Hepatic manifestations of autoimmune rheumatic diseases

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SUMMARY

Autoimmune rheumatic diseases including Systemic Lupus Erythematosus, Rheumatoid Arthritis, Sjogren’s syndrome, Myositis, Antiphospholipid Syndrome, Behcet’s syndrome, Scleroderma and Vasculitides have been associated with hepatic injury by virtue of multisystem immune and inflammatory involvement. Liver involvement prevalence, significance and specific hepatic pathology vary. After careful exclusion of potentially hepatotoxic drugs or coincident viral hepatitis the question remains whether liver involvement emerges as a manifestation of generalized connective tissue disease or it reflects an underlying primary liver disease sharing an immunological mechanism. Commonly recognised features include mild elevation of liver laboratory values and non specific histological images. Hepatic steatosis, nodular regenerative hyperplasia, portal vein obliteration and portal hypertension, features of primary biliary cirrhosis, vascular disorders, granulomatous reactions and rarely portal fibrosis with abnormal lobular architecture are possible histological findings. Diagnosis can be established on serological, histological and clinical features and after careful exclusion of other possible causes. Association between antirheumatic drugs and hepatic dysfunction has been established in the past. Liver involvement may vary from a mild asymptomatic elevation of liver transaminases or cholestasis parameters to a fulminant hepatitis. A review of the literature to determine the association between primary autoimmune rheumatologic disease and associated hepatic abnormalities and the pharmaceutical interventions that are related to liver damage are presented.

Key words: Connective Tissue Disease, Systemic Lupus Erythematosus, Rheumatoid Arthritis, Sjogren’s syndrome, Myositis, Giant-Cell Arteritis, Antiphospholipid Syndrome, Behcet’s syndrome, Scleroderma, Vasculitis, Steatosis, Nodular Regenerative Hyperplasia, portal hypertension, Autoimmune Hepatitis, Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis

1. Introduction

A variety of autoimmune rheumatic diseases including Systemic Lupus Erythematosus, Rheumatoid Arthritis, Sjogren’s syndrome, Myositis, Vasculitis, Antiphospholipid Syndrome, Behcet’s syndrome and Systemic Sclerosis, have been associated with liver involvement and their prevalence, significance and specific hepatic pathology varies. Although advanced liver disease with cirrhosis and liver failure is rarely documented in patients with connective tissue diseases, clinical and biochemical evidence of associated liver abnormalities is commonly identified. Previous treatment with potentially hepatotoxic drugs or coincident viral hepatitis have usually been implicated as predominant causes of liver disorders. However, even after careful exclusion of these aetiologies, the question remains whether to classify the patient as having a primary liver disease with associated autoimmune, clinical, and laboratory features or as having liver disease as a manifestation of generalized connective tissue disease.

Hepatic steatosis, nodular regenerative hyperplasia, portal vein obliteration and portal hypertension, features of primary biliary cirrhosis, vascular disorders, granulomatous reactions and rarely portal fibrosis with abnormal lobular architecture are possible histological findings. (Table 1) In a series conducted in 306 patients (106...
with SLE, 71 with Sjogren’s syndrome, 59 with rheumatoid arthritis, 27 with scleroderma, 30 with polymyositis, and 13 with polyarteritis nodosa) liver disturbance was documented in 43% of these patients and resulted from various causes. Liver disease was characterized by mild and transient elevation of liver laboratory values, minimal change in liver histology. In 8 of 14 patients with histologically proven chronic hepatitis or cirrhosis, hepatotropic virus was identified as the potential evoking agent. Five of 9 patients in whom the hepatic lesion progressed had hepatotropic virus infection (4 with HCV and 1 with HBV), and the other 4 patients suffered from autoimmune liver diseases.4

Association between antirheumatic drugs and hepatic dysfunction has been established in the past. Liver involvement may vary from a mild asymptomatic elevation of liver transaminases or cholestasis parameters to a fulminant hepatitis.

### Rheumatic Disease

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>LIVER DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SYSTEMIC LUPUS ERYTHEMATOSUS</strong></td>
<td>Hepatomegaly, Splenomegaly, Jaundice, ALP-</td>
</tr>
<tr>
<td><strong>ANTIPHOSPHOLIPID SYNDROME</strong></td>
<td>Hepatomegaly, Jaundice, ALP-</td>
</tr>
<tr>
<td><strong>RHEUMATOID ARTHRITIS</strong></td>
<td>ALP-, γ-GT-</td>
</tr>
<tr>
<td><strong>FELTY’S SYNDROME</strong></td>
<td>Hepatomegaly, Portal hypertension, ALP-</td>
</tr>
<tr>
<td><strong>MYOSITIS</strong></td>
<td>Jaundice, ALP-</td>
</tr>
<tr>
<td><strong>SCLERODERMA</strong></td>
<td>Hepatomegaly, Jaundice, liver enzymes-</td>
</tr>
<tr>
<td><strong>SJOGREN’S SYNDROME</strong></td>
<td>liver enzymes-, Jaundice</td>
</tr>
<tr>
<td><strong>Polyarteritis nodosa</strong></td>
<td>Hepatomegaly, Jaundice, liver enzymes-</td>
</tr>
<tr>
<td><strong>Hypersensitivity vasculitis</strong></td>
<td>Hepatomegaly, Jaundice, liver enzymes-</td>
</tr>
<tr>
<td><strong>Granulomatous vasculitis</strong></td>
<td>ALP-, γ-GT-</td>
</tr>
</tbody>
</table>

Table 1: Hepatic manifestations of autoimmune rheumatic diseases. LFT’s=liver function tests.
A Medline search of all published papers and case reports of hepatic involvement in autoimmune rheumatic diseases published between 1966 and 2004 was made.

2. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease sharing multisystem involvement and diverse clinical and serological manifestations, principally affecting women during the child bearing years. Clinically significant hepatic dysfunction is generally regarded as unusual in SLE and previous treatment with potentially hepatotoxic drugs or viral hepatitis have usually been implicated as the most relevant causes for such unusual complications. Yet careful exclusion of such causative factors raises a quite complicated dilemma regarding differential diagnosis between liver disease as a manifestation of SLE or primary liver disease with associated autoimmune clinical and laboratory features resembling SLE.

The frequency of hepatic involvement in SLE is about 8-23% consisting of several pathophysiological features and emerging with clinical signs including hepatomegaly (39%), splenomegaly (6%), jaundice (24%) and finally in 21% of the patients with elevations of liver enzymes or with abnormal liver histology. According to a retrospective study conducted by Gibson and Myers abnormal values where revealed in 55% of 81 patients diagnosed with SLE and 29% of them had no cause for the documented changes other than SLE. In a study by Miller et al, liver enzyme levels were found to be raised in 23% of 260 patients with SLE assessed. The reported incidence of hepatomegaly in SLE varies from 12-55% depending on the series. Cholestatic hepatitis emerging as conjugated hyperbilirubinemia can develop on the ground 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. Finally, there is a case reported of "idiopathic" portal hypertension accompanied by splenomegaly, cytopenia and oesophageal varices.

Pathologically, a wide variety of lesions have been described in the hepatic parenchyma of patients diagnosed with SLE. Liver histology can occasionally reveal steatosis, cirrhosis, chronic hepatitis, hepatic granulomas and centrilobular necrosis, micro abscesses, haemochromatosis, cholestasis, primary biliary cirrhosis and non-specific reactive changes. Hepatic infarction and spontaneous hepatic rupture due to arteritis of hepatic arteries has been reported in an isolated case report of SLE. Excessive fatty infiltration is a common finding and may be attributed either to the disease process itself or to the steroid treatment. During the histological evaluation of 19 patients with SLE and hepatomegaly or abnormal liver function tests, 11 sheared minor alterations in liver biopsy including fatty infiltration, portal tract fibrosis and mild to moderate cellular infiltration and two patients had chronic active hepatitis which progressed to cirrhosis. According to Gibson and Myers, portal inflammation was revealed in 5 of the 81 SLE patients, fatty liver in one and chronic active hepatitis in one patient.

Autoimmune hepatitis ("Lupoid hepatitis") is a chronic necroinflammatory liver disease of unknown origin associated with circulating autoantibodies high serum globulin level and hepatocellular necrosis and inflammation which leads to cirrhosis and hepatic failure. The term "lupoid hepatitis" is inaccurate and reflects the high prevalence of autoantibodies in this disorder. Differential diagnosis between autoimmune hepatitis and SLE-associated hepatitis remains a clinical challenge, for giving rise to the need establishment of more sufficient diagnostic criteria for both diseases. A current definition of lupoid hepatitis includes histological evidence of chronic active hepatitis, exclusion of any possible viral causes and positive antinuclear antibodies or LE cell preparation. Yet it can be distinguished from SLE by the absence, usually, of antibodies to double stranded DNA. Lupoid hepatitis shares common clinical manifestations with SLE such as fever, arthralgia, malaise, loss of appetite and jaundice. Several cases reported in the literature outline the invalidity of the autoimmune hepatitis score, based on specific antibodies such as antibodies to nuclei, smooth muscle and liver microsomes among SLE patients, whereas liver histology should be considered most important flavor at present in establishing a diagnosis. Runyon reported four cases of patients suffering from both SLE and lupoid hepatitis. In each case chronic granulomatous hepatitis, chronic hepatitis or steatosis was histologically observed. Lupoid hepatitis should be regarded as a case of autoimmune hepatitis with SLE phenomena. Recently it has been suggested that circulating antibodies to ribosomal P proteins are strongly collated with severe lupus hepatitis.

Verification of SLE-induced hepatitis or of a SLE-autoimmune hepatitis overlap syndrome requires careful exclusion of drug-toxicity and viral hepatitis. An important part of the liver enzymes abnormalities documented in patients with SLE is attributed to aspirin. Reversible rises of the aminotransferases are quite common and may be accompanied by an increase of alkaline phosphatase activity. Lower salicylate levels than in pa-
tients without SLE are considered eligible for toxicity symptoms to emerge. Furthermore anti-inflammatory agents commonly administered in SLE such as naproxen, fenoprofen, and sulindac have been previously associated with cholestatic hepatitis in lupus patients. Finally there is a case reported in the literature of a drug induced lupus-like syndrome concomitant with severe autoimmune hepatitis in genetically predisposed patient. Regarding the prevalence of virus C infection in patients with SLE a statistically significant difference between SLE patients and a blood donor’s control group doesn’t seem to exist.

3. Antiphospholipid Antibody Syndrome

Antiphospholipid syndrome is a rare autoimmune disorder characterized by acquired venous and arterial thromboses, recurrent fetal losses and thrombocytopenia, in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or antibodies to the protein “cofactor” b2 glycoprotein I. The antiphospholipid antibodies can be found in many conditions such as autoimmune diseases, infections, malignant diseases and use of drugs. Also, they can be found in 2-6.5% of healthy persons without risk of thrombosis. It may be primary, when there is no other condition and secondary when there are other conditions such as SLE, reumatoid arthritis or systemic sclerosis.

Clinical manifestation of the disease rarely complicates the liver, mainly affecting smaller intrahepatic vessels resulting in hepatic vein occlusion and in the development of Budd Chiari syndrome, whereas it is possible for the nodular regenerative hyperplasia of the liver which is a rather pathological syndrome to develop. Liver biopsy is characteristic of Budd-Chiari syndrome with centrifional ischemia and necrosis and sinusoidal congestion. Nodular regenerative hyperplasia is a histological term used to describe diffuse micronodular transformation of the hepatic parenchyma with the nodular zone demarcated by compressed liver cell cords. In each such case reported in the literature patterns of clinical presentation included altered liver function tests or signs and symptoms of portal hypertension. aCL and aPL were positive in most of the cases. Lupus anticoagulant and thrombotic events were documented in addition. Diagnosis can be established only after extensive histological evaluation of the hepatic parenchyma in patients with aPL who develop a pathological liver profile or clinical symptoms of portal hypertension. Finally, according to Elias and Eldor a rise in hepatic enzymes, presumably because of fibrin thrombi in the smaller intrahepatic vessels, also seems to occur in patients with aPL and without any other possible cause.

The antiphospholipid syndrome has been described rarely in patients with autoimmune hepatitis. Antiphospholipid antibodies can be found in many liver diseases, such as chronic hepatitis C, where they can cause thrombosis and thrombocytopenia. Infection with HCV is present 16.7% of patients with thrombotic disorders and anti – cardiolipin antibodies. They can also cause Budd-Chiari syndrome. Patients with autoimmune hepatitis and a history of thrombosis or fetal loss must be submitted to test for antiphospholipid syndrome.

4. Rheumatoid Arthritis

Rheumatoid arthritis (RA), juvenile idiopathic arthritis, Still’s disease and Felty’s syndrome are rheumatoid syndromes sharing a common immunological profile (chain reaction of autoimmunity), all reported to uncommonly involve liver pathology.

Liver involvement is documented in up to 6% of patients with RA emerging in most of the cases as mild elevation of alkaline phosphatase and serum γ glutamyltransferase levels. One hundred and eighty three inpatients with rheumatoid arthritis were extensively investigated and the serum gamma glutamyl transferase level was found elevated in 47% and serum alkaline phosphatase (of liver origin) in 24% of the cases. A concomitant increase in serum aminotransferases was found in 15% of patients with elevated gamma glutamyl transferase levels. Clinical manifestation can rarely conclude in spontaneous hepatic rupture in both patients complicated by extra-articular features and high titer rheumatoid factor and patients presenting with mild seronegative inflammatory arthritis, or it can be attributed to generalize necrotizing hepatic arteritis with infarction and spontaneous liver rupture. Primary biliary cirrhosis (PBC) can also develop.

Non specific histological findings from the hepatic parenchyma accompany RA including Kupffer cell hyperplasia, fatty cell infiltration, and infiltration of periportal areas with mononuclear cells. Rheumatoid nodules scattered throughout the hepatic parenchyma were reported to complicate patients with active RA, presenting in postmortem findings as central zone of cell necrosis with surrounding histiocytes in a palisade arrangement with peripheral fibrosis and a chronic inflammatory cell infiltrate. Pathological liver histology was documented in 65% of 117 unselected patients with RA who were committed to liver biopsy (reactive hepatitis was recognized in 43% and fatty liver in 22% of the patients)
Hepatic manifestations of autoimmune rheumatic diseases

whilst in a more recently published survey non specific 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 present in 74% of 31 RA patients. A review of liver biopsy findings in patients with RA does not suggest a consistent structural abnormality. Most biopsy reports suggest only minor nonspecific changes. In 117 patients with RA and without extra-articular complications 35% of liver biopsy specimens were normal, 43% showed nonspecific hepatitis, and 22% were associated with fatty change. 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 4 were normal. Of the 13 patients with chronic liver disease, diagnoses of one of each of the following were made: PBC, chronic active hepatitis, alcoholic cirrhosis, and amyloidosis. Because primary liver disease was found in 30% of cases, the changes that were 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.

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.

4.1 Felty’s syndrome

The incidence of hepatic involvement in Felty’s syndrome fluctuates among the published series. In one reported study hepatomegaly was revealed in 68% and liver enzyme elevations in 25% of the patients, whilst Blendis et al reported liver involvement in 5 out of 12 patients in his series. Clinical manifestation commonly includes hepatomegaly, abnormal liver chemistry and portal hypertension. Histological findings included diffuse lymphocytic infiltration within the sinusoids, Kupffer cell hyperplasia, periportal fibrosis, macronodular cirrhosis and fatty metamorphosis.

Nodular regenerative hyperplasia of the liver is rarely documented in patients with rheumatoid arthritis but occurs more frequently in patients with Felty’s syndrome. In one autopsy study, up to 35% of patients with Felty’s syndrome and liver function abnormalities exhibited histologic evidence of nodular regenerative hyperplasia. The pathogenesis of Nodular regenerative hyperplasia has not been defined, but vasculitis seems to be important in the initiation and progression of the liver lesion. Associated structural abnormalities result from distortion of liver microarchitecture caused by alternating zones of hyperplastic lobules and compressed zones that interfere with blood flow and are presumed to cause associated portal hypertension. A second cause of portal hypertension is related to splenomegaly with high portal vein flow. Measurements of free and wedged hepatic venous pressure are used to stratify patients by severity and need for medical or surgical management. Hepatic venous pressure gradients (wedged-free hepatic venous pressure) greater than 12 mmHg are associated with significantly more complications, including variceal bleeding.

4.2 Adult Still’s disease

Adult Still’s disease is a syndrome that is similar to seronegative juvenile rheumatoid arthritis with systemic manifestations including intermittent fever, skin rash, lymphadenopathy, splenomegaly, pleuritis, and pericarditis.

Several liver abnormalities were noted in a 10-year retrospective study of 12 patients who fulfilled diagnostic criteria for adult Still’s disease. Fever was present in 100% of patients, and hepatomegaly was present in 41%. Abnormalities in liver function tests were identified in 92% of patients and included 17% of patients with levels of serum aminotransferases that were five times the normal level and 83% of patients with levels that were between two and five times the normal level. All liver abnormalities resolved spontaneously or with treatment. The authors noted that, although serum aminotransferases were elevated significantly, many patients (75%) were asymptomatic. Fever and abnormal levels of serum aminotransferases suggest a diagnosis of adult Still’s disease, especially when accompanied by negative and complete evaluation for infectious disease and malignancy. In a case report, a 48-year-old patient with adult-onset Still disease presented with acute hepatitis with marked hyperferritinemia.

4.3 Treatment toxicity

Liver involvement may vary from a mild asymptomatic elevation of liver transaminases or cholestasis parameters but can also lead in some cases of monotherapy (hydroxy-/chloroquine, sulfasalazine) or combination therapy (methotrexate/MTX+leflunomide) to a fulminant hepatitis.

The published literature of population-based epide-
miological studies reporting the incidence or comparative risk of liver injury resulting from non-steroidal anti-inflammatory drugs (NSAIDs) supplementation allow for the possibility of a small increase in the risk of clinically relevant hepatotoxicity with non-steroidal anti-inflammatory drugs use, but do not sufficiently document that such a risk occurs.61 In a population-based case-control study assessing drug-induced liver injury, using the UK-based General Practice Research Database as the source of information a total of 1,636,792 persons aged 5-75 years old registered in the database from January, 1994 to 31 December, 1999 were followed-up for a total of 5,404,705 person-years. The highest crude incidence rates were found for chlorpromazine, azathioprine, and sulfasalazine (about 1 per 1000 users). A dose-effect was apparent for diclofenac, amoxicillin/clavulanic acid and flucoxacinil. The combination of two or more hepatotoxic drugs increased the risk by a factor of 6.4 In another study conducted in the setting of primary care a total of 22 patients were exposed to NSAIDs (salicylates, diclofenac, ibuprofen, ketoprofen, niflumic acid, flurbiprofen and meloxicam) and a significant association between liver injury and NSAID exposure was verified for the subgroup of women. These patients suffered from hepatocellular (53.3%), cholestatic (20%) or mixed (26.7%) type injury. In 18 cases, liver enzymes returned to normal values after drug withdrawal.68 Finally, diclofenac has been identified as a potential hepatotoxic anti-inflammatory agent, with literature data implying apoptosis mechanism in hepatocytes.64 According to a recently published study the observed gene polymorphisms, resulting in low IL-10 and high IL-4 gene transcription, could provoke a T helper (Th)-2 mediated antibody response to neoantigenic stimulation associated with disease susceptibility.65

Regarding drug induced hepatitis in RA, in numerous cases reported in the literature liver dysfunction was predominately attributed to disease modifying antirheumatic drugs (DMARD’s) such as gold, methotrexate, leflunomide, hydroxychloroquine, sulfasalazine.

A distinct histopathological entity involving the liver in patients treated with gold compounds for RA is documented presenting with prolonged cholestasis and ductopenia66. An immunooallergic underlying mechanism is implied since liver lesions were associated with hypersensitivity syndrome including dermatitis and blood and tissue eosinophilia. According to a series from Landas et al67 56% of such patients presenting liver involvement had well formed lipogranulomas in the lobules compared with a 5% incidence in the control biopsy group. In 20 of these cases pigment was traced in the lipogranulomas and in 7 patients it was found in lipid droplets in portal triads.68

Aggressive medical treatment with MTX has sufficiently been associated with minor liver abnormalities that seem to be reversible.69,70 Regarding MTX there are several case reports of hepatic dysfunction following MTX administration ranging from minor liver abnormalities that seem to be reversible71 to acute liver dysfunction.72 The canals of Herring might represent a target of MTX hepatotoxicity leading to liver fibrosis.73 Numerous studies have investigated the factors associated with toxicity, final dose, and efficacy of MTX. Lack of folate supplementation, untreated hyperlipidemia, and elevated Body Mass Index identify patients receiving MTX at risk for transaminase elevation.74 Additional baseline characteristics predicting the outcome of MTX treatment are mainly prior GI events, body mass index, sex, use of NSAIDs, and creatinine clearance.75 In another study assessing histological changes in 42 patients with RA using light and electron microscopy, patient’s age, length of evolution of the disease, alcohol consumption and biochemical data (gammaglutamate transferase and albumin) were correlated with histological abnormalities whilst the cumulative dose of MTX was not associated with worse histological findings.76 The question remains whether the established guidelines for monitoring methotrexate-related hepatotoxicity with surveillance liver biopsy in patients with psoriasis or rheumatoid arthritis are applicable to these patients.77,78

Leflunomide is a new immunomodulatory agent inhibiting the lymphocyte proliferation associated with the clonal expansion of T cells in rheumatoid arthritis. From a series investigating the incidence and severity of hepatotoxicity in 101 RA patients receiving leflunomide, moderate or severe elevations in liver enzymes were recorded in 8.9% whereas no life threatening elevations were documented.79 An incidence of leflunomide-induced hepatitis in a 67 year old female patient with rheumatoid arthritis is presented supporting a pathogenetic relationship to CYP2C9 polymorphism.80 In another case from the literature the risk of hepatotoxicity by leflunomide in patients with RA is illustrated and suggests that it is possibly related to CYP2C9 polymorphism.81 According to a national cohort study only 5% of leflunomide protocol discontinuers were attributed to elevated liver enzymes.82

Sulfasalazine has been recognised as another possible cause of fulminant immunoallergic hepatitis especially in pediatric patients83 and also it has been associated with the DRESS syndrome (Drug Rash With Eosi-
nephritis And Systemic Symptoms Syndrome).\textsuperscript{54}

Newer DMARDs and the risk of hepatic events in patients with rheumatic diseases has been assessed in a recent study.\textsuperscript{85} The study showed no significant evidence of an excess risk of serious or non-serious hepatic events with the use of leflunomide as compared with methotrexate monotherapy.

Yet, there was an increase in rate ratios of serious events with the use of biologic DMARDs (such as anti-TNF). As far as anti-TNF administration is concerned, pathogenesis of acute severe hepatitis is attributed to the drug’s effect in hepatocyte apoptosis and necrosis.\textsuperscript{86} It seems that TNF-initiated signalling pathways result in a direct apoptotic response as well as potent activation of pro-inflammatory gene expression via activation of the transcription factor nuclear factor-kappa B (NF-kappaB). Since the latter pathway contributes to a series of liver pathologies, inhibition of hepatic NF-kappaB activation is viewed as a potential therapy for tumour necrosis factor-mediated liver injury.\textsuperscript{87}

5. Systemic sclerosis

Systemic sclerosis (Scleroderma-SSc) is a chronic autoimmune rheumatic cause of systematic fibrosis involving not only the skin but also several internal organs. The disease rarely complicates the liver and conflict is documented upon that matter between several published series. According to a number of publications a higher prevalence of liver disease was found in the control groups\textsuperscript{88} whereas in a prospective assessment of visceral scleroderma 52% of the patients were shown to have lengthened prothrombin time or abnormal liver chemistry.\textsuperscript{89} Several hepatic syndromes\textsuperscript{90} have been associated with SSc including PBC, autoimmune hepatitis\textsuperscript{91,92,93}, cirrhosis of unknown origin,\textsuperscript{94} viral infection, “idiopathic” portal hypertension, primary sclerosing cholangitis and nodular regenerative hyperplasia of the liver.

Regarding autoimmune hepatitis, the cases of two patients with the complete CREST variant (calcinosis, Raynaud’s phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia) of SSc who developed autoimmune hepatitis has been presented.\textsuperscript{95} It has been suggested that evaluation for SSc including clinical examination, testing for antinuclear antibodies (especially for anticientromere antibodies) and nailfold capillaroscopy is appropriate when autoimmune hepatitis is noted. An autoimmune hepatitis-REST overlap syndrome has only been reported once.\textsuperscript{96}

PBC is a chronic, cholestatic, autoimmune liver disease, characterized by progressive, non-suppurative, inflammatory destruction of the interlobular and septal biliary ducts with development of periportal inflammation, fibrosis, and cirrhosis.\textsuperscript{97,98} The PBC diagnosis is based on biochemical, immunological and histopathologic findings. Coexistent autoimmune diseases are found in many patients with PBC, and it is not uncommon for the patient to have two or more accompanying autoimmune diseases.\textsuperscript{99,100} Nonhepatic disorders, particularly thyroid and connective tissue disorders, are found in 69% of patients with PBC.\textsuperscript{97} The widespread use of automated biochemical screening tests has resulted in diagnosing an increasing number of asymptomatic patients. Ten percent of PBC patients are asymptomatic at diagnosis, based on routine screening tests or after the diagnosis of another autoimmune disease.

An association between SSc and the liver has been noted through the coexistence of PBC. The prevalence of PBC in patients with SSc is questionable, determined up to 15% and in the majority of the cases involving the variant of limited scleroderma. Several case reports have verified the common autoimmune base of these two diseases on more than coincidental evidences.\textsuperscript{101,102} It is also indicated that anticientromere antibodies (ACA) may function as an early indicator for those PBC patients at risk of developing limited scleroderma in the future.\textsuperscript{103} In patients with PBC, the occurrence of SSc is between 3% and 50% [31-33]. Also according to Shoji et al\textsuperscript{104} there are 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. From another series investigating the presence of nailfold capillary abnormalities and extrahepatic signs of connective tissue disease in patients with PBC, as compared to patients with other chronic liver diseases, a significant association between systemic sclerosis capillary pattern and rheumatic manifestations is indicated. The high prevalence of nailfold capillary abnormalities characteristic of systemic sclerosis in patients with PBC and the correlation with scleroderma manifestations suggests that this capillaroscopic finding could be a useful indicator to investigate rheumatic manifestations in these patients.\textsuperscript{105} Cases of the CREST syndrome have been reported but do not occur as frequently as does SSc.\textsuperscript{106} In patients with PBC, SSc generally is mild, and morbidity is related to the progression of PBC-related liver fibrosis-cirrhosis.\textsuperscript{107}

A patient with chronic infection with hepatitis C virus who developed systemic sclerosis has been report-
Clinical manifestation included severe Raynaud’s phenomenon, progressive skin thickening, painful finger-tip ulcers, dysphagia and Sjögren’s syndrome. There is only one similar case involving hepatitis E virus\textsuperscript{109} with systemic sclerosis and also there is a case report of chronic aggressive hepatitis AB-Ag negative on the ground of systemic sclerosis and also there is a case report of chronic liver histology.

The association of nodular regenerative hyperplasia of the liver with limited scleroderma has been widely quoted, yet only a handful of cases have been reported. The case of a patient with limited scleroderma, raised alkaline phosphatase and IgM, positive ACA and AMA, portal hypertension and histological findings of nodular regenerative hyperplasia of the liver without evidence of PBC has been reported.\textsuperscript{111}

Another rare case of SSc complicated by idiopathic portal hypertension with severe anaemia has been reported from Japan.\textsuperscript{112}

Finally clinical association has been implied between Primary Sclerosing Cholangitis and SSc\textsuperscript{113} attributed to a shared evoking event which seems to be the deposition of abnormal collagen in the bile duct epithelium. Overlap in the clinical and biochemical features of Primary Sclerosing Cholangitis and PBC and luck of clinically significant signs of the disease, results in liver involvement underestimated.

6. Sjögren’s syndrome

Sjögren’s syndrome is a chronic inflammatory autoimmune exocrinopathic disease that predominantly affects the salivary and lachrymal glands.

An association with PBC, autoimmune hepatitis, viral hepatitis and cryptogenic cirrhosis has been assessed and needs further investigation. The incidence of liver involvement in primary Sjögren’s syndrome is reported at 6% to 7%\textsuperscript{114,115} whilst the incidence of an overlap primary Sjögren’s-cryptogenic cirrhosis syndrome is determined at approximately 22.2\%,\textsuperscript{116} Abnormal liver function tests were demonstrated in 27% of patients with primary Sjögren’s syndrome and diagnosis of PBC was established in four patients and autoimmune CAH in two.\textsuperscript{117} In each case whether a primary hepatic disorder coexists or whether it emerges as a complication of the primary autoimmune disease can only be estimated in terms of liver histology.

Some studies indicate that the pathogenic process responsible for the hepatic damage (mainly in the case of PBC) and for the salivary gland destruction could be similar,\textsuperscript{118} both epithelial populations inappropriately expressing class II HLA molecules and in both cases CD4 positive T cells predominating. Yet 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 antiglial mitochondria antiglial antibodies-AMA). Regarding the clinical value of autoantibodies as serological markers used to predict autoimmune liver diseases in Sjögren’s syndrome, it is indicated that patients with AMA develop PBC, and high-titre smooth muscle antibodies-SMA and antinuclear antibodies are the most specific indicators for autoimmune hepatitis.\textsuperscript{119} In another study, AMA is suggested as the most sensitive indicator of underlying PBC in patients with primary Sjögren’s syndrome.\textsuperscript{120} The prevalence of PBC demonstrated among several series ranges around 6%. According to another relevant study histological evidence of focal sialadenitis was revealed in 95% of patients with PBC with anti-La antibodies being detected in sera from 38% of patients with PBC\textsuperscript{121}. There is an overlap between CREST, Sjögren’s syndrome, thyroid hyperplasia and chronic hepatitis.\textsuperscript{122}

Sjögren’s syndrome can be complicated by autoimmune hepatitis although this is not the common case. Literature research disclosed only a handful of such cases.\textsuperscript{123,124} In such a report a patient with Sjögren’s syndrome and cholestatic autoimmune hepatitis who developed acute liver failure during her hospitalization is presented\textsuperscript{125}. Diagnosis was established on serological, histological and clinical features and after careful exclusion of other possible causes.

Several viruses including herpes viruses and retroviruses have been incriminated in Sjögren’s syndrome development. The prevalence of hepatitis B, C and E viruses and of herpes viruses was studied in Norwegian and Russian patients and a statistically significant difference in the reported incidence regarding HBV, HCV, and HEV serological markers was indicated\textsuperscript{126}. The prevalence of HCV antibodies in patients with primary Sjögren’s syndrome has been estimated at between 14-19%\textsuperscript{127} whilst HCV viraemia ranges between 0-19% (the prevalence of HCV infection in the general population is approximately 1\%). Finally, in a number of cases, detection of HCV-RNA in the salivary glands of a Sjögren’s syndrome-like patient suggested that a direct infection of the salivary glands by HCV could play an important role in the pathogenesis of sialadenitis.\textsuperscript{128,129} Patients with Sjögren’s syndrome and HCV virus infection are prone to develop complications from the liver (reaching 100\% in one study).\textsuperscript{130}
7. Behcet’s Disease

A rare case of entero-Behcet’s disease complicated with esophageal ulcers, systemic sclerosis, chronic hepatitis C, and pancytopenia has been described.131

Polymyositis (PM) is an autoimmune inflammatory disorder mainly affecting the muscles yet in one third of the cases it has been associated with autoimmune rheumatic disorders and in one tenth with a malignancy.132 The diagnosis of PM is based on clinical, biochemical, immunological and histological findings. Association between PM and other connective tissue diseases is well known. Classical laboratory values assessed for diagnostic purposes such as aspartate aminotransferase, alanine aminotransferase and LDH levels can often be mistakenly attributed to hepatic disease. Misinterpretation of these values results in significant delays in diagnosis and institution of appropriate drug treatment.

Association between autoimmune hepatitis and PM has been previously reported. The patient presented fulfilled the diagnostic criteria for both diseases and his serum contained an autoantibody reacting with mitochondrial proteins in immunodiffusion.133

The association between PBC and PM is rare.134 Only nine cases have been described in English literature.135 The co-occurrence of a severe progressive myopathy and mild PBC has been published (two patients), where the primary pathologic process appeared to be an idiopathic myopathy distinct from typical PM.137 In five previous reports PBC antedated myositis by 1-6 years.138,139,140 was diagnosed simultaneously in three others, 141,142 and myositis preceded PBC in one case.143 Other causes of inflammatory myopathies, such as endocrine, neuromuscular, metabolic, toxic, sarcoidosis or infectious disorders should be ruled out on clinical and laboratory grounds. Finally hepatocellular carcinoma has been described in association with PM in two cases.144 The pathogenesis of PM is not well defined, but several studies suggested that genetic factors, viral infections or autoimmune mechanisms may be involved. On the other hand, the cause of PBC also remains unknown, but the association of PBC with a variety of autoimmune disorders suggested a similar mechanism. Common findings that characterized these diseases are the presence of serum autoantibodies and the lymphocytic infiltration in tissue biopsies. These often affect women; genetic factors may also be important. It is suggested that patients with rheumatic or thyroid diseases with abnormal liver chemistry tests should be investigated for PBC. Therefore it is indicated that certain attention should be drawn to laboratory values during the assessment of PM in view of a concomitant autoimmune disease.

9 The vasculitic syndromes

9.1 Polyarteritis nodosa group

Polyarteritis nodosa is a systemic necrotising vasculitis developing secondary to the deposition of soluble immune complexes to medium-sized muscular arteries.

Gocke and colleagues firstly documented Polyarteritis associated with hepatitis B surface antigenemia in the 70’s.145,146

Hepatic disease complicating the classical manifestation of polyarteritis nodosa syndromes is uncommon but has more than exceptionally been described in the literature. From a recently published series involving pathologic study of 160 cases of collagen diseases affecting the liver, hepatic arteritis presenting the feature of the polyarteritis nodosa type of necrotising arteritis was found in 27 autopsy patients.147 Liver involvement can range from hepatomegaly with or without jaundice to signs of extensive hepatic necrosis. Isolated incidences of multiple spontaneous visceral hepatic hematomas,148 hepatic aneurysms,149,150 development of post-infantile giant cell hepatitis-autoimmune hepatitis overlap syndrome,151 intrahepatic-perihepatic haemorrhage accompanying acute appendicitis,152 acute liver failure153 and atrophy of the left hepatic lobe154 are revealed through the literature indicating a more than coincidental clinical association with the presence of necrotising vasculitis. The mechanism of hepatic infarction in polyarteritis nodosa is diffuse compromise of main and collateral arterial blood supply and subsequent vessel obliteration due to vasculitis. Infarction of the liver is uncommon due to the liver’s dual blood supply and generous collateral circulation. In arteriography, aneurismal dilatation and narrowing of the intrahepatic arteries can be seen.

Symptomatic hepatobiliary involvement is uncommonly described in patients with polyarteritis nodosa.155,156

Similar syndromes presenting with clinical verifications including allergic angiitis and granulomatosis like Chung Strauss syndrome have been associated with liver infarction157 or primary biliary cirrhosis158. Finally microscopic polyangiitis has been scarcely associated with primary biliary cirrhosis159 and liver dysfunction preceding rapidly progressive necrotizing glomerulonephritis.160

9.2 Hypersensitivity vasculitis

Hypersensitivity vasculitis is a term applied to a het-
erogenous group of disorders that are thought to represent a hypersensitivity reaction to an antigenic stimulus such as a drug or an infectious agent. In the majority of the reported cases, patients manifest involvement of the post-capillary venules whilst a smaller subgroup of patients is reported in which arterioles are predominately involved. Henoch-Schonlein purpura is a quite typical hypersensitivity vasculitis syndrome and although pathogenetic association has been evidenced in published cases of hepatic disease evoking as a manifestation of Henoch-Schonlein purpura are rare. From such a series hepatobiliary involvement in children with hypersensitivity vasculitis defined as elevated serum liver enzymes, hepatomegaly and abnormal sonographic findings were established in 20 out of the 225 tested patients.

9.3 Granulomatous vasculitis

Granulomatous vasculitis are systemic diseases involving large muscular arteries with mononuclear cell and often giant cell infiltration within the walls of the involved arteries. Wegener’s granulomatosis, giant cell arteritis, Takayasu arteritis, lymphomatoid granulomatosis and cranial arteritis are clinical verifications of that same pathological procedure.

Several studies demonstrate a possible association between giant cell arteritis and granulomatous liver disease. From a series regarding giant-cell arteritis (temporal arteritis) liver changes were demonstrated in six elderly patients. Three of these patients had been diagnosed with polymyalgia rheumatica. Histologically, fatty infiltration was revealed in four and pericentral congestion in five patients, star-cell nodules in one and fatty infiltration was revealed in four and pericentral congestion in five patients. Bromsulphalein test was abnormal in all, but rapidly became normal after giant cell arteritis was successfully treated with corticoids. The pathogenesis of the liver changes is unclear yet it is suggested that they are typical of giant-cell arteritis. Gross cholestatic dysfunction and primary biliary cirrhosis both evoke as other possible features of the giant arteritis.

Hepatic dysfunction may emerge as a rare manifestation of polymyalgia rheumatica. A case report of a patient with polymyalgia rheumatica and significantly elevated alkaline phosphatase levels that demonstrated granuloma formation and massive infiltration of the portal spaces with lymphocytes in liver histology, is documented in the literature. The alkaline phosphatase elevation was favourably influenced by low dose steroid therapy. Polymyalgia rheumatica has once been described in association with giant cavernous hepatic hemangioma. Resection of the latter lesion resulted in complete definite resolution of rheumatologic complaints. Furthermore an overlap between PBC and polymyalgia rheumatica syndrome has been reported. There is no sufficient evidence supporting participation of hepatitis B virus infection in the pathogenesis of polymyalgia rheumatica, neither is a statistically significant difference in the prevalence of hepatitis serological markers established in patients with polymyalgia rheumatica. Granulomas typically improve after corticosteroid therapy.

As far as Takayasu’s arteritis is regarded sufficient clinical evidence of the disease’s association with primary biliary cirrhosis and autoimmune hepatitis and liver cirrhosis on the ground of chronic HBV virus infection is documented in published cases from the literature. Finally there is a case report of a patient with systemic granulomatous necrotizing vasculitis presenting pathological liver histology.

9.4 Kawasaki syndrome

Liver involvement mainly including hepatobiliary dysfunction and gallbladder hydrops emerges as a rarely documented manifestation of Kawasaki syndrome. According to several series from the literature Kawasaki syndrome should be added to the etiological list of painful febrile icterus in young patients especially when persistent fever and jaundice coexist. Obstructive jaundice, abdominal pain, hepatomegaly and abnormal liver function tests are sufficiently indicative of hepatic involvement and they precede typical Kawasaki symptoms. Therapeutic measures include supplementation of intravenous immunoglobulins and aspirin, although one case of Kawasaki disease complicating the liver has been attributed to aspirin therapy.

10. Conclusions

There is an association between autoimmune rheumatic diseases and the liver. Asymptomatic hepatomegaly and elevation of liver function tests is commonly observed. Liver involvement in autoimmune rheumatic diseases is a matter of great clinical challenge evoking several questions upon diagnostic criteria for liver diseases and the presence of overlap syndromes. PBC is the most prevalent. Vasculitis of the liver may result in hepatic rupture. Nodular regenerative hyperplasia may cause morbidity from portal hypertension. However, serious liver disease is infrequent and histologic abnormalities are mild and non-specific caused by systemic inflammation. Steatosis is the most common finding. Only in ex-
tremely rare cases do liver disorders influence the course of the underlying rheumatic disease yet a physician should remain vigilant to the liver pathology searching for those serological markers used to predict autoimmune liver diseases. Clinicians following up patients with autoimmune rheumatic diseases should further investigate them for autoimmune liver injury when elevated values of serum liver function tests are present.

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