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Rheumatological Impacts on the Liver

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ABSTRACT

Sometimes, rheumatological diseases are associated with liver affections. Many aetiological factors are involved as coexisting autoimmune liver disease, the direct involvement of the liver parenchyma, or the impact of medical treatments on the liver. Immunosuppressive agents may have impact on the in apparent viral infections of the liver; resulting in some pathological lesions; that may not be expected to be related to rheumatic disease.

Many rheumatic diseases can affect the liver with various degrees of histopathological lesions being not specific to such comorbidities and are also based on clinical features that are common to other chronic liver diseases.

HCV-related rheumatic diseases result from infection with HCV. Overlap and liver diseases associated with rheumatic arthritis are relatively common; where we depend on the prevailing symptoms for management.

Keywords: *Rheumatic Arthritis, HCV, Liver Diseases, Diagnosis, Management*

INTRODUCTION

Mostly; Systemic rheumatologic diseases are associated with liver abnormalities. This may be due to the presence of a coexisting autoimmune liver disease, the direct involvement of the liver parenchyma, or due to the effect of treatment on the liver. Moreover, immunosuppressive drugs may have effects on underlying viral infections. The liver may be affected due an underlying disease or due to the toxicity of therapies and the medical complications of extrahepatic diseases.

Many rheumatic diseases can affect the liver with different histopathological lesions. These lesions are not specific to such comorbidities and depend on clinical features that are common to other chronic liver affections [1]. On the other hand, the primary immune diseases of the liver are autoimmune hepatitis (AIH);representing 100 cases per million [2], primary biliary cirrhosis (PBC) demonstrating400 cases per million [3], and primary sclerosing cholangitis (PSC) of 150 cases per million [4] and [5]. PBC and PSC represent biliary/cholestatic diseases and affect liver parenchyma only. Gholestasis is demonstrated trough liver biochemistry profile. Concerning AIH; it results from hepatocyte damage with a typical hepatitis pattern of liver investigations.

Inspite that liver involvement in patients with rheumatic arthritis shows typical clinical picture, but, the histopathological depends on the primary liver conditions [6]. In case of AIH [7] ; it shows portal- parenchymal interface hepatitis with abundant lymphocyte and plasma cell infiltration, that crosses the limiting plate and invades the liver parenchyma [2], On the other hand , in PBC ;focal intrahepatic small bile duct obliteration and granulomas are seen.[8].This is associated with portal inflammation, subsequent periportal hepatitis, fibrous septa, bridging necrosis and, finally, frank cirrhosis. Concerning PSC; it can affect all bile ducts; resulting in 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 [4].So, affection of small-duct can provide a diagnostic evidence.

Liver histology is mostly different in rheumatic diseases with hepatic involvement. In patients with liver enzyme abnormalities undergoing liver biopsy ; we can find either chronic active hepatitis, chronic persistent hepatitis, cirrhosis, nodular regenerative hyperplasia, fibrosis, steatosis, and granulomas , along with less

specific findings such as mild chronic inflammatory cell infiltrate of the portal space [9, 10]. Moreover, vascular involvement; especially intrahepatic small vessel arteritis, Budd-Chiari syndrome, or isolated portal hypertension, can be found. It is to be mentioned that drug-induced liver injury is significantly more frequent than primary disease-related liver involvement. Also, concurrent viral hepatitis or opportunistic infections have to be excluded in rheumatic patients. Also, amyloidosis may be a cause of liver involvement in chronic systemic rheumatic diseases [11].

Among patients with arthritis, liver affection has been recorded in cases of rheumatoid arthritis (RA) and its variants. In those cases of RA; abnormal liver function tests were varying with disease activity; especially elevated alkaline phosphatase, representing 18 to 50% of patients with RA. Proceeding further 65% of unselected patients with RA had abnormal liver biopsies; being with mild portal chronic inflammatory infiltrate of the portal tract and small foci of necrosis in 50% of cases , and with fatty liver in 25% of patients [12].

Clinically; Overlap Syndrome was reported in cases showing a clinical picture of two or more immunologic diseases in the same time. Overlap syndromes may include AIH and PBC or PSC. Manifestations include both hepatitis and cholestatic biochemical profiles and histological features suggestive of AIH and PBC or PSC. It was reported that AIH and PBC overlap syndrome occurred in 10% of adults with AIH or PBC, whereas AIH and PSC overlap syndrome has been found in up to 49% of children, adolescents, and young adults with AIH or PSC. Change from one to another liver disease is sometimes possible and may take years [13]. Although 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. Moreover, AIH and PBC overlap syndrome has been described in patients with Systemic lupus erythematosus LE [14].

In general, AIH, PBC, and PSC may develop in patients with systemic rheumatic diseases. Still, there is a need for an accurate prevalence of overlap diseases; mostly data are from case records or from biopsies of patients with liver enzyme abnormalities [14].

Treatment of autoimmune liver diseases are essentially based on corticosteroids and immunosuppressant drugs; such as methotrexate and azathioprine. The exception is in case of PBC; for which ursodeoxycholic acid (UDCA) is the only established treatment [15].However, the combination of UDCA and immunosuppressants, albeit rational, failed to prove effective. On the other hand, methotrexate has been shown to be without adverse effects, with or without concomitant UDCA [16], but was burdened by significant side effects in randomized clinical trials [17]. Regarding AIH, corticosteroids represent the cornerstone of currently utilized regimens [18]. The latter is considered the best 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 resolution of liver inflammatory infiltrate at histopathology. Moreover, in cases of incomplete response or relapse, a long-term maintenance regimen with azathioprine is needed. Salvage therapy includes cyclosporine or mycophenolate mofetil, although more solid data are awaited [18] and new frontier therapeutic approaches may prove beneficial [19].

Management of overlap syndromes between PBC and AIH is empirical and is guided by the predominant manifestations of the disease. Corticosteroids and UDCA are suggested for patients with AIH and PBC with higher serum alkaline phosphatase and transaminases [20].

Experimentally 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 demonstrated potential benefits for nonalcoholic steatohepatitis and PSC; however, AIH and hepatosplenic T-cell lymphoma have also been reported [21].

The liver is frequently involved in the adverse events of systemic treatments utilized in rheumatology. Hepatitis virus reactivation and drug-related liver injuries are important causes for liver involvement in rheumatology with the use of more potent immunosuppressants such as biologics [22, 23] or hematopoietic stem cell transplantation [24].We can find some recommendations on the use of immunomodulatory molecules in patients with chronic liver disease according to the American College of Rheumatology in 2008 for RA [25], 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 [26, 27], and clinical guidelines are available for viral hepatitis and inflammatory bowel disease treatment [28].

Diseases may present a mild liver involvement related to the underlying disease activity; that is, subsequently, transient. Progressive liver involvement is related to the coexistence of viral hepatitis or autoimmune liver diseases with obviously opposite results of the proposed systemic immunosuppressive treatments. Also, 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 [29].

Clinically; rheumatic diseases are problems, including pain, in the joints, muscles and connective tissue. HCV-related rheumatic diseases result from infection with HCV. Painful joints and muscles combined with fatigue are usually the first and most common complaints.

Less often, joint swelling and inflammation of blood vessels can occur [30]. The explanation of the joint and muscle complications of HCV infection is that the body's immune system fights against the virus. The virus constantly multiplies in the blood and liver, and constantly stimulates the immune system. So, a wide variety of rheumatic problems may occur over time. They are ranging from arthritis and "cryoglobulinemia" to kidney failure. Symptoms of HCV infection are often absent, so a doctor must know about the connection between hepatitis C and rheumatic disease in order to know which tests to run. HCV-related joint and muscle problems can cause discomfort and make it harder to do daily activities. [31].

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