based on characteristic clinical and

Table 10.2 Characteristics of autoimmune hepatitis types 1 and 2 (Krawitt 4)

<i>variable</i>	<i>type 1</i>	<i>type 2</i>
characteristic autoantibodies	ANA smooth-muscle antibody anti-actin antibody autoantibodies to soluble liver antigen and liver–pancreas antigen atypical p-ANCA	antibody to liver–kidney microsome 1 antibody to liver cytosol
geographic variation	worldwide	worldwide; rare in North America
age at presentation	any age	predominantly children and young adults
sex of patients	female in about 75% of cases	female in about 95% of cases
association with other autoimmune diseases	common	common
clinical severity	broad range	generally severe
histopathologic features at presentation	broad range	generally advanced
treatment failure	infrequent	frequent
relapse after drug withdrawal	variable	common
need for long-term maintenance	variable	about 100%

biochemical findings, circulating autoantibodies and abnormalities of serum globulins.^{4,5}

High-titre smooth-muscle antibodies have been found indicators for future development of AIH.⁸

Disease associations

AIH may occur in conjunction with a variety of autoimmune disorders.⁶ Examples are ulcerative colitis, celiac disease, rheumatoid arthritis, vitiligo, discoid lupus erythematosus, systemic sclerosis, autoimmune hemolytic anemia and Sjögren's syndrome. Arthralgia of small joints is common, and arthritis may be particularly trouble some.

One presentation of AIH is in the setting of medications, or herbal agents, used for other diseases. Minocycline and statins may trigger AIH.^{4,5}

Treatment

Treatment options rely on immunosuppressive therapy. Standard medications for initial and maintenance regimens are still considered to be prednisolone alone or in combination with azathioprine. In autoimmune hepatitis (AIH) and on ursodeoxycholic acid in cholestatic conditions. The worst outcome is end stage of liver disease for which liver transplantation remains the only therapeutical approach.^{4,5}

Prognosis

Long periods of subclinical disease may also ensue after presentation. In patients who have a spontaneous

or pharmacologically induced remission, the histologic findings may revert to normal or inflammation may be confined to portal areas. In this setting, cirrhosis may become inactive and fibrosis may diminish or disappear.

Complications of AIH are those seen in any progressive liver disease and primary hepatocellular carcinoma is an expected, although uncommon, consequence. There are no established guidelines for hepatocellular carcinoma screening in cirrhosis associated with AIH. A reasonable approach would be surveillance with an ultrasound and -fetoprotein every year.^{4,5}

2. Primary biliary cirrhosis and autoimmune cholangitis

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease in progressive bile-duct injury from portal and periportal inflammation can result in progressive fibrosis and eventual cirrhosis. Evidence to date suggests that immunological and genetic factors might cause the disease. Affected individuals are typically middle-aged women with asymptomatic rises of serum hepatic biochemical variables. Fatigue, pruritus, or unexplained hyperlipidaemia at initial presentation suggests PBC. Antimitochondrial antibodies (AMA) are nearly diagnostic of the disease. Disease identification is important because effective medical treatment with

Table 10.3 Extrahepatic autoimmune disorders associated with primary biliary cirrhosis ¹¹

<i>disorder</i>	<i>prevalence (%)</i>
keratoconjunctivitis sicca	75
renal tubular acidosis	50
gallstones	30
arthritis	20
thyroid disease	15
systemic sclerosis	15
Raynaud's phenomenon	10
CREST syndrome	5

ursodeoxycholic acid can halt disease progression and extend survival free of liver transplantation.¹¹

Clinical manifestations

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Histopathology

Histological classification schemes have categorised the disease into four stages.

Stage 1 is associated with portal-tract inflammation from predominantly lymphoplasmacytic infiltrates, resulting in destruction of septal and interlobular bile ducts up to 100 µ in diameter. Focal-duct obliteration with granuloma formation has been termed the florid duct lesion, and is judged almost pathognomonic for primary biliary cirrhosis when present.

Stage 2 entails periportal extension of inflammation. Cholangitis, granulomas, and ductular proliferation are most typically seen.

Stage 3 is dominated by septal or bridging fibrosis. Ductopenia (defined as loss of >50% of interlobular bile ducts) becomes more frequent, resulting in cholestasis and raised hepatic copper deposition within periportal and paraseptal hepatocytes.

Stage 4 accords with biliary cirrhosis. Because of increased sampling variability from liver biopsy specimens in the disease, the highest recognised stage should be used to establish extent of involvement.¹¹

A diagnosis of antimitochondrial antibody-negative primary biliary cirrhosis cannot be made without a liver biopsy specimen.¹¹

Diagnosis

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Disease associations

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Treatment

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Prognosis

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Autoantibodies in PBC

Between 90% and 95% of people with antimitochondrial antibody in serum, at titres of 40 or greater, have PBC. Seropositivity for this antibody is not specific to the disease, but remains highly sensitive (98%). ANA and smooth muscle antibody arise in 35% and 66% of patients with PBC, respectively.

Serum anticentromere antibodies in patients affected by the CREST syndrome (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasias) are noted in 10–15% of instances. Absence of seropositivity for antimitochondrial antibody in patients with clinical features suggestive of PBC has been termed autoimmune cholangitis. Serum autoantibodies, including antinuclear antibody, smooth muscle antibody, and anticarbonic anhydrase, are usually present. Of note, no difference seems to be present in natural history or responsiveness to ursodeoxycholic acid treatment in patients with autoimmune cholangitis compared with those with antimitochondrial antibody-positive PBC. An overlap syndrome between PBC and autoimmune hepatitis arises in fewer than 10% of patients.

It has been found that patients with IF-AMA usually develop symptomatic PBC upon a 5 year follow-up. It is likely that patients without IF-AMA, who express PBC-specific AMA, are in early, asymptomatic stage of the disease. High-titre IF-AMA is the most specific indicators for PBC.⁸

PBC is a rather uncommon development in patients with primary SS. The disease appears to be pathologically mild, with a propensity for slow progression, as assessed clinically, biochemically, and histologically.¹⁰

Standard medication is ursodeoxycholic acid and liver transplantation in end stage liver disease.^{4,5}

[antimitochondrial antibodies (AMA) are associated with PBC / increased serum IgM]

3. Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC)

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No specific marker is found in PSC, since anticytoplasmic neutrophil antibodies with perinuclear pattern (atypical p-ANCA) are also detected in a substantial proportion of type 1 AIH cases.

4. Overlap syndromes

Clinical, histologic, and serologic profiles of overlap syndromes differ from the classic features of AIH, PBD, and PSC. Many different terms have been used to describe patients with features of both AIH and PBC.⁵

B. Other liver diseases

1. Granulomatous hepatitis

A possible association between granulomatous hepatitis and Sjögren's syndrome has been suggested.⁷ Granulomatous hepatitis is a histological description and may have many causes such as sarcoidosis and hypersensitivity reactions to drugs.

2. Hepatitis C

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PANCREATIC DISEASES

1. Autoimmune pancreatitis

Autoimmune pancreatitis (AIP) is a rare disorder often associated with multiple autoimmune diseases like rheumatoid arthritis, inflammatory bowel disease and Sjögren's syndrome. The cause and pathogenesis are not known. Antinuclear antibodies (ANA) or elevated serum levels of IgG4, a systemic autoimmune disease association and positive response to oral steroid therapy support the idea of autoimmune mechanisms involved in the pathogenesis of AIP.¹²

Clinical presentation

AIP is a disease with usually mild symptoms, severe attacks of abdominal pain are not typical. Typically, pancreatic calcifications and pseudocysts are absent.

Jaundice and/or pancreatic mass are frequent signs, and both make the differential diagnosis with pancreatic cancer difficult.¹⁹ AIP is rarely associated with diabetes mellitus and exocrine pancreatic dysfunction.

Presentation as a pancreatic mass

Single or multiple pancreatic masses have been described in patients with Sjögren's syndrome mimicking pancreatic carcinoma. The mass may compress the main pancreatic duct, or common bile duct causing jaundice. Infiltrates are similar to those

in the salivary glands consisting of CD4-positive T-lymphocytes. Failure to recognize the real nature of the pancreatic mass (pseudotumor) can lead to inappropriate surgery.

Histology

Periductal lymphoplasmacytic infiltration is invariably present in AIP, followed in order of frequency by periductal fibrosis and venulitis. These changes are absent in chronic pancreatitis associated with pseudo cysts, calculi, pancreas divisum and/or duodenal wall inflammation.¹⁸

Diagnosis

The lack of specific biochemical markers is a major drawback in the diagnosis of AIP. The Japan Pancreas Society proposed diagnostic criteria for AIP as the presence of antibodies, pancreas enlargement and pancreatic duct narrowing, lymphoplasmatic infiltration, response to corticosteroid therapy, and association with other autoimmune diseases such as autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, sialoadenitis, inflammatory bowel disease and Sjögren syndrome.¹⁹

Serology

Autoantibodies to carbonic anhydrase (CA), an enzyme abundantly present in the epithelium of pancreatic ducts, may be a useful tool for the differential diagnosis of pancreatic cancer and other pancreatic disorders. Compared with the prevalence of antibodies to carbonic anhydrase II (anti-CAII) in healthy subjects, a significantly higher prevalence of the antibody was detected in patients with autoimmune pancreatitis (88.9%), Sjögren's syndrome (67.6%), and alcoholic chronic pancreatitis (45.8%). No positive results were obtained among patients with pancreatic cancer.¹⁵

Association with cholangitis

AIP is frequently associated with sclerosing cholangitis (SC). SC with AIP has a cholangiographic appearance that is often confused with primary SC (PSC) but only SC responds well to corticosteroid therapy. Detailed study of cholangiographic findings allows discrimination of SC with AIP from PSC.¹⁶

Treatment and prognosis

Oral prednisolone is effective in most cases to reduce the size of the mass and the clinical problems.^{13,14} AIP treated with oral prednisolone has a favorable long-term outcome based on the morphological findings and assessments of pancreatic function.¹⁷

A case has been reported of a patient with primary

Sjögren's syndrome who developed relapsing AIP to steroids but responded successfully to rituximab therapy.¹²

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