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REVIEW

Liver involvement in subjects with rheumatic disease

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Abstract

The liver is often overlooked as a target organ, with pathology either secondary to an underlying disease or due to the toxicity of therapies and the medical complications of extrahepatic diseases. It is thus important for the clinical rheumatologist to be aware of the diagnostic procedure to monitor liver injury. Indeed, systemic rheumatologic diseases may be associated with liver abnormalities secondary to the presence of a coexisting autoimmune liver disease (particularly primary biliary cirrhosis or autoimmune hepatitis), the direct involvement of the liver parenchyma, or the impact of medical treatments (particularly methotrexate) on the liver. In addition, the rheumatologist should be aware of the impact of immunosuppressive agents on underlying viral infections, particularly viral hepatitis. We review herein the data on the role of the liver in the clinical management of systemic rheumatic diseases.

Introduction

The liver is amongst the largest lymphoid organs and acts not only as a site of tolerance but also as a primary line of defense in mucosal immunobiology [1]. Additionally, there is a critical interplay within the liver between the primary role of protection against infections and the seemingly contrary role of maintaining tolerance. This interplay becomes particularly important in the case of chronic viral hepatitis, in which the immune response often becomes relatively ineffective. In contrast, there is increasing evidence for the critical role of the liver in modulating the immune response in autoimmune and chronic inflammatory diseases [2-4]. This is represented by the central role of the liver microcirculation in maintaining immune tolerance while initiating an adequate response to infectious agents; examples of the implications of these phenomena are illustrated by the putative role of molecular mimicry in the onset of autoimmune diseases [1].

A wide spectrum of rheumatic diseases can affect the liver with various degrees of involvement and histopathological features; these features are not specific to such comorbidities and are based on clinical features that are common to other chronic liver diseases [5]. In contrast, the primary immune diseases of the liver are autoimmune hepatitis (AIH) [6], primary biliary cirrhosis (PBC) [7], and primary sclerosing cholangitis (PSC) [8]. These three major autoimmune liver diseases have prevalence rates of 100 cases per million (AIH), 400 cases per million (PBC), and 150 cases per million (PSC) [9]. PBC and PSC are primarily biliary/cholestatic diseases with involvement of liver parenchyma only as a secondary manifestation; as such, their liver biochemistry profile reflects cholestasis. AIH results from hepatocyte damage with a typical hepatitis pattern of liver tests.

Liver histology for the rheumatologist

Liver involvement in patients with rheumatic disease manifests typical, although not specific, histopathological features that may pose a dilemma with primary liver conditions [10]. The typical liver histology of AIH [11] includes portal–parenchymal interface hepatitis with abundant lymphocyte and plasma cell infiltrates that cross the limiting plate and invade the liver parenchyma [6], while focal intrahepatic small bile duct obliteration and granulomas are typical of PBC [12] together with portal inflammation, subsequent periportal hepatitis, fibrous septa, bridging necrosis and, ultimately, frank cirrhosis. PSC can affect bile ducts of any size and is thus characterized by damage, atrophy, and loss of medium and large-size bile ducts within or outside the liver, leading to concentric periductal fibrosis and obliteration of bile ducts [8]; in the case of small-duct PSC, only liver histology can provide evidence in the diagnostic process.

Liver histology is not peculiar in systemic rheumatic diseases with hepatic involvement, and different patterns can be observed in patients with liver enzyme

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Table 1. Histopathology of liver involvement in systemic rheumatic diseases

Histological definition	Features
Chronic active hepatitis	Piecemeal necrosis with mononuclear cell infiltrate
Chronic persistent hepatitis	Chronic inflammatory infiltration of the portal tract with preserved lobular architecture and without portal fibrosis
Cirrhosis	Diffuse liver degeneration characterized by fibrous tissue and regenerative nodules
Fibrosis	Abnormal production of fibrous tissue in response to liver injury
Steatosis	Abnormal retention of lipids within hepatocytes
Cholangitis	Inflammation of bile ducts
Reactive hepatitis	Aspecific and mild inflammatory cell infiltrate of portal spaces
Nodular regenerative hyperplasia	Diffuse nodularity of the liver without fibrosis
Granulomas	Aggregate of epithelioid cells surrounded by lymphocytes
Idiopathic portal hypertension	Increased blood pressure in the veins of the portal system not due to liver diseases
Arteritis	Vessel wall inflammation
Giant cell hepatitis	Presence throughout the liver of enlarged multinucleated hepatocytes with abundant cytoplasm
Massive hepatic necrosis	Diffuse hepatocyte necrosis

abnormalities undergoing liver biopsy or in autoptical studies. The common histological features are summarized in Table 1. Chronic active hepatitis, chronic persistent hepatitis, cirrhosis, nodular regenerative hyperplasia, fibrosis, steatosis, and granulomas are the major findings reported in rheumatic diseases, along with less specific findings such as mild chronic inflammatory cell infiltrate of the portal space [13,14]. Vascular involvement is not uncommon and has been described as intrahepatic small vessel arteritis, Budd–Chiari syndrome, or isolated portal hypertension. Drug-induced liver injury is significantly more frequent than primary disease-related liver involvement and concurrent viral hepatitis or opportunistic infections have to be ruled out in rheumatic patients. Finally, amyloidosis is a rare cause of liver involvement in chronic systemic rheumatic diseases [15].

The liver and connective tissue disease

Liver involvement in connective tissue diseases is not uncommon, but the liver is not the major organ target. In systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and primary Sjögren's syndrome (pSS), serologic liver dysfunction and histological lesions have been described in numerous descriptive studies mostly based on case series.

Abnormal liver function tests are common in patients with SLE – being reported in 3 to 29% of the patients [14], often during disease exacerbations [16]. Numerous histopathological patterns can be found in liver biopsies of SLE patients, including small artery vasculitis reported in up to 21% of the patients [17], nonalcoholic fatty liver diseases in 20 to 73%, nodular regenerative hyperplasia in 5.7%, chronic persistent or active hepatitis in 2.4%, and cirrhosis in 1.1% or fibrosis in 0.8% [17,18]. Moreover, anecdotal cases of giant cell hepatitis, granulomatous hepatitis, massive hepatic necrosis, cholangitis, isolated portal hypertension, Budd–Chiari syndrome, and liver infarction have also been described. End-stage liver disease is a very infrequent finding [14], while cases of Budd–Chiari syndrome have been reported in association with antiphospholipid syndrome. Moreover, antiphospholipid antibodies have been shown to be involved in small artery intrahepatic damage and in the pathogenesis of nodular regenerative hyperplasia.

Gastrointestinal involvement occurs invariably in SSc. In a large cohort of patients, some minor degree of liver involvement has been reported in 1.1% of the cases – while at autopsy liver fibrosis was found in 8.8% of patients, slightly more prevalent compared with non-SSc controls [19]. The association between SSc and PBC is more significant and a common pathogenetic trait has been suggested [20].

Finally, liver involvement is considered the most common non-exocrine feature in pSS [14,21], presenting as abnormal liver function tests in 27 to 49% of the patients [22]. In two-thirds of the cases cholestasis is found at liver biochemistry, and in up to 50% of cases AIH or PBC is associated with pSS. When presenting as a primary disease-related internal organ involvement, liver disease in pSS is associated with inflammation markers similar to other systemic manifestations of the diseases [23].

The liver and vasculitis

Vasculitis can affect every organ of the digestive system but the liver is not commonly involved. Liver involvement is limited to polymyalgia/Horton's arteritis, polyarteritis nodosa, Wegener's granulomatosis, and Behçet's disease [24]. Abnormal liver function tests commonly manifest a cholestatic pattern with elevated alkaline phosphatase and γ-glutamyl transferase levels that characterize up to

62% of patients with rheumatic polymyalgia [25]. Polymyalgic patients with elevated liver enzymes have an increased risk to develop Horton's arteritis [26].

Liver involvement occurs in a variable proportion (16 to 56%) of patients affected by polyarteritis nodosa, although clinical manifestations related to liver disease are quite rare; conversely, necrotizing arteritis of the liver has been found in the vast majority of patients with polyarteritis [27]. Liver injury is rare in Wegener's granulomatosis. Both granulomatous necrotizing hepatic involvement and mild nonspecific lobular hepatitis have been described. Liver involvement is rarely observed in patients with Behçet's disease, with a predominance of Budd–Chiari syndrome.

The liver and arthritis

Among patients with arthritis, hepatic involvement has been reported only in cases of rheumatoid arthritis (RA) and its variants. Nevertheless, liver injury is not generally recognized as a significant extra-articular feature of RA. Abnormal liver tests varying with disease activity, mainly elevated alkaline phosphatase, have been reported in 18 to 50% of patients with RA. Similarly, 65% of unselected patients with RA had abnormal liver biopsies – one-half having mild portal chronic inflammatory infiltrate of the portal tract and small foci of necrosis, and one in four having fatty liver [28]. As in SLE, drug-induced liver injury is frequent in RA, especially during nonsteroidal anti-inflammatory drug (NSAID) and methotrexate treatments. Liver involvement has also been reported in Felty's syndrome as liver enlargement (68%) and a rise in alkaline phosphatase (25%). Liver histology demonstrates diffuse lymphocyte infiltrate, periportal fibrosis with lymphocytic infiltration, and portal hypertension. Liver enlargement and elevated aminotransferases have also been reported in adult-onset Still's diseases, while liver biopsies have demonstrated aspecific mild portal infiltrate of limited significance [29]. Cases of acute liver failure, however, have also been reported.

The liver and overlap syndromes

Patients with signs and symptoms of two or more immunologic diseases are considered as having overlap syndromes. Overlap syndromes may include AIH and PBC or PSC, as largely reported in the literature (illustrated in Table 2); patients with overlap syndromes manifest both hepatitis and cholestatic biochemical profiles and histological features suggestive of AIH and PBC or PSC. AIH and PBC overlap syndrome has been reported in almost 10% of adults with AIH or PBC, whereas AIH and PSC overlap syndrome has been found in 1.4 to 49% of children, adolescents, and young adults with AIH or PSC. Transition from one to another liver disease is sometimes possible in a time frame of months to years [30]. While cases of anti-mitochondrial antibody-negative PBC and AIH overlap syndromes have been described, there is no clear evidence for the existence of a PBC/PSC overlap syndrome. In addition, AIH and PBC overlap syndrome has been described in patients with SLE, SSc, and pSS [31].

Table 2. Prevalence of liver disease overlap syndromes in selected rheumatic patients

	AIH	PBC	PSC	References
AIH	–	4.2 to 9%	1.4 to 49.1%	[30]
SLE	2.7 to 20%	2.7 to 15%	1 case	[18,27,31]
pSS	6 to 47%	35 to 57%	11 cases	[31,34,35]
SSc	11 cases	51.2%	1 case	[31-33]

AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; pSS, primary Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

AIH, PBC, and PSC may develop in patients with systemic rheumatic diseases (Table 2). The accurate prevalence of overlap diseases is unknown because of a variety of flaws encountered in the available prevalence studies. The majority of data reported only case reports, while in case series the liver histology is derived from autoptical investigations or liver biopsies performed on selected patients frequently with liver enzyme abnormalities.

While in patients with SLE the prevalence of AIH and PBC seems similar among patients with liver abnormalities, in SSc patients PBC has been reported in 51.2% of the cases with liver dysfunction [32] and in more than 50% of patients with a CREST (calcinosis, Raynaud, esophagopathy, sclerodactily, teleangectasia) variant [33], and AIH is rare – only 11 cases have been reported – while only one case of SSc/PSC comorbidity has been described.

A higher frequency of AIH and PBC has been reported in pSS patients with liver dysfunction undergoing hepatic biopsies: these rates ranged between 6 and 47% and between 35 and 57%, respectively [34]. Eleven cases of SS and PSC have been published and all of the patients also had chronic pancreatitis, while in our series SS was a frequent comorbidity condition in PBC cases [35]. A vast number of single case reports are available. As an example, AIH has been described in polymyositis/dermatomyositis, RA, Still's disease, polymyalgia, and polyarteritis nodosa [36]. On the other hand, PBC has been described in polymyositis/dermatomyositis, RA, Still's disease, polymyalgia, Churg–Strauss's disease, microscopic polyangiitis, Behcet's disease, and Schonlein–Henoch purpura. Finally, PSC has been exceptionally reported in association with rheumatic diseases.

The liver and medical therapies in rheumatology

Therapeutic strategies for the treatment of autoimmune liver disease are essentially based on corticosteroids and

immunosuppressant drugs such as methotrexate and azathioprine. The exception is provided by PBC, for which ursodeoxycholic acid (UDCA) is the only established treatment [37]. The combination of UDCA and immunosuppressants, albeit rational, failed to prove effective or sufficiently safe in most cases. Conversely, methotrexate has been shown to be virtually void from consistent adverse effects in the treatment of real-life patients with or without concomitant UDCA [38] while being burdened by significant side effects in randomized clinical trials [39]. A simpler scenario is provided by AIH, for which corticosteroids represent the cornerstone of currently utilized regimens [40]. This treatment should be considered for all patients with AIH regardless of the disease activity at presentation and should be continued until 24 months to achieve normalization of liver tests and, ideally, resolution of liver inflammatory infiltrate at histology. In cases of incomplete response or relapse, a long-term maintenance regimen with azathioprine is justified. Salvage therapy includes cyclosporine or mycophenolate mofetil, although more solid data are awaited [40] and new frontier therapeutic approaches may prove beneficial [41].

Management of overlap syndromes between PBC and AIH is empirical and guided by the predominant manifestations of the disease. Indeed, patients with AIH and PBC with higher serum alkaline phosphatase and transaminases are candidates for treatment with corticosteroids and UDCA [42].

Of note, potential benefits have been proposed for anti-TNFα treatments in autoimmune liver diseases although human data are scanty. In a murine model, anti-TNFα antibodies proved to be effective in reducing liver inflammation, necrosis, and fibrosis. Reports on the impact of anti-TNFα therapy in patients with inflammatory bowel diseases or other rheumatologic diseases and concomitant liver diseases [43] demonstrated potential benefits for nonalcoholic steatohepatitis and PSC; however, AIH and hepatosplenic T-cell lymphoma have also been reported [43].

Several are the implications of concomitant liver disease for the therapeutic intervention in rheumatologic diseases; in fact, the liver is frequently involved in the adverse events of systemic treatments utilized in rheumatology. A complete discussion goes beyond the aims of the present review article, but it is easy to foresee that hepatitis virus reactivation and drug-related liver injuries are rapidly becoming a major cause for liver involvement in rheumatology with the use of more potent immunosuppressants such as biologics [44,45] or hematopoietic stem cell transplantation [46]. Detailed recommendations on the use of immunomodulatory molecules in patients with chronic liver disease were reported by the American College of Rheumatology in 2008 for RA [47] while the American Association for the Study of Liver Diseases also presented practice guidelines in 2009 for the management of patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) chronic infection needing immunosuppressive therapy [48,49], and clinical guidelines are available for viral hepatitis and inflammatory bowel disease treatment [50]. These guidelines support the view that the alanine aminotransferase (ALT) level, anti-HBsAg, anti-HBsAb, anti-HBcAb IgG and, in selected cases, HBV DNA, along with anti-HCV antibodies and HCV RNA, should be tested before an immunosuppressant treatment is initiated [47,50,51]. Currently, a preventive antiviral treatment is recommended in patients with an active chronic HBV infection (HBsAg-positive, elevated ALT and serum HBV DNA levels >2,000 IU/ml) and in patients with chronic HCV infections without extrahepatic contraindications [47,50].

Prophylactic treatment is recommended in patients needing nonbiologic or biologic disease-modifying antirheumatic drugs with inactive HBV (HBsAg-positive, normal ALT and HBV DNA <2,000 IU/ml; or HBsAg-negative and anti-HBcAb-positive with or without HBsAb, normal ALT and HBV DNA <50 IU/ml), and to be considered in resolved HBV infection (HBsAg-negative, HBsAb-positive and/or anti-HBcAb-positive, normal ALT and HBV DNA <50 IU/ml) together with monitoring of ALT levels and serum HBV DNA in cases of long-term lamivudine use [47,50]. Disease-modifying antirheumatic drugs such as methotrexate and leflunomide are contraindicated in cirrhosis secondary to chronic HBV and HCV infections, whether treated or untreated, for all Child–Pugh stages [47], while biologics are contraindicated in both chronic HBV and HCV, whether treated or untreated, for those with significant liver injury, defined as chronic Child–Pugh classes B or C [47]. Immunosuppressant regimens including glucocorticoids appear to have the highest risk of HBV reactivation and HCV replication, so steroid-sparing treatment should be adopted when possible although low doses appear to be safe [48]. Finally, the use of NSAIDs should be carefully evaluated in patients with liver cirrhosis regardless of the etiology based on the risk of renal injury secondary to tubular ischemia. Referral clinical immunology textbooks report the risk of liver injury related to the use of classical anti-inflammatory treatments such as acetaminophen, NSAIDs, or methotrexate despite the rarity of such events in clinical trials [52].

The American College of Rheumatology guidelines indicate that when the levels of ALT are greater than twofold the upper normal limit, the initiation of disease-modifying antirheumatic drugs such as methotrexate, leflunomide, and sulfasalazine is contraindicated, while recommendations on when to discontinue the drug are not provided [47]. Further, recent prospective data put

such risk in a more accurate perspective. As an example, the risk of liver injury following acetaminophen intake is now well defined and recognizes a dose-dependent increase, with doses as high as 4 g/day proven to be safe in patients with chronic viral hepatitis or recent alcohol abuse as well as in patients with compensated liver cirrhosis [53]. Conversely, the appearance of NSAID-induced liver injury appears to be dose independent while the new scenarios of biologic-induced autoimmune hepatitis [54] will warrant further studies on the long-term outcomes. A most recent study on the impact of methotrexate on liver function tests demonstrated a reasonably safe profile for this medication if properly used [55], thus suggesting that dedicated studies are necessary to detect the detrimental potential of immunomodulatory treatments. The issue of drug-induced liver injury became important with the discovery of the possible implications of occult hepatitis B infection [56] and the subsequent impact on the widespread use of monoclonal antibodies [57] in carriers and cases of chronic infections [58]. Finally, we should expect that the use of hematopoietic stem cell transplantation will also impact liver biology [59,60].

The liver in the present and future of rheumatology

Among patients with systemic rheumatic diseases, those with connective tissue diseases may present a mild liver involvement mainly related to the underlying disease activity that is, subsequently, transient. Progressive liver involvement is generally related to the coexistence of viral hepatitis or autoimmune liver diseases with obviously opposite results of the proposed systemic immunosuppressive treatments. Overlap diseases should be considered once hepatitic and/or cholestatic biochemical profiles, either simultaneously or consecutively, are not clearly explained by liver involvement of a rheumatic disease or by coincidental infection or drug toxicity. Finally, we encourage perspective studies to determine the impact in clinical practice of old and new treatments on the liver biology to overcome ancient beliefs [61] and pave the way for the new exciting developments in the field of biologics [62].

This article is part of the series *Comorbid conditions in subjects with rheumatic diseases*, edited by Daniel Aletaha and Thomas Dörner. Other articles in this series can be found at http://arthritis-research.com/series/comorbid

Abbreviations

AIH, autoimmune hepatitis; ALT, alanine aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; NSAID, nonsteroidal anti-inflammatory drug; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TNF, tumor necrosis factor; UCDA, ursodeoxycholic acid.

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Competing interests

The authors declare that they have no competing interests.

Published: 30 June 2011

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doi:10.1186/ar3319
Cite this article as: Selmi C, *et al.*: Liver involvement in subjects with rheumatic disease. *Arthritis Research & Therapy* 2011, **13:**226.