

# Immune Components of Liver Damage Associated with Connective Tissue Diseases

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## Abstract

Autoimmune connective tissue diseases are associated with liver abnormalities and often have overlapping pathological and clinical manifestations. As a result, they can present great clinical challenges and evoke questions about diagnostic criteria for liver diseases. Moreover, discriminating between liver involvement as a manifestation of connective tissue disease and primary liver disease can be challenging since they share a similar immunological mechanism. Most patients with connective tissue diseases exhibit liver test abnormalities that likely result from coexisting, primary liver diseases, such as fatty liver disease, viral hepatitis, primary biliary cirrhosis, autoimmune hepatitis, and drug-related liver toxicity. Liver damage can be progressive, leading to cirrhosis, complications of portal hypertension, and liver-related death, and, therefore, must be accurately identified. In this review, we highlight the challenges facing the diagnosis of liver damage associated with connective tissue disease and identify immune mechanisms involved in liver damage associated with connective tissue diseases.

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## Introduction

The liver is the largest lymphoid organ of the body and is known to be involved in the immune response against pathogens and the maintenance of tolerance to

self-molecules.<sup>1,2</sup> In autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), primary Sjögren's syndrome (SS), myositis, antiphospholipid syndrome (aPS), Behcet's syndrome, scleroderma and vasculitis, primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC), liver damage can occur from an autoimmune reaction. It may produce a biochemical picture of cholestatic damage (with elevated alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT)) or hepatocellular (with elevated alanine transaminase (ALT) and aspartate transaminase (AST)). Advanced disease with liver failure and cirrhosis is extremely rare in patients with connective tissue disease. Many descriptive case studies of patients with SLE, SS and systemic sclerosis (SSc), serologic liver test alterations, and histological lesions have been found (Table 1). In the majority of cases, liver histology demonstrated only minor changes, and the coexisting primary liver disease was often overlooked. The mechanism of elevated portal vein pressure and the pathological changes causing portal hypertension vary with each disease. Portal hypertension is commonly classified according to the location of obstructive changes along the vascular system: prehepatic, intrahepatic, and post-hepatic with intrahepatic portal hypertension further subdivided into pre-sinusoidal and post-sinusoidal. A typical example of prehepatic portal hypertension is extrahepatic portal vein thrombosis, while a purely post-hepatic portal hypertension example is the Budd-Chiari syndrome (BCS) commonly due to membranous obstruction of the inferior vena cava.<sup>3-5</sup> Nevertheless, the main cause of biochemical liver abnormalities in patients with connective tissue diseases (CTD) is treatment with potentially hepatotoxic drugs or coexisting viral hepatitis.<sup>1</sup> Fibrotic autoimmune diseases are characterized pathogenetically by an inflammatory process that induces and sustains robust fibrosis. This is due to the production of an array of biological factors activating fibroblast proliferation and collagen secretion. While advanced liver disease such as cirrhosis and liver failure are rare in patients with CTD, abnormal liver function tests are quite common,<sup>6</sup> and liver histology may reveal a variety of subclinical liver diseases. In particular, unusual liver lesions, such as nodular regenerative hyperplasia (NRH), have been reported with increasing frequency in patients with CTDs<sup>7,8</sup> (Table 2). On the other hand, acute or progressing liver involvement is generally related to viral hepatitis reactivation or to a concomitant autoimmune liver disease.<sup>1</sup>

**Keywords:** Systemic lupus erythematosus; Antiphospholipid syndrome; Autoimmune hepatitis; Rheumatoid arthritis; Sjögren's syndrome; Scleroderma; Abnormal liver tests.

**Abbreviations:** AIH, autoimmune hepatitis; ANA, antinuclear antibody; ALP, alkaline phosphatase; ALT, alanine transaminase; aPS, antiphospholipid syndrome; AST, aspartate transaminase; CTD, connective tissue disease; ELISA, enzyme linked immunoassay; GGT, gamma glutamyltransferase; IIF, indirect immunofluorescence; NRH, nodular regenerative hyperplasia; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; RA, rheumatoid arthritis; SS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

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**Table 1. Diagnostic feature of autoimmune liver diseases**

Disease	Markers	Histology
Anti-phospholipid syndrome	aPL, aCL	Nodular regenerative hyperplasia
	Budd-Chiari syndrome	
	Hepatosplenomegaly	
	Jaundice	
Felty's syndrome	Raised ALT	Kupffer cell hyperplasia
	Hepatomegaly	Steatosis
	Portal hypertension	Mild portal tract fibrosis
	Raised ALP	Nodular regenerative hyperplasia
Myositis	Jaundice	Chronic active hepatitis (rare)
	Raised ALP	Primary biliary cirrhosis
Rheumatoid arthritis	Raised ALP	Kupffer cell hyperplasia
	Raised $\gamma$ -glutamyltransferase	Steatosis
Scleroderma	Hepatomegaly	Cirrhosis
	Prothrombin time	Primary biliary cirrhosis
	Jaundice Raised liver enzymes	Nodular regenerative hyperplasia
Sjögren's syndrome	Raised liver enzymes	Primary biliary cirrhosis
	Jaundice	Chronic active hepatitis
	AMA, anti-Ro/La	Cryptogenic cirrhosis
Systemic lupus erythematosus	Anti- DS DNA	Steatosis
	Hepatomegaly	Chronic active hepatitis
	Jaundice	
	Raised ALT	

**Table 2. Liver Pathologies in patients with autoimmune diseases**

Pathology	Description
Chronic active hepatitis (CAH)	Piecemeal necrosis defined as the destruction of liver cells at the interface between parenchyma and connective tissue with a predominantly mononuclear inflammatory infiltrate. Aggregation of lymphocytes and macrophages surrounds the hepatocytes with a spreading wave of necrosis. As the liver parenchyma is destroyed, sheets of connective tissue are laid down, which initially contain an inflammatory infiltrate resulting in a "maple leaf" configuration to the portal tract.
Chronic persistent hepatitis (CPH)	CPH is characterized by chronic inflammatory infiltration of portal tracts with preserved lobular architecture and little or no portal fibrosis with expanded tracts. 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.
Lipoid 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	Characterized by diffuse nodularity of the liver with little or no fibrosis and has been found in association with autoimmune disease, drug treatment, and a variety of hematological disorders.
Primary biliary cirrhosis	PBC is an autoimmune inflammatory disorder associated with a high serum titer of anti-mitochondrial antibodies. Histological appearance is 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 with fibrosis and obliteration of the bile ducts. It is strongly associated with inflammatory bowel.

### Systemic lupus erythematosus

SLE is a chronic autoimmune disease that affects multiple organs and presents with diverse clinical and serological manifestations. It affects principally women during the child bearing years. Although it is very unusual to find significant hepatic dysfunction in SLE patients, unusual liver complications have been linked to the treatment with potentially hepatotoxic drugs or viral hepatitis. Careful exclusion of such causative factors raises challenges regarding differential diagnosis between liver disease associated with SLE and primary liver disease having clinical and diagnostic features resembling SLE.<sup>9</sup> The differential diagnosis between autoimmune hepatitis and SLE-associated hepatitis remains a clinical challenge and better diagnostic criteria for both diseases need to be established. A current definition of (lupoid) autoimmune hepatitis includes histological evidence of chronic active hepatitis, positive antinuclear antibodies or LE cells, and exclusion of any other causes, including possible viral causes. It can usually be distinguished from SLE by the absence of antibodies to double-stranded DNA.

The reported frequency of hepatic involvement in SLE is 8-23%.<sup>10-12</sup> It consists of several pathophysiological features, and clinical signs, including hepatomegaly (39%), splenomegaly (6%), jaundice (24%), and elevations of liver enzymes or abnormal liver histology (21%).<sup>13</sup> According to a retrospective study conducted by Gibson and Myers, abnormal values were present in 55% of 81 patients diagnosed with SLE, and 29% of those had no cause for the documented changes other than SLE. In a study by Miller *et al.*, liver enzyme levels were elevated in 23% of 260 patients with SLE.<sup>14,15</sup> The reported incidence of hepatomegaly in SLE varied from 12-55% depending on the series. Cholestatic hepatitis emerging as conjugated hyperbilirubinemia can develop in a background of neonatal lupus erythematosus, an uncommon passive autoimmune disease caused by transplacental passage of anti-Ro/SSA and/or anti-La/SSB and anti-U1RNP maternal autoantibodies. In this condition, idiopathic portal hypertension can be accompanied by splenomegaly, cytopenia, and esophageal varices.<sup>16</sup>

In a histologic review of 73 patients with SLE, Matsumoto *et al.* identified a number of coexisting primary liver disorders: fatty liver (73%), nodular regenerative hyperplasia (NRH) (7%), viral hepatitis (4%), PBC (3%), and autoimmune hepatitis (3%).<sup>17</sup> Case reports have been published describing additional liver diseases in patients with SLE; including primary sclerosing cholangitis,<sup>18</sup> autoimmune cholangiopathy, granulomatous hepatitis,<sup>19</sup> and idiopathic portal hypertension.<sup>20</sup> Vascular disorders of the liver secondary to antiphospholipid syndrome associated with SLE include BCS, hepatic infarction, and hepatic rupture.<sup>21,22</sup>

Autoimmune hepatitis (AIH) and lupus-associated hepatitis can be difficult to differentiate given their common clinical and serologic manifestations. Histologic findings may be helpful as AIH characteristically shows periportal inflammation and piecemeal necrosis with dense lymphoid infiltrates, whereas lupus-associated hepatitis shows predominantly mild lobular inflammation without piecemeal necrosis on histology.<sup>23-26</sup> Anti-ribosomal P antibodies, which are not found in patients with AIH, are present in a significant proportion (69%) of patients with lupus-associated hepatitis and may aid in differentiating the two entities.<sup>16</sup> Clarifying the diagnosis has important prognostic and therapeutic

implications, as lupus-associated hepatitis has a more benign course and does not require corticosteroid therapy.<sup>27,28</sup>

The liver is generally not a major target organ for damage in SLE, and, as such, abnormalities of liver function are not included in classification and diagnostic criteria for SLE. Abnormal liver function tests are common in SLE, being found in up to 50% of patients at some point of the disease course,<sup>13,14</sup> and the main causes are disease activity, drug toxicity, and rarely an overlapping primitive autoimmune liver disease. In 23% of patients with SLE and liver test abnormalities, no cause for liver test abnormality was identified. Elevated liver tests were shown to correlate with disease activity<sup>15</sup> and to improve with steroid treatment.<sup>13</sup>

### Antiphospholipid syndrome

APS is characterized by a wide variety of hemocytopenic and vaso-occlusive manifestations, including acquired thrombosis, recurrent fetal losses, and thrombocytopenia associated with autoantibodies directed against phospholipids (antiphospholipid antibodies or aPLs), mainly cardiolipin antibodies (anticardiolipin antibodies (aCL)).<sup>29-31</sup> Recently,  $\beta_2$ -glycoprotein-I (b2GPI) was described as one of the major target antigens for aPLs.<sup>32,33</sup> The aPLs have been found in many conditions, such as infection, malignancy, and drugs use. Also, they were found in 5% of healthy people without risk for thrombosis. Therefore, aPLs may be primary when there is no other condition and secondary when there are other conditions, such as SLE, RA, or SSc.<sup>34</sup>

APS has been described rarely in patients with autoimmune hepatitis.<sup>16,35-37</sup> APLs are found in many liver diseases, such as chronic hepatitis C (HCV), where they can cause thrombosis and thrombocytopenia. Infection with HCV is present in 7% of patients with thrombotic disorders and anti-cardiolipin antibodies, and they can also cause BCS. Patients with autoimmune hepatitis and a history of thrombosis or fetal loss must undergo testing for aPS.<sup>38-41</sup>

APS-related liver manifestations are mainly of vascular origin, including thrombosis of major arterial or venous vessels based on microthrombosis. However, non-thrombotic liver injury has also been reported. Moreover, aPLs were shown to be involved in small artery intrahepatic damage and in the pathogenesis of NRH, while cases of BCS were reported in association with APS in 5% of the cases.<sup>42,43</sup> The association of aPL positivity with BCS was described for the first time in a report in 1984, and since then, a few more cases have been described in literature. BCS is a clinical and pathological entity characterized by structural and functional abnormalities of the liver resulting from obstruction of the outflow of hepatic venous blood. The role of aPL in BCS is unclear, and it has been suggested that the aPL production is just secondary to the liver damage. However, in other reports, aPLs were detected before the onset of the syndrome. The findings strongly suggest that aPL may be the cause of the syndrome. BCS might be considered as the first clinical manifestation of aPS.

### Rheumatoid arthritis

RA is a systemic autoimmune disease characterized by joint involvement and a number of extra-articular manifestations. RA, Still's disease, and Felty's syndrome are rheumatoid syndromes sharing a common immunological profile.<sup>44,45</sup> Liver involvement has been documented in up to 6% of

patients with RA, presenting in most cases as mild elevations in ALP and serum GGT levels.<sup>46,47</sup> Clinical manifestations rarely include spontaneous hepatic rupture in patients complicated by extra-articular features and high titers of rheumatoid factor or mild sero-negative inflammatory arthritis. It can be attributed to necrotizing hepatic arteritis with infarction and spontaneous liver rupture.<sup>48,49</sup> PBC may also develop.<sup>50,51</sup>

In a recently published survey, nonspecific changes, such as inflammatory cell infiltration of the portal tracts, small scattered foci of liver cell necrosis, increased centrilobular lipofuscin deposits, and occasional fat containing hepatocytes, were reported in 74% of 31 RA patients.<sup>52</sup> However, a review of liver biopsy findings in patients with RA did not identify a consistent structural abnormality. Most biopsy reports suggested only minor nonspecific changes. In 117 patients with RA without extra-articular complications, 35% of liver biopsy specimens were normal, 43% showed nonspecific hepatitis, and 22% were associated with fatty change.<sup>53</sup> In another group of 31 patients with more severe RA and biochemical evidence of liver dysfunction, 23 (74%) liver biopsy specimens had nonspecific reactive changes, 4 (13%) suggested chronic liver disease, and only four were normal. Of the 13 patients with chronic liver disease, one of each of the following diagnoses were made: PBC, chronic active hepatitis, alcoholic cirrhosis, and amyloidosis. Because primary liver disease was found in 30% of cases, the changes attributed to RA may have been overestimated. Although liver biopsies are not done routinely in the management of RA, the results of most liver biopsies are consistent with chronic inflammation.<sup>54</sup> These findings suggest that, except for mild elevation in levels of serum aminotransferases, liver abnormalities are not common in RA.

Patients with unexplained liver abnormalities require further testing to exclude autoimmune hepatitis, alcoholic cirrhosis, amyloidosis, and PBC. Histologic findings in patients with RA are variable. In a retrospective review study of RA patients autopsies, Ruderman *et al.* found that the majority of samples had hepatic congestion, steatosis, and portal tract inflammation, whereas only 15 cases had normal liver parenchyma.<sup>55</sup> However, Rau and colleagues have shown only mild and generally nonspecific changes in liver biopsies from patients with RA.<sup>56</sup>

In RA patients, wide ranges of primary liver disorders have been reported, including PBC, autoimmune hepatitis, and autoimmune cholangiopathy. Other rare conditions, including NRH, idiopathic portal hypertension, and spontaneous hepatic rupture secondary to vasculitis, have also been reported.<sup>49,57-60,61</sup> RA is generally defined as the combined presence of arthropathy and the rheumatoid factor (RF). However, similarity in extrahepatic manifestations of primary liver disorders might be confusing. Autoantibodies, such as anti-cyclic citrullinated peptide (anti-CCP), have been shown to be reliable markers for RA compared with arthropathy associated with chronic HCV, AIH, or PBC.<sup>62</sup>

### Sjögren's syndrome

SS is an autoimmune disease that typically presents with dryness of eyes (keratoconjunctivitis sicca) and mouth (xerostomia). Other organs such as liver, spleen, lung, and kidney may be involved. Abnormal liver tests with increased AST and ALT have been reported with and without RA. In primary SS, studies have shown the presence of anti-mitochondrial

antibodies (AMA).<sup>47</sup> Half of patients with both SS and rheumatoid arthritis and 10% of those with primary SS have positive AMA similar to PBC with evidence of hepatic disease.<sup>63-65</sup>

Specific liver disease was detected in 50% of SS patients with liver test abnormalities. In the remaining 50% of patients, there was no explanation for the liver test abnormality,<sup>66</sup> which is similar to other studies.<sup>66,67</sup> In general, AMA detection was usually accompanied by histopathologic abnormalities consistent with PBC. In a series of 300 patients with SS, serum liver enzyme elevations and AMA screening found that 7% of patients with SS had either subclinical (2%) or asymptomatic (5%) liver disease as manifested by elevated liver enzyme levels and positive AMA test results.<sup>65,68</sup> In this large study, chronic active hepatitis or cirrhosis was rarely observed. It was concluded that liver involvement in primary SS is rare and subclinical, but can present with histopathologic features of PBC. AMA is the most sensitive indicator of underlying liver pathology in primary SS patients.<sup>69,70</sup> Long-term follow-up of these patients might be required to determine the risk of progression and treatment follow-up.

Some studies regarding hepatic involvement in SS have attempted to evaluate a causal role for HCV in the pathogenesis of SS. One study found a 13% prevalence of chronic HCV in these patients, with histopathologic evidence of chronic active hepatitis in those who underwent biopsy.<sup>67</sup> It was suggested that the coexistence of HCV and SS explains the higher incidence of cirrhosis and chronic active hepatitis in these patients. Alternatively, the prevalence of HCV in the patients studied may have contributed to the pathogenesis of SS in certain cases. Several studies have shown that the prevalence of chronic HCV infection among patients with SS was higher than the general population, ranging from 12% to 19%.<sup>71,72</sup> The presence of sicca symptoms (dryness of the eyes and mouth), lymphocytic infiltration of salivary glands, and serum autoantibodies in patients with HCV infection suggested that HCV may even be the cause of SS in some cases. Other investigators, however, pointed out subtle differences in the clinical, immunologic, and histologic characteristics of patients between HCV-related SS and primary SS patients without HCV infection (e.g., a lower prevalence of sicca symptoms, a lower frequency of anti-Ro/SS-A and anti-La/SS-B antibodies, and a higher prevalence of cryoglobulinemia and hypocomplementemia). The pathogenic role of HCV in SS remains unclear, although HCV infection may be involved in the pathogenesis of SS in subgroups of patients. Conversely, HCV infection may produce extrahepatic manifestations that may mimic SS.<sup>71-75</sup> In clinical practice, it is reasonable to recommend that abnormal liver parameters in patients with SS should prompt testing for HCV infection.

The pathogenic process underlying hepatic (mainly in the case of PBC) and salivary gland damage and destruction could be similar because both epithelial populations inappropriately express class II HLA molecules and CD4 (+) T cells predominate. In each case, the autoimmunity profile is easily distinguishable due to the wide range of differentiating antibodies (in primary SS, anti-Ro and anti-La antibodies predominate, while in PBC, the predominant specific autoantibodies are anti-mitochondrial antibodies-AMA). Autoantibodies as serological markers are clinically valuable in the prediction of autoimmune liver diseases in SS. In patients with AMA who develop PBC, the titer of smooth



muscle antibodies (SMA) is higher. Antinuclear antibodies are the most specific markers for autoimmune hepatitis.<sup>68</sup> AMA was suggested to be the most sensitive marker for the detection of underlying PBC in patients with primary SS.<sup>69</sup> In several series, the prevalence of PBC was reported to be approximately 6%. Histological evidence of focal sialadenitis was detected in 95% of patients with PBC, and anti-La antibodies were detected in sera from 38% of patients with PBC.<sup>70</sup> An overlap between CREST, SS, thyroid hyperplasia, and chronic hepatitis has been reported.<sup>76</sup>

### Systemic sclerosis

Systemic sclerosis (scleroderma SSc) is a multiple organ disease with inflammation and fibrosis that regularly involves the skin and the blood vessels; other organs such as lungs, heart, gastrointestinal tract, kidneys, and musculoskeletal system are frequently affected.<sup>77</sup> Scleroderma is classified into two major subsets, which are distinguished by the extent of skin thickening: limited and diffuse cutaneous scleroderma.<sup>78</sup>

Primary biliary cirrhosis is the most commonly reported liver disorder in patients with SSc. Scleroderma occurrence in patients with primary biliary cirrhosis is between 7% and 12%.<sup>79,80</sup> Only a minority of patients with primary biliary cirrhosis-associated SSc show the diffuse type of SSc, rather than the limited cutaneous type, and they generally have a positive AMA. Also, they commonly have anticentromere Ab, an antibody frequently found in patients with limited cutaneous SSc.<sup>79-81</sup> Therefore, testing for anticentromere Ab may be helpful in the evaluation of SSc in patients with known primary biliary cirrhosis. Although the liver disease in patients with primary biliary cirrhosis-associated SSc may progress to cirrhosis and result in liver-related morbidity, mortality is more commonly due to other systemic complications of SSc and not the liver disease.<sup>79</sup>

Fibrotic autoimmune diseases are characterized by an inflammatory process, which induces and sustains robust fibrosis. This is due to the expression of large number of biological factors which activates fibroblast proliferation and collagen secretion. Among the various fibrogenic factors in autoimmune diseases, interleukin-1 (IL-1), IL-6, and TGF- $\beta$  have a relevant role.<sup>82,83</sup> Interestingly, these three cytokines are also involved in generation/differentiation and activity of a particular T cell subpopulation, the Th17 cells. Th17 lymphocytes constitute a T cell subtype characterized by the capacity to produce and secrete IL17. This T helper cell subset is independent of typical Th1 and Th2 subpopulations, which secrete either IFN- $\gamma$  or IL-4/IL-5/IL-13, respectively.<sup>84</sup> Recent studies clarified the requirements for Th17 lymphocyte differentiation from circulating naïve or memory CD4+ T cells. When naïve T cells are the starting population for Th17 cell generation, a cytokine milieu of pro-inflammatory factors (such as IL-1 $\beta$ , IL-6, IL-23, IL-21) and low TGF- $\beta$  levels is required to induce the Th17 profile. When CD4+ memory T cells are the Th17 precursors, IL-21 and IL-23 are required to expand and stabilize the commitment of Th17 lymphocytes. In this instance, Th17 cells release an array of effector cytokines including, IL-17A, IL-17F, IL-22, and IL-26. At the molecular level, IL-6, IL-21, and IL-23 together with low TGF $\beta$  concentration induce expression of STAT3 and ROR $\gamma$ t transcription factors that are involved in Th17 differentiation.<sup>85-89</sup>

Importantly, abnormal activation/expansion of Th17 cells linked to the activity of inflammatory cytokines such as IL-6

and IL-23 has been shown to correlate with autoimmune diseases such as multiple sclerosis (MS), RA, inflammatory bowel disease, and psoriasis.<sup>90-98</sup> Recently, analysis of liver infiltrating cells suggested that immune responses skewed toward Th17 cell generation could be involved in the pathogenesis of PBC in humans. In fact, the immunohistochemical analysis of liver specimens from control and PBC subjects demonstrated a significantly higher concentration of IL17-positive cells in patients compared to controls.<sup>99</sup> Th17 cell expansion was a common feature associated with a relative contraction of Th1 responses.

Concerning the regulatory T cell compartment, quantitative and qualitative alterations were observed in both diseases. However, while PBC patients showed defects only in the CD8+ Treg subset, SSc patients showed abnormalities in both CD4+, and CD8+ Treg subpopulations. The CD8+ Treg subset seemed to be the most active in the pathogenic cascade leading to fibrotic disease onset and maintenance.<sup>100</sup> Dendritic cells also play a major role in inflammatory process associated with liver fibrosis.<sup>101</sup>

A study by Connolly and colleagues<sup>102</sup> found a potential role for dendritic cells in mediating the proinflammatory environment in a model of liver fibrosis induced by six weeks of three-times-weekly injections of thioacetamide and leptin. CD11c+ cells accumulated in the fibrosed livers and were a mixed population. However, many expressed MHCII and CD40. The isolated CD11c+ cells stimulated natural killer cells and T cells *in vivo* and *in vitro*, suggesting that these CD11c+ cells were comprised of, at least in part, true dendritic cells. Depletion of CD11c+ cells resulted in remarkable reductions in the levels of TNF- $\alpha$ , IL-6, and other inflammatory cytokines in the cultures of nonparenchymal cells, indicating a role for CD11c+ cells in initiating or sustaining a proinflammatory environment in the fibrosed liver.<sup>102</sup> Also, CD11c+ cells cultured with hepatic stellate cells can adopt a proinflammatory phenotype or differentiate into myofibroblasts during activation,<sup>103</sup> resulting in increased expression of proinflammatory mediators and increased proliferation of hepatic stellate cells.

This supports the notion that dendritic cells can directly modulate hepatic stellate cell activity that is, in part, dependent on TNF- $\alpha$ , presumably from the CD11c+ cells.<sup>102</sup> The requirement for CD11c+ cells in fibrosis was not tested. However, this study suggested that dendritic cells or other CD11c+ cells could potentially contribute to the inflammatory aspects of fibrosis. The contribution to fibrosis-associated inflammation is reminiscent of the proposed role of renal CD11c+ cells in the study discussed above,<sup>104</sup> and it is possible that the two studies are describing related cells in different organs. Of note, Gr1+CD11b+F4/80 myeloid cells were found by Karlmark and colleagues<sup>105</sup> to accumulate in early CCl4-induced injury and late CCl4-mediated fibrosis. The accumulation of these cells was dependent on whether CCR2 and CCR2-/- mice had attenuated fibrosis that could be rescued by injection of Gr1+ cells.<sup>105</sup> Whether these inflammatory monocytes are related to the CD11c+ cells described by Connolly and colleagues remains to be determined.<sup>102</sup> It will also be of interest to understand whether long-term depletion of CD11c+ cells using tools such as the CD11c-DTR mice affects parameters of fibrosis.<sup>106,107</sup>

The role of dendritic cells in pathogenesis of scleroderma and fibrosis is still not fully understood. Evidence to date supports the idea that dendritic cells may contribute to a proinflammatory cytokine environment, resulting in

abnormally high levels of IL-10 similar to scleroderma patients<sup>108,109</sup> and direct modulation of the activity of fibroblast-type cells. The proinflammatory role may be a double edged sword, as the inflammation that begets fibrosis may also be required for resolution of fibrosis. IL-10 may be responsible for both profibrotic and antifibrotic roles.<sup>2,110</sup> The exact role of dendritic cells remains still to be determined.

## Conclusions

Abnormal liver tests are common in patients with rheumatologic disorders. Liver test abnormalities include a hepatocellular injury pattern (increased aminotransferases), a cholestatic pattern (increased ALP with or without increased bilirubin), and a mixed picture. Evaluation does not often reveal an identifiable cause of the biochemical abnormality. Such nonspecific abnormalities are likely to be of little clinical significance, and no specific management is required. Serious progressive liver injury does occur, more often in the context of a coexisting primary liver disease or pharmacotherapy. An underlying primary liver disease for which treatment might be beneficial (e.g., immunosuppressive drugs for autoimmune hepatitis, interferon for viral hepatitis, ursodeoxycolic acid for PBC) should be sought. Testing for AMA, anti-smooth muscle antibodies, and HCV may be particularly helpful. Increased frequency of liver testing after initiation of anti-rheumatic treatment should raise the suspicion for drug-induced liver injury, as many anti-rheumatic drugs have documented hepatotoxicity and can cause reactivation of hepatitis B.

## Conflict of interest

None

## Author contributions

Designing and writing this manuscript (AAC, YAS, MA, KB).

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