Liver Involvement in Patients with Systemic Autoimmune Diseases

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ABSTRACT

Liver disease in SAD could be the consequence of various factors such as fatty infiltration, drug toxicity, and super-added infection by hepatotropic viruses, vascular thrombosis, diabetes, or overlap with autoimmune hepatitis (1). The most SAD patients could develop a mild transient abnormal liver function test during the disease course. Liver histology described in SAD is mostly based on needle biopsy. SAD have frequent subclinical liver disease with variably raised liver enzymes. Reported incidences of palpable liver in SAD range from 12% to 55% (2).

Clinical, inactive SAD have frequently been observed to have subclinical liver involvement. Increasingly, diffuse nodular regenerative hyperplasia of liver is reported with SAD, many with portal vein occlusion. Obliterative fibro inflammation of the terminal portal tract was observed in all diffuse nodular regenerative hyperplasia of the liver (DNRH) cases (3).

Keywords: systemic autoimmune diseases, liver, laboratory tests
In patients with SAD and abnormal liver function tests, histological examination of the liver is most frequently of value in indicating drug-induced liver damage. Significant chronic liver disease is common, but usually clinically apparent (4). Although hepatic manifestations are rare, the clinician should remain vigilant and aware of the existence of these diseases which may occur concomitantly or serially (5).

Patients with liver disease should be treated as soon as possible, especially those patients with jaundice or persistent increase of liver enzymes beyond three times normal values (6).

Knowledge of liver involvement in SAD is important for the accurate diagnosis of liver injury and to avoid unnecessary examination and treatment (7,8).

Systemic lupus erythematosus

More recently, liver involvement in systemic lupus erythematosus (SLE) is considered to have more clinical significance. Liver disease has been shown to be a common complication of SLE. 21% of the patients were defined as having liver disease on the basis of abnormal liver histology or the repeated two-fold or greater increase in two or more liver function tests. Elevated liver enzymes were observed in 81% and palpable liver was observed in 33% (7).

Differentiating features for autoimmune hepatitis (AIH) from SLE-related liver disease are heavy portal and periportal lymphoid inflammation, hepatocyte pseudorosette, and dominant portal tract plasma cell infiltration in AIH and heavier lobular inflammation in SLE. In SLE cases was reported a high incidence of DNRH. Diffuse nodular regenerative hyperplasia is a rare disorder characterized by diffuse micronodular transformation of the hepatic parenchyma with the nodular zone demarcated by compressed liver cell cords. Etiopathogenesis for DNRH in SLE is an immune complex deposit in small vessels resulting in obliterative venopathy. In SLE patients at autopsy, liver congestion was found to be the commonest histological changes followed by a fatty liver. Hepatocytic steatosis is usually attributed to steroid therapy in SAD which has been contradicted by some recent studies as it was observed only in a small percentage of patients who were on steroids. There have been reports of patients with overlapping SLE and AIH, thus confusing the diagnosis of liver disease in SLE patients (9-12).

Primary antiphospholipid syndrome

A variety of hepatic abnormalities may be seen in association with antiphospholipid syndrome (APS). The most of the cases of DNRH associated with SAD had antiphospholipid antibodies (aPL). Clinical manifestation of the disease rarely complicates the liver, mainly affecting smaller intrahepatic vessels resulting in hepatic vein occlusion and in the development of Budd-Chiari syndrome (13).

Myositis

Polymyositis (PM) is an autoimmune inflammatory muscle disorder. The term dermatomyositis (DM) is applied when PM is associated with a characteristic skin rash. The most sensitive enzyme assay is creatine kinase (CK); however levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) are also abnormally high. In the absence of CK determination, rises in AST, ALT, and LDH levels are often mistakenly attributed to hepatic disease. Inflammatory myositis is sometimes wrongly diagnosed as liver disease, delaying appropriate treatment. In the assessment of PM, attention should be drawn to the rise in serum alkaline phosphatase in view of the possible association between the two diseases (1-4).

Primary Sjögren’s syndrome

A limited number of studies have examined liver involvement in primary Sjögren’s syndrome (SS). Clinically unapparent but potentially significant chronic liver disease was found predominantly in patients with SICCA syndrome. The Sjögren’s complex has been associated with primary biliary cirrhosis (PBC), chronic autoimmune hepatitis (CAH) and cryptogenic cirrhosis. The incidence of liver disease in patients with primary SS (without rheumatoid arthritis, RA) was 6%. The association of primary SS with CAH and cryptogenic cirrhosis was 22.2%. The exact prevalence of PBC in primary SS is unknown. It should be noted that primary SS and PBC share many common features. In both conditions the inflammation starts around the ducts and both epithelial populations inappropriately express class II HLA molecules. CD4 positive T cells predominate in severe PBC lesions and salivary gland lesions in primary SS (2-5).
Systemic sclerosis

The hepatic involvement is rare. The liver disease usually associated with systemic sclerosis (SSc) is PBC. About 15% of patients with PBC have been reported to have SSc. The association of SSc with PBC is well known. SSc cases had mildly deranged liver enzymes with bridging fibrosis resulting in a vaguely nodular liver due to incomplete nodule formation. The liver disease usually associated with SSc is PBC. Diffuse nodular regenerative hyperplasia of the liver is a rare complication in patients with SSc. The relationship with primary sclerosing cholangitis (PSC) and SSc is extremely rare, but might be expected on the basis of the widespread disturbance of connective tissue in SSc, with abnormal collagen being deposited in the bile duct epithelium. Liver biopsies are not usually done as hepatic involvement in SSc has usually been considered non-specific (4,5).

Rheumatoid arthritis

Liver involvement is documented in up to 6% of patients with RA emerging in most of the cases as mild elevation of alkaline phosphatase and serum γ-glutamyltransferase levels. RA causes extra-articular manifestations which are rare and exceptionally serious in the liver. The most important hepatic disorders associated with RA are: intrahepatic portal hypertension without cirrhosis, amyloidosis, drug hepatotoxicity and viral interferences. Liver function tests may be abnormal in up to 65% of patients with RA and mainly involve increases of alkaline phosphatase and serum γ-glutamyltransferase levels. The histology of the liver in RA is non-specific and includes the findings of Kupffer cell hyperplasia, fatty cell infiltration, and infiltration of periportal areas with mononuclear cells (6).

Methotrexate is proposed for the treatment of inflammatory disorders such as RA. The liver toxicity of methotrexate has been investigated and prolonged treatment can induce liver fibrosis. Liver enzymes elevations during methotrexate therapy are a frequent but transient problem. Abnormal ALT/AST levels developed in 14-35% of patients with RA initiating disease-modifying antirheumatic drugs require laboratory monitoring. These findings should help inform monitoring for potential hepatotoxicity in these patients. Well documented liver toxicity of methotrexate led the American College of Rheumatology to provide guidelines about monitoring patients. Non-specific histological findings from the hepatic parenchyma accompany RA including Kupffer cell hyperplasia, fatty cell infiltration, and infiltration of periportal areas with mononuclear cells. Rheumatoid nodules scattered throughout the hepatic parenchyma were reported to complicate patients with active RA. Patients with unexplained liver abnormalities require further testing to exclude autoimmune hepatitis, alcoholic cirrhosis, amyloidosis, and PBC (4).

Adult Still’s disease

Adult Still’s disease is a syndrome that is similar to seronegative juvenile rheumatoid arthritis. Abnormalities in liver function tests were identified in 92% of patients and included 17% of patients with levels of serum aminotransferases that were five times the normal level and 83% of patients with levels that were between two and five times the normal level. Although serum aminotransferases were elevated significantly; many patients (75%) were asymptomatic (2).

Felty’s syndrome

Felty’s syndrome (RA, splenomegaly, and neutropenia) rarely involves the liver. The incidence of hepatic involvement in Felty’s syndrome fluctuates among the published series. Clinical manifestation commonly includes hepatomegaly, abnormal liver chemistry and portal hypertension. Histological findings included diffuse lymphocytic infiltration within the sinusoids, Kupffer cell hyperplasia, fatty cell infiltration, and infiltration of periportal areas with mononuclear cells (6).

Vasculitic syndromes

In addition, the hepatic vessels can be affected directly by such systemic diseases as vasculitis. The liver is affected in a variety of systemic diseases involving the vessels. Vasculitis involves the liver not infrequently. Known causes include polyarteritis nodosa (PN), SLE, RA, and temporal (giant cell) arteritis. The intrahepatic vessels may show fibrinoid necrosis, and
aneurysms and hemorrhage may be found. In patients with PN and mixed cryoglobulinemia, liver biopsy may be of value diagnostically, revealing serious liver disease with prognostic and therapeutic implications. Polyarteritis nodosa is of particular interest because it may be related to hepatitis B infection. Liver involvement can range from hepatomegaly with or without jaundice to signs of extensive hepatic necrosis. The liver in such patients typically show an active vasculitis in the setting of a liver showing minimal histologic evidence of damage by the chronic hepatitis. The pathogenesis of nodular regenerative hyperplasia has not been defined, but vasculitis seems to be important in the initiation and progression of liver structural lesions. Obstructive jaundice, abdominal pain, hepatomegaly and abnormal liver function tests are sufficiently indicative of hepatic involvement and they precede typical Kawasaki symptoms (14).

**REFERENCES**


**CONCLUSIONS**

It is important for the rheumatologist to be aware of, and monitor for, dysfunction of the liver not only as a result of pharmacotherapy but also as a primary disorder associated with rheumatic disease. There is an association between systemic autoimmune diseases and the liver. Asymptomatic hepatomegaly and elevation of liver function tests is commonly observed. Patients with liver disease should be treated as soon as possible, especially those patients with jaundice or persistent increase of liver enzymes beyond three times normal values. Hepatic manifestations in SAD include chronic hepatitis, primary biliary cirrhosis, and nodular regenerative hyperplasia.

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