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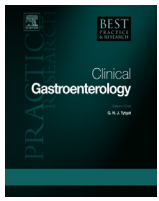

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Liver abnormalities in connective tissue diseases

Maria De Santis, MD, PhD, Physician Scientist [a,b], Chiara Crotti, MD, Physician [a], Carlo Selmi, MD, PhD, Assistant Professor of Rheumatology [a,b,*]

[a] *Division of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center, Rozzano, Milan, Italy*
[b] *BIOMETRA Department, University of Milan, Milan, Italy*

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A B S T R A C T

The liver is a lymphoid organ involved in the immune response and in the maintenance of tolerance to self molecules, but it is also a target of autoimmune reactions, as observed in primary liver autoimmune diseases (AILD) such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. Further, the liver is frequently involved in connective tissue diseases (CTD), most commonly in the form of liver function test biochemical changes with predominant cholestatic or hepatocellular patterns. CTD commonly affecting the liver include systemic lupus erythematosus, antiphospholypid syndrome, primary Sjögren's syndrome, systemic sclerosis, dermatomyositis, polimyositis, and antisynthetase syndrome, while overlap syndromes between AILD and CTD may also be diagnosed. Although liver cirrhosis and failure are extremely rare in patients with CTD, unusual liver conditions such as nodular regenerative hyperplasia or Budd–Chiari syndrome have been reported with increasing frequency in patients with CTD. Acute or progressing liver involvement is generally related to viral hepatitis reactivation or to a concomitant AILD, so it appears to be fundamental to screen patients for HBV and HCV infection, in order to provide the ideal therapeutic regimen and avoid life-

Abbreviations: CTD, connective tissue disease; AILD, autoimmune liver disease; SLE, systemic lupus erythematosus; pSS, primary Sjogren syndrome; SSc, systemic sclerosis; PM, polymiositis; DM, dermatomyositis; AS, anti-syntehase syndrome; NRH, nodular regenerative hyperplasia.

* Corresponding author. Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis School of Medicine, Genome and Biomedical Sciences Facility, 451 Health Sciences Drive, Suite 6515, Davis, CA 95616, USA. Tel.: +1 530 752 2884; fax: +1 530 752 4669.
E-mail addresses: carlo.selmi@humanitas.it, cfselmi@ucdavis.edu (C. Selmi).

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threatening reactivations. Finally, it is important to remember that the main cause of biochemical liver abnormalities in patients with CTD is a drug-induced alteration or coexisting viral hepatitis. The present article will provide a general overview of the liver involvement in CTD to allow rheumatologists to discriminate the most common clinical scenarios.

Introduction

The liver represents the largest lymphoid organ, being involved in the immune response against pathogens and in the maintenance of tolerance to self molecules [1]. Nevertheless, it can also be a target of autoimmune reaction, as observed in primary liver autoimmune diseases, such as autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). From a rheumatologist viewpoint, the liver is frequently affected by connective tissue diseases (CTD), particularly when the affection is mirrored by liver test abnormalities and may produce a biochemical picture with the predominance of cholestatic (with elevated alkaline phosphatase [ALP] and gamma-glutamyl transferase [GGT]) or hepatocellular (with elevated alanine transaminase [ALT] and aspartate transaminase [AST]) damage. We should also note, however, that advanced disease with liver cirrhosis and failure is extremely rare in patients with CTD (Table 1).

In systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and primary Sjögren's syndrome (pSS), serologic liver test alterations and histological lesions have been described in numerous descriptive studies mostly based on case series. The prevalence of autoimmune liver disease (AILD) in CTD is described by Table 2. In the majority of the cases, liver histology will demonstrate only minor changes and the biochemical findings can be ascribed to the primary affection, even though, in a small number of patients an overlap syndrome with a coexisting primary liver disease should not be overlooked. In this setting, the liver damage is usually progressive, frequently complicated by cirrhosis and portal hypertension. Nevertheless, the main cause of biochemical liver abnormalities in patients with CTD is the presence of previous treatments with potentially hepatotoxic drugs or coexisting viral hepatitis.

Systemic lupus erythematosus

SLE is a multiorgan CTD classically associated to skin rash, glomerulonephritis, serositis, haematological and central nervous system abnormalities. The liver is generally not a major target organ for damage and, as such, abnormalities of liver function are not included in the classification and diagnostic criteria of SLE. Nevertheless, abnormal liver function tests are common in SLE, being found in up to 50% of patients at some point of the disease course [2] and the main causes are disease activity and drug toxicity and only rarely an overlapping primitive autoimmune liver disease. In 20% of cases liver test abnormalities occur during disease flares, while in 23% of SLE cases with abnormalities in liver functions no cause for pathological liver tests can be identified [3]. Elevated liver tests has been shown to correlate with disease activity and to improve with steroid treatment and a chronic active hepatitis – termed 'lupoid hepatitis' by some authors – is described in up to 5% of patients with SLE. Antibodies to ribosomal P protein has been shown to strongly correlate with lupus hepatitis, being detected in a significant proportion of patients (69%) [4]. In this setting, histology demonstrates predominantly mild lobular inflammation without piecemeal necrosis. There are no clear recommendations about the opportunity to perform a liver biopsy: we suggest this procedure when there is an increase of

Table 1
Prevalence of liver injury in the most common connective tissue diseases.

Disease	Enzyme alterations	Biochemical profile	Histologic alterations
Sjogren's syndrome	50%	cholestatic > hepatocellular	18%
SLE	30%	cholestatic < hepatocellular	20%
Systemic sclerosis	1%	cholestatic > hepatocellular	9%