Liver and pancreatic disorders

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. 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, 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 10.1 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
biochemical findings, circulating autoantibodies and abnormalities of serum globulins.\textsuperscript{4,5} High-titre smooth-muscle antibodies have been found indicators for future development of AIH.\textsuperscript{8}

**Disease associations**
AIH may occur in conjunction with a variety of autoimmune disorders.\textsuperscript{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 troublesome.

One presentation of AIH is in the setting of medications, or herbal agents, used for other diseases. Minocycline and statins may trigger AIH.\textsuperscript{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 therapeutic approach.\textsuperscript{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.\textsuperscript{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

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

<table>
<thead>
<tr>
<th>variable</th>
<th>type 1</th>
<th>type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>characteristic autoantibodies</td>
<td>ANA smooth-muscle antibody, anti-actin antibody, autoantibodies to soluble liver antigen and liver–pancreas antigen, atypical p-ANCA</td>
<td>antibody to liver–kidney microsome 1, antibody to liver cytosol</td>
</tr>
<tr>
<td>geographic variation</td>
<td>worldwide</td>
<td>worldwide; rare in North America</td>
</tr>
<tr>
<td>age at presentation</td>
<td>any age</td>
<td>predominantly children and young adults</td>
</tr>
<tr>
<td>sex of patients</td>
<td>female in about 75% of cases</td>
<td>female in about 95% of cases</td>
</tr>
<tr>
<td>association with other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>autoimmune diseases</td>
<td>common</td>
<td>common</td>
</tr>
<tr>
<td>clinical severity</td>
<td>broad range</td>
<td>generally severe</td>
</tr>
<tr>
<td>histopathologic features at</td>
<td>broad range</td>
<td>generally advanced</td>
</tr>
<tr>
<td>presentation</td>
<td>infrequent</td>
<td>frequent</td>
</tr>
<tr>
<td>relapse after drug withdrawal</td>
<td>variable</td>
<td>common</td>
</tr>
<tr>
<td>need for long-term maintenance</td>
<td>variable</td>
<td>about 100%</td>
</tr>
</tbody>
</table>
is important because effective medical treatment with ursodeoxycholic acid can halt disease progression and extend survival free of liver transplantation.\textsuperscript{11}

**Clinical manifestations**

**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 μm 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.\textsuperscript{11}

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

**Disease associations**

**Treatment**

**Prognosis**

**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 anticientromere 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 ant carcic anhydrase, are usually present. Of note, no differences seem 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.\textsuperscript{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.\textsuperscript{10}

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

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

<table>
<thead>
<tr>
<th>disorder</th>
<th>prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>keratoconjunctivitis sicca</td>
<td>75</td>
</tr>
<tr>
<td>renal tubular acidosis</td>
<td>50</td>
</tr>
<tr>
<td>gallstones</td>
<td>30</td>
</tr>
<tr>
<td>arthritis</td>
<td>20</td>
</tr>
<tr>
<td>thyroid disease</td>
<td>15</td>
</tr>
<tr>
<td>systemic sclerosis</td>
<td>15</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>10</td>
</tr>
<tr>
<td>CREST syndrome</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 10.3 Extrahepatic autoimmune disorders associated with primary biliary cirrhosis\textsuperscript{11}
3. Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic progressive cholestatic liver disease characterized by inflammation and fibrosis of bile ducts, leading to the formation of bile duct strictures. PSC eventually develops into cirrhosis, portal hypertension and hepatic failure in the majority of patients.20

Clinical and diagnosis presentation of PSC

The clinical presentation of PSC is variable. Symptoms include right upper quadrant abdominal discomfort, fatigue, pruritus, and weight loss. Episodes of cholangitis (i.e., fever and chills) are uncommon features at presentation, in the absence of prior biliary surgery or instrumentation such as endoscopic retrograde cholangiography (ERC).

Physical examination is abnormal in about half of symptomatic patients at the time of diagnosis; jaundice, hepatomegaly, and splenomegaly are the most frequent abnormal findings. Many patients with PSC are asymptomatic with no physical abnormalities at presentation. The diagnosis is made incidentally when persistently cholestatic liver function tests are investigated. 60-80% of patients with PSC have concomitant inflammatory bowel disease, most often ulcerative colitis.

Magnetic resonance cholangiography (MRC), which is non-invasive and avoids radiation exposure, has become the diagnostic imaging modality of choice when PSC is suspected. Sensitivity and specificity of MRC is ≥80% and ≥87%, respectively, for the diagnosis of PSC. However, patients with early changes of PSC may be missed by MRC, and ERC still has a useful role in excluding large duct PSC where MRC views may not be optimal.20

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.

Course of PSC

When cirrhosis is present in a patient with PSC, portal hypertension will gradually develop.

Hepatic osteodystrophy is a metabolic bone disorder associated with chronic liver diseases. The diagnosis is made by bone mineral density measurement whereby osteopenia is characterized by a T-score between 1 and 2.5 standard deviations below the density observed in young normal individuals, and osteoporosis as a T-score beneath 2.5. The incidence of osteoporosis in PSC is between 4 and 10%

Patients with PSC are at risk for developing cholangiocarcinoma. The 10-year cumulative incidence is 7-9% in recent studies.

The estimated 10-year survival for PSC patients is about 65% in a population based study, but large individual variations exist.

Treatment of PSC

Treatments which are efficacious in other cholestatic liver diseases have been tested in PSC with a limited degree of success.

Ursodeoxycholic acid (UDCA) is an effective treatment of primary biliary cirrhosis. UDCA has, therefore, also been investigated for the treatment of PSC. Small pilot trials of UDCA demonstrated biochemical and histological improvement in PSC patients using doses of 10–15 mg/kg/day. However, the role for UDCA in slowing the progression of PSC-related liver disease is as yet unclear and high dose UDCA may be harmful (see Chapman et al 20).

Treatment with corticosteroids and other immunosuppressant agents have not demonstrated any improvement in disease activity or in the outcome of PSC. Small randomized, placebo-controlled or pilot trials have investigated the role of agents with immunosuppressive potency like prednisolone, budesonide, azathioprine, cyclosporin, methotrexate, mycophenolate, and tacrolimus, agents with TNFα antagonizing effects like pentoxifyllin, etanercept and anti-TNF monoclonal antibodies and antifibrotic agents like colchicine, penicillamine, or pirfenidone. There is no evidence that any of these drugs are efficacious and, therefore, none can be recommended for classic PSC.

Liver transplantation for PSC is highly successful with 5-year survival rates of about 85% in patients receiving deceased donor allografts. Disease recurrence occurred in 20-25%, after 5-10 years in patients, from the transplant procedure.20

Secondary sclerosing cholangitis is characterized by a similar biliary stricturing process due to identifiable causes such as long-term biliary obstruction, infection, and inflammation which in turn leads to destruction of bile ducts and secondary biliary cirrhosis. IgG4-positive sclerosing cholangitis might represent a separate entity.
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.

B. Other liver diseases

1. Granulomatous hepatitis

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

2. Hepatitis C

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.

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. 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 bili 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.

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.

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.

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.

Treatment and prognosis

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