

## REVIEW

## Hepatic manifestations of autoimmune rheumatic diseases

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Hepatic manifestations in autoimmune disease include chronic active hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and nodular regenerative hyperplasia. These diseases are rare and may occur concomitantly or serially. Clinicians must be aware of the possibility of liver disease so that it can be treated as soon as possible.

The liver is the largest gland in the body, weighing 1500 g, with many complex functions, including that of manufacture, degradation, and detoxification of numerous compounds. These include formation of bile and urea. The liver also synthesises 25-hydroxy-cholecalciferol and manufactures plasma proteins. It metabolises cholesterol, fat, polypeptide hormones, and reduces and conjugates adrenocortical and gonadal steroid hormones. Detoxification of drugs and toxins is also another vital role of the liver. These functions of the liver allow for the body's maintenance of homeostasis.

A wide variety of rheumatic diseases affects the liver and their prevalence, significance, and specific hepatic pathology varies. 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. In this review a critical analysis of liver involvement in the main autoimmune rheumatic diseases—namely, systemic lupus erythematosus (SLE), primary antiphospholipid syndrome (APS), polymyositis, primary Sjögren's syndrome (SS), scleroderma, rheumatoid arthritis (RA), and Felty's syndrome, is described.

Table 1 shows the principal forms of hepatic abnormality.

### Methodology

A Medline search of all published papers and case reports of hepatic involvement in the aforementioned rheumatic diseases, published between 1966 and 2001, was made.

### SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is a chronic autoimmune disease characterised by multisystemic involvement and diverse clinical and serological manifestations, principally affecting women during the child bearing years. It seems likely abnormalities in apoptosis may be important.<sup>1</sup>

Clinically significant hepatic disease is generally regarded as unusual in SLE. However, in a retrospective review of the spectrum of liver

disease in 238 patients with SLE published over 20 years ago<sup>2</sup> the clinical changes included hepatomegaly (39%), splenomegaly (6%), jaundice (24%), and 21% of the patients were defined as having liver disease on the basis of abnormal liver histology or the repeated twofold or greater increase in two or more liver function tests. These abnormalities were thought primarily to be due to SLE as other causative factors such as viral hepatitis or drug toxicity were excluded. Liver histology was available in 33 patients and included the following findings: steatosis (n = 12 cases), cirrhosis and chronic active hepatitis (n = 4), hepatic granulomas and centrilobular necrosis (n = 3), chronic persistent hepatitis and microabscesses (n = 2), and one case each of haemochromatosis, cholestasis, primary biliary cirrhosis, and non-specific reactive changes. Therefore nine (4.4%) of the patients with SLE had serious chronic liver disease—namely, cirrhosis, chronic active hepatitis and primary biliary cirrhosis, and three had died from hepatic failure at the time of review.

“Hepatic disease may be more common in SLE than is usually thought”

The study also indicated that the incidence of mucosal ulcers, cytopenia, and thyroid disease was significantly higher in the group with than in the group without liver disease; in contrast, arthralgias were significantly less common in the group with liver disease. An explanation for these associations was not readily apparent.

Runyon's observational study gives a detailed, comprehensive report of their cohort of patients with SLE but relied heavily on the record keeping by the attending doctor. Although the persistent increases of liver enzymes and histological analyses were objective measures of liver disease, the incidence of hepatomegaly appears to have been measured clinically and no mention was made of radiological confirmation of this clinical sign. However, this study does illustrate that the occurrence of liver disease, which is not routinely screened for in SLE, was significant in their cohort. It also illustrated that treatment could

**Abbreviations:** ACA, anticentromere antibodies; aCL, anticardiolipin antibodies; AMA, antimitochondrial antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; CAH, chronic active hepatitis; DM, dermatomyositis; HCV, hepatitis C virus; LDH, lactate dehydrogenase; NRHL, nodular regenerative hyperplasia of the liver; PBC, primary biliary cirrhosis; PM, polymyositis; RA, rheumatoid arthritis; PSC, primary sclerosing cholangitis; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome

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**Table 1** Major forms of hepatic abnormalities recorded in patients with autoimmune rheumatic diseases

Abnormality	Definition/comment
Chronic active hepatitis	The morphological hallmark of CAH is piecemeal necrosis. This is defined as the destruction of liver cells at the interface between parenchyma and connective tissue together with a predominantly mononuclear inflammatory infiltrate. Clusters of lymphocytes and macrophages encircle or invaginate hepatocytes with a spreading wave of necrosis. As the liver parenchyma is destroyed sheets of connective tissue are laid down, which initially also contain an inflammatory infiltrate resulting in a 'maple leaf' configuration to the portal tract.
Chronic persistent hepatitis	CPH is characterised by chronic inflammatory infiltration of portal tracts with preserved lobular architecture and little or no portal fibrosis, although the tracts are expanded. There is no significant piecemeal necrosis. CPH disease is mostly stationary and in many instances resolves spontaneously, far more frequently than CAH.
Hepatomegaly	Defined clinically as a palpable liver and usually but not always confirmed by ultrasound or CT scanning or at post mortem.
Lupoid hepatitis	A combination of CAH with LE cell phenomena. May be distinguished from SLE by the absence of antibodies to double stranded DNA.
Nodular regenerative hyperplasia of the liver	Characterised by diffuse nodularity of the liver with little or no fibrosis, and has been found in association with autoimmune disease, after drug treatment and a variety of haematological disorders.
Primary biliary cirrhosis	PBC is an autoimmune inflammatory disorder associated with a high serum titre of antimitochondrial antibodies. Histological appearances divided into four stages: (I) florid bile-duct lesions with lymphoid aggregates (II) ductular proliferation (III) scarring (septal fibrosis and bridging) (IV) cirrhosis.
Primary sclerosing cholangitis	A chronic inflammatory disorder that ultimately results in fibrosis and obliteration of the bile ducts. It is strongly associated with inflammatory bowel disease and runs an unpredictable course.

improve the outcome as proved by an improvement in liver enzymes and in a few cases histological analysis on repeat liver biopsy.

Another systematic study of 19 patients with SLE who had hepatomegaly or abnormal liver function tests showed that six of these patients had normal or insignificant changes in liver histology; 11 showed minor alterations, including fatty change, portal tract fibrosis, mild to moderate cellular infiltration, and two had chronic active hepatitis which had progressed to cirrhosis.<sup>3</sup> In a study of 18 unselected patients with SLE five had normal liver histology and 13 showed the same minor changes previously described.<sup>4</sup>

The incidence of hepatomegaly in SLE varies from 12 to 55%, depending on the series.<sup>5-10</sup> None of the studies which note hepatomegaly define how it was determined and therefore one speculates that this diagnosis was made clinically, which of course can be subjective and open to inter- and intraobserver error. Pathologically a wide variety of lesions may be seen. Excessive fatty infiltration (steatosis) is a common finding and may occur as part of the disease process itself rather than secondary to steroid treatment.<sup>11</sup>

Lupoid hepatitis was first described by Joske and King in 1955 and formally named by Mackay in 1956. The patients are generally young women with chronic active hepatitis and positive LE preparations. The current working definition of lupoid hepatitis includes (a) liver pathology consistent with chronic active hepatitis; (b) absence of evidence for active viral hepatitis; and (c) positive antinuclear antibodies or LE cell preparation. Although fever, arthralgia, malaise, loss of appetite, and jaundice are common in patients with lupoid hepatitis, many classical physical findings associated with SLE (for example, rashes, other organ involvement) are typically absent. Four patients with both conditions were

reported by Runyon.<sup>1</sup> In one patient, bridging superimposed on severe chronic granulomatous hepatitis had occurred. This patient subsequently died from post-necrotic cirrhosis. Chronic active hepatitis (CAH) became chronic persistent hepatitis in one patient and steatosis in another. Patients with CAH and features of SLE should probably be considered as having both diseases, so that the liver lesion should be treated appropriately while careful vigilance is maintained for the other life threatening manifestations of SLE.

In recent years the classification of autoimmune hepatitis based on specific autoantibodies, such as antibodies to nuclei, smooth muscle, and liver microsome, has been proposed.<sup>12</sup> Two cases have been reported of new autoantibodies to transfer RNA related antigens in patients with SLE associated with autoimmune hepatitis.<sup>13</sup> In a retrospective study by Fox *et al* unexplained deranged liver function tests were found to be uncommon in their cohort of 200 patients (2.5%).<sup>13a</sup> They concluded these abnormalities were rarely of clinical significance and there was no association with ribosomal P antibodies.

Gibson and Myers in a retrospective study of liver enzyme patterns in 81 patients with SLE, found that 55% had abnormal values and 29% had no cause for these changes other than the SLE.<sup>14</sup> Portal inflammation was seen in five, fatty liver in one, and chronic active hepatitis in another. Liver enzyme levels were found to be raised in 23% of 260 patients with SLE assessed in a study by Miller *et al*.<sup>15</sup> In 15%, a cause other than SLE for the abnormality was found. Alcohol was implicated in five patients. No progression of the abnormalities occurred over a two year follow up period in four patients. This was the only prospective study found in our review. A prospective study gives a more rigorous control and consistency of data acquisition, and in this study 100

controls without SLE but who were seen in the rheumatic disease unit were also included. The controls were selected to yield a sex ratio and mean age comparable with that of the SLE group. None of the control group had abnormal tests of liver function related to their disease and the tests were explained by excessive alcohol intake and in one case metastatic carcinoma of the liver. In 12 of 15 patients, changes in alanine aminotransferase levels were concordant with systemic lupus activity, while in two, chronic rises of these levels were seen with fluctuations discordant with lupus activity. Two patients had raised alkaline phosphatase levels only.

Aspirin plays an important part in the production of liver enzyme abnormalities in patients with SLE. Reversible rises of the aminotransferases are quite common<sup>16, 17</sup> and may be accompanied by an increase of alkaline phosphatase activity. The toxicity appears to occur at lower salicylate levels than in people without lupus. Compounds such as the non-steroidal anti-inflammatory drugs, including naproxen,<sup>18</sup> fenoprofen,<sup>19</sup> and sulindac,<sup>20</sup> may cause cholestatic hepatitis in lupus patients.

In summary, although liver involvement of patients with SLE is uncommon, clinically significant manifestations can occur de novo or secondary to pharmacological agents. It is therefore important to be aware and monitor patients for such complications.

### PRIMARY ANTIPHOSPHOLIPID ANTIBODY SYNDROME

The APS is defined by clinical features of arterial and venous thrombosis, recurrent pregnancy loss and thrombocytopenia, and the presence of antiphospholipid antibodies (aPL), essentially anticardiolipin antibodies (aCL) and antibodies with lupus anticoagulant activity.

A variety of hepatic abnormalities may be seen in association with APS. Seven reports of hepatic vein occlusion resulting in Budd-Chiari syndrome have been published.<sup>21-27</sup> The antibodies may also be of importance in the pathogenesis of other hepatic lesions, some of which have a vascular basis and involve smaller intrahepatic vessels.<sup>28</sup>

In 1998 Perez-Ruiz *et al* suggested a possible role of the aPL in the pathogenesis of nodular regenerative hyperplasia of the liver (NRHL).<sup>28a</sup> NRHL is a rare disorder characterised by diffuse micronodular transformation of the hepatic parenchyma with the nodular zone demarcated by compressed liver cell cords. To date 10 patients with NRHL related to aPL have been reported: eight women and two men, with a mean age of 44 years (range 15-76). Patterns of clinical presentation included altered liver function tests or signs and symptoms of portal hypertension (hepatosplenomegaly, ascites or oesophageal variceal bleeding). aCL were positive in nine patients and lupus anticoagulant in six. Published reports suggest that most of the cases of NRHL associated with systemic autoimmune disease had aPL and other thrombotic events. Therefore, the diagnosis of NRHL should be considered and liver specimens obtained for histological evaluation in patients with aPL who develop persistently altered liver function tests or who present with signs and symptoms of portal hypertension.

A rise in hepatic enzymes, presumably because of fibrin thrombi in the smaller intrahepatic vessels, also seems to occur in patients with aPL without any obvious explanation and was first reported by Elias and Eldor in 1984.<sup>29</sup>

### MYOSITIS

Polymyositis (PM) is an autoimmune inflammatory muscle disorder. The term dermatomyositis (DM) is applied when PM is associated with a characteristic skin rash.

One third of cases are associated with various autoimmune rheumatic disorders, and perhaps one tenth with a malignancy. The incidence of this paraneoplastic syndrome is

higher in men, especially those with DM, than in women over the age of 55 years. Any neoplasm can be responsible for this association, with the most common malignancies being lung, ovary, uterus, gastrointestinal tract, prostate, and myeloproliferative disorders. Hitherto, only two cases of hepatocellular carcinoma associated with PM have been reported.<sup>30</sup>

The inflammatory myopathies, such as PM or DM are characterised by the development of proximal and often symmetrical muscle weakness that develops slowly, generally over weeks to months. Vague constitutional complaints may also be noted, such as malaise, weight loss, and arthralgias. The critical tests for establishing or confirming the diagnosis of these inflammatory myopathies are measurement of serum muscle enzyme levels, electromyography, and muscle biopsy. The most sensitive enzyme assay is creatine kinase; however, levels of aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase (LDH) are also abnormally high. In the absence of creatine kinase determination, rises in aspartate aminotransferase, alanine aminotransferase, and LDH levels are often mistakenly attributed to hepatic disease. The picture may be further confused by the presence of the non-specific constitutional complaints, all of which may be seen in association with most forms of hepatitis. Four cases of patients with biopsy proven inflammatory myositis, who initially were diagnosed as having a liver disease because of raised levels of serum transaminases and LDH, have been described. The misinterpretation of these values resulted in significant delays in diagnosis and institution of appropriate drug treatment.

*“Inflammatory myositis is sometimes wrongly diagnosed as liver disease, delaying appropriate treatment”*

An association between adult PM and chronic active hepatitis has been described in one case report. This patient presented with all the criteria for the diagnosis of PM and pathological and serological findings consistent with chronic active hepatitis. In addition, the patient's serum contained an unusual autoantibody reacting with mitochondrial proteins (M-B) in immunodiffusion.<sup>31</sup>

Primary biliary cirrhosis (PBC) is a chronic progressive cholestatic liver disease of unknown aetiology associated with a multiplicity of antibodies such as antimitochondrial antibodies (90%), rheumatoid factor (70%), and anti-dsDNA (22%). To date only six cases of PM associated with PBC have been reported in English publications<sup>32</sup>; all the patients were women. Two patients with PBC and PM had concomitant scleroderma and one patient had an associated Raynaud's phenomenon. In three patients, PBC antedated the PM by 1-6 years, in two patients, the disease was diagnosed simultaneously, and only in one case did PM precede PBC (table 2). Therefore, 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.

### RHEUMATOID ARTHRITIS

Liver function tests may be abnormal in up to 6% of patients with RA<sup>32, 33</sup> and mainly involve increases of alkaline phosphatase and serum  $\gamma$ -glutamyltransferase levels.<sup>34</sup> In a study of 98 patients with RA, 12 showed increases of both alkaline phosphatase and  $\gamma$ -glutamyltransferase levels, but isoenzyme alkaline phosphatase studies disclosed that in three of seven patients, an increase in bone isoenzyme was responsible for the rise of alkaline phosphatase. In the others, the liver isoenzyme alone was raised, and in one patient, both were raised.

The histology of the liver in RA is non-specific and includes the findings of Kupffer cell hyperplasia, fatty cell infiltration,

**Table 2** Summary of six cases of PM associated with PBC

Age	Sex	Associated disease	Presenting disease	Presenting symptoms	Time elapsed to development of 2nd disease (months)
48	F	Primary SS	PBC	Asymptomatic	72
58	F	None	PBC	Asymptomatic	12
30	F	Primary SS	PBC	Rt. hypochondriac pain	24
45	F	Raynaud's	PM	Weakness	7
68	F	None	PBC-PM	Weakness, fatigue, pruritus, jaundice	NA
52	F	None	PM	Weakness, fatigue	NA

NA, not applicable.

and infiltration of periportal areas with mononuclear cells.<sup>35</sup> Rau *et al* carried out liver biopsies on 117 unselected patients with RA, many of whom had normal liver function tests, and found abnormal hepatic histology in 65%.<sup>36</sup> "Reactive" hepatitis was present in 43% and fatty liver in 22%. Non-specific reactive changes were also found in 74% of 31 patients with RA in yet another study.<sup>37</sup> These changes consisted of mild chronic inflammatory cell infiltration of the portal tracts, small scattered foci of liver cell necrosis, increased centrilobular lipofuscin deposits, and occasional fat containing hepatocytes. Definite liver disease was present in only four patients.

### FELTY'S SYNDROME

Felty's syndrome (RA, splenomegaly, and neutropenia) rarely involves the liver. Blendis *et al* reported that five out of 12 patients in his series had hepatomegaly and rise of serum alkaline phosphatase.<sup>38</sup> Liver histology in eight patients showed diffuse lymphocytic infiltration within the sinusoids and Kupffer cell hyperplasia.

Three patients had periportal fibrosis with lymphocytic infiltration and one had macronodular cirrhosis. There was no correlation between abnormal liver chemistry and the histological findings. The incidence of hepatic involvement is unknown but in one series, hepatomegaly was found in 68% and abnormalities of liver blood testing were noted in 25% of these patients studied.<sup>39</sup>

Portal hypertension with oesophageal varices and gastrointestinal bleeding may be a major complication in Felty's syndrome. Seven patients with this complication had mild liver enzyme abnormalities and liver histology showed mild portal tract fibrosis, lymphocytic infiltration, and fatty metamorphosis.<sup>40</sup>

Nodular regenerative hyperplasia of the liver, which is an unusual histological finding, has been seen in Felty's syndrome. Among the five patients Blendis reported with this finding, three patients had an increase of serum alkaline phosphatase and evidence of portal hypertension. Nodular regenerative hyperplasia was not found in 51 patients with RA or in 21 with other autoimmune rheumatic diseases.

### SCLERODERMA

Scleroderma is a multisystem autoimmune rheumatic disorder characterised by fibrosis in the skin and a number of internal organs, although hepatic involvement is rare.

Liver disease found in association with scleroderma was first described by Milbradt in 1934. Liver disease has not been considered a significant feature of scleroderma and, in a large series, a higher prevalence of liver disease was found in the control populations.<sup>41, 42</sup> However, in a retrospective review of postmortem findings in scleroderma, hepatomegaly and cirrhosis were both more common in a matched control group. In a prospective assessment of the extent of visceral involvement in scleroderma 16/31 (52%) patients were shown to have abnormal liver function tests or lengthened

prothrombin times.<sup>43</sup> In a review of 727 patients with scleroderma only 8 (1.1%) had hepatic involvement.<sup>44</sup>

The liver disease usually associated with scleroderma is PBC. PBC was first described in 1950<sup>45</sup> and is a chronic autoimmune liver disease with progressive inflammatory obliteration of medium sized intrahepatic biliary ducts, predominantly affecting middle aged women. The disease usually presents with pruritus followed by slowly progressive jaundice. It is characterised serologically by antimitochondrial antibodies (AMA), usually existing in 90–95% of patients with PBC,<sup>45</sup> and histologically by chronic non-suppurative destructive cholangitis.

Although the prevalence of PBC in patients with scleroderma is not clear, about 15% of patients with PBC have been reported to have scleroderma, with most of these having the variant of limited scleroderma. In a detailed study of 83 patients with PBC 14 (17%) were found to have scleroderma, which was usually confined to mild cutaneous changes and loss of oesophageal peristalsis. The association of limited scleroderma and PBC was first described by Murray-Lyon *et al* in 1970,<sup>46</sup> who described two cases of PBC and limited scleroderma. A further six cases were added by Reynolds *et al*<sup>47</sup> and, subsequently, many individual and multiple case reports have emerged linking limited scleroderma with PBC. O'Brien *et al* in 1972 described the first case in which PBC and scleroderma, without features of limited scleroderma, were associated.<sup>48</sup> These cases have remained small in number, but the association of PBC and scleroderma seems to be more than coincidental and suggests that these two diseases might have a common autoimmune basis. This is supported by studies which indicate that anticentromere antibodies (ACA) tend to occur in association with AMA.

In one study 22/558 (3.9%) patients were found to have evidence of limited scleroderma with PBC. Of these, limited scleroderma predated the diagnosis of PBC in 59% (and 91% were also diagnosed with Sjögren's syndrome). All 22 patients, who clinically had limited scleroderma, tested positive for ACA. It was suggested that testing for ACA may provide an indication of those at risk of developing limited scleroderma in the future. The authors suggested the acronym "PACK" to encompass the major components of the syndrome (PBC, ACA, CREST, and keratoconjunctivitis). This study suggested rather than proved a specific association between PBC and limited scleroderma.<sup>49</sup> It is likely that the association is genuine, as the simultaneous occurrence of limited scleroderma with other forms of liver disease has not been recognised by clinicians. However, the study did not include control patients with other cholestatic disease (for example, sclerosing cholangitis) and other immune mediated liver diseases (for example, autoimmune chronic active hepatitis).

Because ACA have been detected not only in scleroderma but also in other autoimmune disease,<sup>50–52</sup> including PBC,<sup>53, 54</sup> it has been of interest to study the clinical significance of ACA. Three major centromere antigens have been recognised.

One study attempted to identify the major epitope of ACA in sera from patients with PBC and to classify the correlation between the presence of ACA epitopes and the clinical features in patients with PBC. The serological results obtained were compared with clinical features of limited scleroderma in PBC. Forty one patients with PBC were studied. Ten of 16 (63%) patients with ACA had one or more features of limited scleroderma. The higher incidence of Raynaud's phenomenon seen in ACA positive patients with PBC than in ACA negative patients with PBC suggests a close association of the presence of ACA with clinical features of limited scleroderma in patients with PBC. From the results of this study it was proposed that there is a subset of patients with PBC: patients with scleroderma who are ACA positive, who differ from both ACA negative PBC scleroderma and PBC non-scleroderma patients, based on their clinical features and epitopes to which their ACA reacted.<sup>55</sup>

Lymphocytic infiltration of bile ducts and salivary gland ducts in PBC and Sjögren's syndrome, respectively, is also well known. The similar features in the two organs may be indicative of a common mechanism for the two associated disorders and perhaps even a shared evoking agent or event. In scleroderma the possibility that lymphocytes stimulate autologous fibroblasts to overproduce collagen<sup>56</sup> is intriguing and the possibility that a similar mechanism might apply in PBC merits investigation.

NRHL is a rare complication in patients with scleroderma. After the first report of NRHL associated with limited scleroderma was made in 1973,<sup>57</sup> the association of NRHL with limited scleroderma has been widely quoted, but only a handful of cases have been reported. Furthermore, a new clinical entity of limited scleroderma with NRHL and PBC has been proposed. These have been cases of limited scleroderma associated with NRHL in which there were serological and biochemical abnormalities characteristic of PBC. An overlap syndrome between NRHL, PBC, and limited scleroderma may exist. McMahon *et al* reported a case of a patient with limited scleroderma, raised alkaline phosphatase and IgM, positive ACA and AMA.<sup>58</sup> The patient had evidence of portal hypertension, with a liver biopsy that showed changes consistent with NRHL and without histological evidence of PBC.

The relationship with primary sclerosing cholangitis (PSC) and scleroderma is extremely rare,<sup>59</sup> but might be expected on the basis of the widespread disturbance of connective tissue in scleroderma, with abnormal collagen being deposited in the bile duct epithelium. Most patients with PSC remain asymptomatic for a considerable period of time even with cholestatic abnormalities of the liver function tests. Our literature search disclosed only one case report of PSC in scleroderma.<sup>60</sup> Several reasons are possible for the sparse number of cases reported. Liver biopsies are not usually done as hepatic involvement in scleroderma has usually been considered non-specific, and secondly the clinical course of PSC is asymptomatic in many cases and often with normal liver function tests. There is also a considerable overlap in the clinical and biochemical features of PSC and PBC, the latter disease being a well known association of scleroderma.

### PRIMARY SJÖGREN'S SYNDROME

Primary Sjögren's syndrome (primary SS) is a chronic inflammatory autoimmune exocrinopathic disease that affects predominantly the salivary and lachrymal glands.

A limited number of studies have examined liver involvement in primary SS. Christiansson first mentioned the association of primary SS with liver disease in 1954.<sup>61</sup> The Sjögren's complex has been associated with PBC, chronic autoimmune hepatitis, and cryptogenic cirrhosis. Whaley *et al* reported the incidence of liver disease in patients with primary SS (without RA) as 6%.<sup>62</sup> Later, it was further

demonstrated that the association of primary SS with CAH and cryptogenic cirrhosis was 22.2%.<sup>63</sup>

In one study, 300 patients with primary SS were investigated for liver disease using clinical, biochemical, immunological, and histological data. Seven per cent of patients showed evidence of liver disease either sub-clinical (2%) or asymptomatic (5%) with raised liver enzymes. In 6.6% AMA were detected by immunofluorescence.<sup>64</sup>

The clinical course of AMA positive histologically presenting patients with PBC is not known. However, the authors stated that after more than seven years' follow up of some of these patients, cirrhosis had not been seen. The authors concluded that liver disease in patients with primary SS was rare, subclinical, and did not lead to cirrhosis and that AMA were the most sensitive indicator of underlying liver disease in patients with primary SS. A similar study, with a smaller sample of patients, concluded that abnormal liver function tests in patients with primary SS are common and may indicate associated autoimmune liver disease. Lindgren *et al* demonstrated abnormal liver function tests in 12/45 (27%) patients with primary SS. Based on established clinical criteria, including liver biopsy, a diagnosis of PBC was established in four patients and autoimmune CAH in two.<sup>65</sup> Manthorpe *et al* found AMA in 5% of patients with primary SS and smooth muscle antibodies in 30%, with corresponding figures for secondary SS being 23% and 37% respectively.<sup>66</sup>

Vogel *et al* studied 12 patients with primary SS, in whom deranged liver function tests were found in four. However, liver biopsies only showed non-specific changes. The authors concluded that these changes should be interpreted not as an independent liver disease but as accompanying symptoms of the main, autoimmune disease.<sup>67</sup> It therefore appears that the question of whether SS is a sign of a liver complaint, or vice versa, can be answered only by a liver biopsy.

An overlap between PBC and primary SS has been well known since the early work of Golding *et al*<sup>68</sup> and Alarcon-Segovia *et al*.<sup>68</sup> The exact prevalence of PBC in primary SS is unknown, but Shearn diagnosed PBC in 5/80 (6%) patients with primary SS. Hansen *et al* found histological evidence of focal sialadenitis in 95% of patients with PBC, with anti-La antibodies being detected in sera from 38% of patients with PBC.<sup>69</sup> 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 biliary cirrhosis lesions and salivary gland lesions in primary SS. Thus in both disease entities common pathogenetic mechanisms operate despite the fact that their autoantibody profiles are different. In patients with primary SS anti-Ro and anti-La antibodies predominate while in PBC the predominant specific autoantibodies are AMA.

Viral infection has long been suspected as a potential cause of primary SS because several viruses (mainly herpes viruses and retroviruses) have been incriminated in its development and a possible relationship between primary SS and hepatitis C virus (HCV) was postulated in 1992.<sup>70</sup> Haddad *et al* reported the occurrence of characteristic histological changes of Sjögren's complex in the salivary glands of patients with HCV infection.<sup>70</sup> The prevalence of antibodies to HCV in patients with primary SS has been reported to be between 14 and 19%<sup>71</sup> by enzyme linked immunosorbent assay (ELISA). Using polymerase chain reaction, detection of HCV viraemia in patients with primary SS ranges between 0 and 19%. This is significantly higher than the prevalence of HCV infection found in the general population (1%). In comparison with patients with primary SS without HCV infection, patients

**Table 3** Main associations of liver disease in rheumatic autoimmune diseases

Disease	Signs	Histology
Antiphospholipid syndrome	Budd-Chiari syndrome Hepatosplenomegaly Jaundice Raised ALT	Nodular regenerative hyperplasia
Felty's syndrome	Hepatomegaly Portal hypertension Raised ALP	Kupffer cell hyperplasia Steatosis Mild portal tract fibrosis Nodular regenerative hyperplasia
Myositis	Jaundice Raised ALP	Chronic active hepatitis (rare) Primary biliary cirrhosis
Rheumatoid arthritis	Raised ALP Raised $\gamma$ -glutamyltransferase	Kupffer cell hyperplasia Steatosis
Scleroderma	Hepatomegaly Prothrombin time Jaundice Raised liver enzymes	Cirrhosis Primary biliary cirrhosis Nodular regenerative hyperplasia
Sjögren's syndrome	Raised liver enzymes Jaundice	Primary biliary cirrhosis Chronic active hepatitis Cryptogenic cirrhosis
Systemic lupus erythematosus	Hepatomegaly Jaundice Raised ALT	Steatosis Chronic active hepatitis

with this infection had a higher prevalence of hepatic involvement (100% in one study).<sup>72</sup>

The detection of AMA in the serum of patients with primary SS with or without raised liver enzymes is highly indicative of early liver disease in patients with primary SS. Abnormal liver function tests alone are frequent and should suggest autoimmune liver disease.

## CONCLUSION

Hepatic manifestations in autoimmune disease include chronic active hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and nodular regenerative hyperplasia. This review highlighted the main associations of liver disease in rheumatic autoimmune diseases (table 3). Although hepatic manifestations are rare, the clinician should remain vigilant and aware of the existence of these diseases which may occur concomitantly or serially. 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.

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## REFERENCES

- Wylie AH, Kerr JFR, Curie AK. Cell death: the significance of apoptosis. *Int Rev Cytol* 1980;**68**:251–306.
- Runyon RA, LaBrecque DR, Asuras S. The spectrum of liver disease in SLE. Report of 33 histologically proved cases and review of the literature. *Am J Med* 1980;**69**:187–94.
- Mackay IK, Taft II, Cowling DC. Lupoid hepatitis and the hepatic lesions of SLE. *Lancet* 1959;**5**:65–9.
- Chwalinska-Sadowska H, Milewski B, Maldyk H. Clinical and immunopathological evaluation of pathological changes in the liver in collagenoses. *Mater Med Pol* 1976;**8**:421–8.
- Dubois EL, Tuffanelli DL. Clinical manifestations of SLE. *JAMA* 1964;**190**:104–11.

- Ropes MW. SLE Cambridge: Howard University Press, 1976;**40**:56.
- Jessar RA, Lamont-Havers RW, Mayan C. Natural history of lupus erythematosus disseminatus. *Ann Int Med*, 1953;**38**:717–31.
- Estes D, Christian DL. The natural history of SLE by prospective analysis. *Medicine (Baltimore)* 1971;**50**:84–95.
- Kofman S, Johnson GC, Zimmerman HJ. Apparent hepatic dysfunction in SLE. *Arch Intern Med* 1955;**95**:669–76.
- Rothfield NF. SLE. *Rheumatic diseases: diagnosis and management*. Philadelphia: Lippincott, 1977:765.
- Hoyumpa AM, Greene HL. Fatty liver, biochemical and clinical considerations. *Am J Dig Dis* 1975;**20**:1142–70.
- Abuaf N, Johanet C, Homberg J. Autoantibodies in autoimmune chronic active hepatitis. *Autoimmune liver diseases*. New York: Raven Press, 1991:93–109.
- Satoh T, Hirakata M, Yoshida T, Matsumara M, Miyachi K. SLE associated with autoimmune hepatitis. Two cases with novel autoantibodies to transfer RNA-related antigens. *Clin Rheumat* 1997;**16**:305–9.
- Fox RA, Reichlin MW, Reichlin M, Isenberg DA. Liver function test abnormalities in systemic lupus erythematosus [abstract]. *Br J Rheumatol* 1997;**36**(Suppl):S10.
- Gibson T, Myers AR. Subclinical liver disease in systemic lupus erythematosus. *J Rheumatol* 1981;**8**:752–9.
- Miller MH, Urowitz MB, Gladman DD. The liver in SLE. *Q J Med* 1984;**211**:401–9.
- Seaman WE, Ishak KG, Plotz PH. Aspirin-induced hepatotoxicity in patients with systemic lupus erythematosus. *Ann Int Med* 1974;**80**:1–8.
- Travers RL, Hughes GR. Salicylate hepatotoxicity in SLE: a common occurrence? *BMJ* 1978;**ii**:1532–3.
- Law IP, Knight H. Jaundice associated with naproxen. *NEJM* 1976;**295**:1201.
- Stennet DJ, Simonson W, Hall CA. Fenoprofen induced hepatotoxicity. *Am J Hosp Pharm* 1978;**35**:901.
- Dhand AK, LaBrecque DR, Metzger J. Sulindac (Clinoril) hepatitis. *Gastroenterology* 1981;**80**:585–6.
- Mackworth-Young CG, Melia WM, Harris EN, Gharavi AE, Sivathondan Y, Derue G, et al. The Budd-Chiari syndrome. Possible pathogenic role of antiphospholipid antibodies. *J Hepatol* 1986;**3**:83–6.
- Averbuch M, Levo Y. Budd-Chiari syndrome as the major thrombotic complication of SLE with lupus anticoagulant. *Ann Rheum Dis* 1986;**45**:435–7.
- Van Steenberg W, Beyls J, Vermeylen J, Fevery J. "Lupus" anticoagulant and thrombosis of the hepatic veins (Budd-Chiari syndrome). Report of three patients and review of the literature. *J Hepatol* 1986;**3**:87–94.
- Roudot-Thoraval F, Gouault-Heilmann, Zafrani ESS, Barge J, Dhumeaux D. Budd-Chiari syndrome in a patient with the lupus anticoagulant. *Gastroenterology* 1985;**88**:605.
- Bernstein ML, Salusinsky-Sternbach M, Bellefleur M, Esseltine DW. Thrombotic and hemorrhagic complications in children with lupus anticoagulant. *Am J Dis Child* 1984;**138**:1132–5.

- 26 **Vermylen J**, Blockmans D, Spitz B, Deckmyn H. Thrombosis and immune disorders. *Clin Haematol* 1986;**15**:393-412.
- 27 **Pomeroy C**, Knodell RG, Swaim WR, Arneson P, Mahowald ML. Budd-Chiari syndrome in a patient with the lupus anticoagulant. *Gastroenterology* 1984;**86**:158-61.
- 28 **Cervera R**, Asherson RA, Lie TJ. Clinicopathological correlations of the antiphospholipid syndrome. *Semin Arthritis Rheum* 1995;**24**:262-72.
- 28a **Perez-Ruiz F**, Zera-Mendoza AC. Nodular regenerative hyperplasia of the liver and antiphospholipid antibodies. *J Clin Gastroenterol* 1998;**27**:90-1.
- 29 **Elias M**, Eldor A. Thromboembolism in patients with the "lupus-type" circulating anticoagulant. *Arch Intern Med* 1984;**144**:510-15.
- 30 **Wong KO**. Dermatomyositis: a clinical investigation of twenty-three cases in Hong Kong. *Br J Dermatol* 1969;**81**:844-7.
- 31 **Bradley JD**, Pinals RS, Gupta R. Chronic active hepatitis associated with polymyositis. *J Rheumatol* 1985;**12**:368-71.
- 32 **Cockel R**, Kendall MJ, Becker JF. Serum biochemical values in rheumatoid disease. *Ann Rheum Dis* 1971;**30**:166-70.
- 33 **Webb J**. Liver disease in rheumatoid arthritis and Sjögren's syndrome: prospective study using biochemical and serological markers of hepatic dysfunction. *Ann Rheum Dis* 1975;**34**:70-81.
- 34 **Beck PR**. Butanol extraction of serum and urinary gamma-glutamyl transferase and its application in clinical diagnosis. *Ann Clin Biochem* 1978;**15**:151-6.
- 35 **Lefkowitz AM**, Farrow IJ. The liver in RA. *Ann Rheum Dis* 1955;**14**:162-8.
- 36 **Rau R**, Pfenninger K, Boni A. Liver function tests and liver biopsies in patients with rheumatoid arthritis. *Ann Rheum Dis* 1975;**34**:198-9.
- 37 **Mills PR**, Macsween RN, Dick WC, More IA, Watkinson G. Liver disease in rheumatoid arthritis. *Scott Med J* 1980;**25**:18-22.
- 38 **Blendis LM**, Ansell ID, Jones KL. Liver in Felty's syndrome. *BMJ* 1970;**ii**:131-5.
- 39 **Sienknecht LW**, Urowitz MB, Pruzansk W. Felty's syndrome: clinical and serological analysis of 34 cases. *Ann Rheum Dis* 1977;**36**:500-7.
- 40 **Klofthorn RW**, Steigerwald JC, Mills DM. Oesophageal varices in Felty's syndrome: a case report and review of the literature. *Arthritis Rheum* 1976;**19**:150-4.
- 41 **D'Angelo WA**, Fries JF, Masi AT, Shulman LE. Pathologic observations in systemic sclerosis (scleroderma): a study of 58 autopsy cases and 58 matched controls. *Am J Med* 1969;**46**:428-40.
- 42 **Tuzzanelli DL**, Winklemann RK. Systemic scleroderma: a clinical study of 727 cases. *Arch Dermatol* 1961;**84**:359-71.
- 43 **Bartholomew LG**, Cain JC, Winkelmann RK, Baggenstoss AH. Chronic disease of the liver associated with systemic scleroderma. *Am J Dig Dis* 1964;**9**:43-55.
- 44 **Chen J**. Liver, gall and pancreas. In: Liu TH, Liu TH, Li WH, eds. *Diagnostic pathology*. Beijing: People Health Press, 1995:242.
- 45 **Ahrens EH Jr**, Payne MA, Kunkel HG, Eisenmenger WJ, Blondheim SH. Primary biliary cirrhosis. *Medicine (Baltimore)* 1950;**29**:264-80.
- 46 **Murray-Lyon IM**, Thompson RPH, Ansell ID, Williams R. Scleroderma and primary biliary cirrhosis. *BMJ* 1970;**iii**:258-9.
- 47 **Reynolds TB**, Denison EK, Frankl HD, et al. New syndrome-combination of primary biliary cirrhosis, scleroderma and hereditary haemorrhagic telangiectasia [abstract]. *Gastroenterology* 1970;**58**:290.
- 48 **O'Brien ST**, Eddy WM, Krawitt EL. Primary biliary cirrhosis associated with scleroderma. *Gastroenterology* 1972;**62**:118-21.
- 49 **Powell FC**, Schroeter AL, Dickson ER. Primary biliary cirrhosis and the CREST syndrome: a report of 22 cases. *Q J Med* 1987;**62**:75-82.
- 50 **Kallenberg CGM**, Pastoor GW, Wouda AA, The TH. Antinuclear antibodies in patients with Raynaud's phenomenon: clinical significance of anti-centromere antibodies. *Ann Rheum Dis* 1982;**41**:382-7.
- 51 **Seibold JR**, Trontell MC. Anticentromere antibody and primary pulmonary hypertension. *J Rheumatol* 1982;**9**:607-9.
- 52 **McCarty GA**, Rice JR, Rembe ML, Barada FA Jr. Anticentromere antibody. Clinical correlations and association with favourable prognosis in patients with scleroderma variants. *Arthritis Rheum* 1983;**26**:1-7.
- 53 **Bernstein RM**, Callender ME, Neuberger JM, Hughes GR, Williams R. Anticentromere antibody in primary biliary cirrhosis. *Ann Rheum Dis* 1982;**41**:612-14.
- 54 **Makinen D**, Fritzler M, Davis P, Sherlock S. Anticentromere antibodies in primary biliary cirrhosis. *Arthritis Rheum* 1983;**26**:914-17.
- 55 **Shoji I**, Takagi T, Kasukawa R. Anticentromere antibody and CREST syndrome in patients with primary biliary cirrhosis. *Intern Med* 1992;**31**:1348-55.
- 56 **LeRoy EC**. Increased collagen synthesis in scleroderma skin fibroblasts in vitro: a possible role in the regulation or activation of the scleroderma fibroblast. *J Clin Invest* 1974;**54**:880-9.
- 57 **Lurie B**, Novis B, Bank S, Silber W, Botha JBC, Marks IN. CREST syndrome and nodular transformation of the liver—a case report. *Gastroenterology* 1973;**64**:457-61.
- 58 **McMahon RFT**, Babbs C, Warnes TW. Nodular regenerative hyperplasia of the liver, CREST syndrome and primary biliary cirrhosis: an overlap syndrome? *Gut* 1989;**30**:1430-3.
- 59 **Bartholomew LG**, Cain JC, Woolner LB. Sclerosing cholangitis: its possible association with Riedel's struma and fibrous retroperitonitis. *N Engl J Med* 1963;**269**:8-12.
- 60 **Fraile G**, Rodriguez-Garcia, Moreno A. Primary sclerosing cholangitis associated with systemic sclerosis. *Postgrad Med J* 1991;**67**:189-92.
- 61 **Cristiansson J**. Corneal changes in a case of hepatitis. *Acta Ophthalmol* 1954;**32**:161.
- 62 **Whaley K**, Goudie RB, Williamson J, Nuki G, Dick WC, Buchanan WW. Liver disease in Sjögren's syndrome and rheumatoid arthritis. *Lancet* 1970;**ii**:861-3.
- 63 **Golding PL**, Bown A, Mason AMS, Taylor E. Sicca complex in liver disease. *BMJ* 1970;**iv**:340-2.
- 64 **Skopouli FN**, Barbatis C, Moutsopoulos HM. Liver involvement in primary Sjögren's syndrome. *Br J Rheumatol* 1994;**33**:745-8.
- 65 **Lindgren S**, Manthorpe R, Eriksson S. Autoimmune liver disease in patients with primary Sjögren's syndrome. *J Hepatol* 1994;**20**:354-8.
- 66 **Manthorpe R**, Permin H, Tage-Jensen U. Auto-antibodies in Sjögren's syndrome with special reference to liver-cell membrane antibody (LMA). *Scand J Rheumatol* 1979;**8**:168-72.
- 67 **Vogel C**, Wittenborg A, Reichart P. Involvement of liver in Sjögren's syndrome. *Oral Surg* 1980;**50**:26-9.
- 68 **Alarcon-Segovia D**, Diaz JE, Fishben E. Features of Sjögren's syndrome in primary biliary cirrhosis. *Ann Intern Med* 1973;**79**:31-6.
- 69 **Hansen BU**, Lindgren S, Eriksson S, Henricsson V, Larsson A, Manthorpe R, et al. Clinical and immunological features of Sjögren's syndrome in patients with primary biliary cirrhosis with emphasis on focal sialadenitis. *Acta Med Scand* 1988;**224**:611-19.
- 70 **Haddad J**, Deny P, Munz-Gotheil C, Ambrosini JC, Trinchet JC, Pateron D, et al. Lymphocytic sialadenitis of Sjögren's syndrome associated with chronic hepatitis C virus liver disease. *Lancet* 1992;**339**:321-3.
- 71 **Garcia-Carrasco**, Ramos M, Cervera R, Font J, Vidal J, Munoz FJ, et al. Hepatitis C virus infection in primary Sjögren's syndrome: prevalence and clinical significance in a series of 90 patients. *Ann Rheum Dis* 1997;**56**:173-5.
- 72 **Esteban JL**, Esteban R, Vladomiu L, Lopez-Talavera JC, Gonzalez A, Hernandez JM, et al. Hepatitis C antibodies among risk groups in Spain. *Lancet* 1989;**ii**:294-6.