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CASE REPORT

Late-onset systemic lupus erythematosus-associated liver disease

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Abstract Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease, which predominantly affects women under 50 years old. Although liver disease is not included in the diagnostic criteria, abnormal liver tests are common among patients with SLE and, in a significant proportion of those patients, no other underlying condition can be identified. We described a case of liver involvement in late-onset SLE presenting with a predominantly cholestatic pattern. Other conditions associated with abnormal liver tests were excluded, and the patient showed a prompt response to steroid therapy. The spectrum of the liver involvement in SLE is discussed, with emphasis on the differential diagnosis with autoimmune hepatitis.

Keywords Systemic lupus erythematosus · Autoimmune hepatitis · Steatosis · Cholestasis

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that predominantly affects women under 50 years of age and involves multiple organ systems, mainly the kidneys, cardiovascular system, skin, and central nervous system [1]. Although liver involvement is not included in the classical diagnostic criteria, patients with SLE have a 25–50% lifetime chance of developing abnormal liver tests [2, 3]. Possible causes of liver injury include drug-induced hepatitis, viral hepatitis, Budd-Chiari syndrome, veno-occlusive disease, nodular regenerative hyperplasia, and primary biliary cirrhosis. Interestingly, autoimmune hepatitis (AIH) does not appear to occur with increased frequency in these patients [4], and in about one-third of SLE patients with abnormal liver tests, no underlying cause is apparent [3], characterizing the so-called *SLE-associated liver disease*. We report a case of late-onset SLE-associated liver disease, and we provide a review of related literature, emphasizing the differential diagnosis with autoimmune hepatitis (AIH).

Case report

A 62-year-old woman was admitted with a 3-month history of fever, weight loss, and diffuse ecchymosis. She had no history of hypertension, diabetes, dyslipidemia, alcohol consumption, or other comorbidities. Her BMI was 23.9 kg/m^2. On examination, she was slightly somnolent but oriented in time and space. Some ecchymosis in trunk and mild pallor were noted. The liver was palpable 4 cm below the right costal margin, but the spleen was not enlarged.

Laboratory evaluation on admission revealed a hematocrit of 22%, platelets 46,000/mm^3, total leukocytes 7,600/mm^3, total protein 6.6 g/dl, albumin 1.9 g/dl, gamma-globulin 3.6 g/dl, total bilirubin 1.2 mg/dl (direct fraction 0,8 mg/dl), aspartate aminotransferase (AST) 187 IU/l,

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alanine aminotransferase (ALT) 87 IU/l (normal, up to 41 IU/l), alkaline phosphatase (ALP) 1,198 IU/l, gamma-glutamyl transpeptidase (GGT) 605 IU/l, and prothrombin activity 74% (INR 1.2). Other routine laboratory tests such as fasting blood glucose, cholesterol (LDL and HDL), and triglycerides levels were in the normal range. HIV and hepatitis B and C serologies were negative, and antinuclear antibody (ANA) was positive in a titer of 1/640 with a homogenous pattern. An abdominal ultrasound and head CT were unremarkable.

These findings suggested the diagnosis of AIH (probable AIH, according to the International Autoimmune Hepatitis Group's criteria, i.e., 12-point pre-treatment), although a diagnosis of primary biliary cirrhosis (PBC) was also considered. However, additional tests revealed positive DNA and SM antibodies, negative anti-smooth muscle antibodies (ASMA), and negative antimitochondrial antibodies (AMA). A 24-h urine test showed a total protein level of 1.74 g/24 h, and the kidney biopsy was suggestive of Class II SLE nephritis. Liver biopsy (Fig. 1) showed severe macrovesicular steatosis, zone 3 ballooning, and mixed inflammatory infiltrate, as well as mild fibrosis in perivenular and perisinusoidal regions.

Based on the American College of Rheumatology's criteria, the diagnosis of SLE was made and oral prednisone was started at 1 mg/kg/day. A complete normalization of aminotransferases levels (Fig. 2) and ALP (Fig. 3) was achieved within 45 days of treatment.

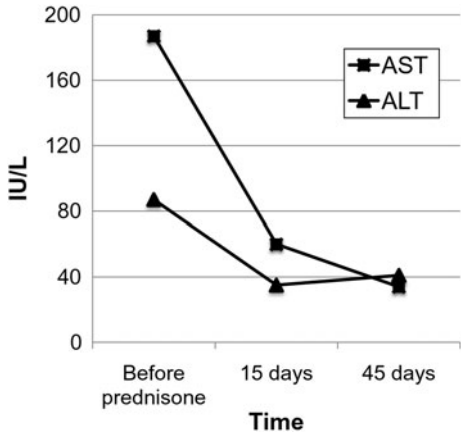

Fig. 2 Serum levels of transaminases, before and after steroid therapy (*AST* aspartate aminotransferase, *ALT* alanine aminotransferase)

Discussion

The spectrum of liver dysfunction in patients with SLE is not completely elucidated. In a retrospective study, 43 out of 238 patients with SLE showed signs of liver disease, defined by abnormal histological findings and/or twofold or greater increase in at least four determinations of AST, ALT, AP, GGT, and LDH [2]. Liver disease was noted as early as 4 years before the diagnosis of SLE, but 45% of the patients had both diagnostics at the same year. Liver

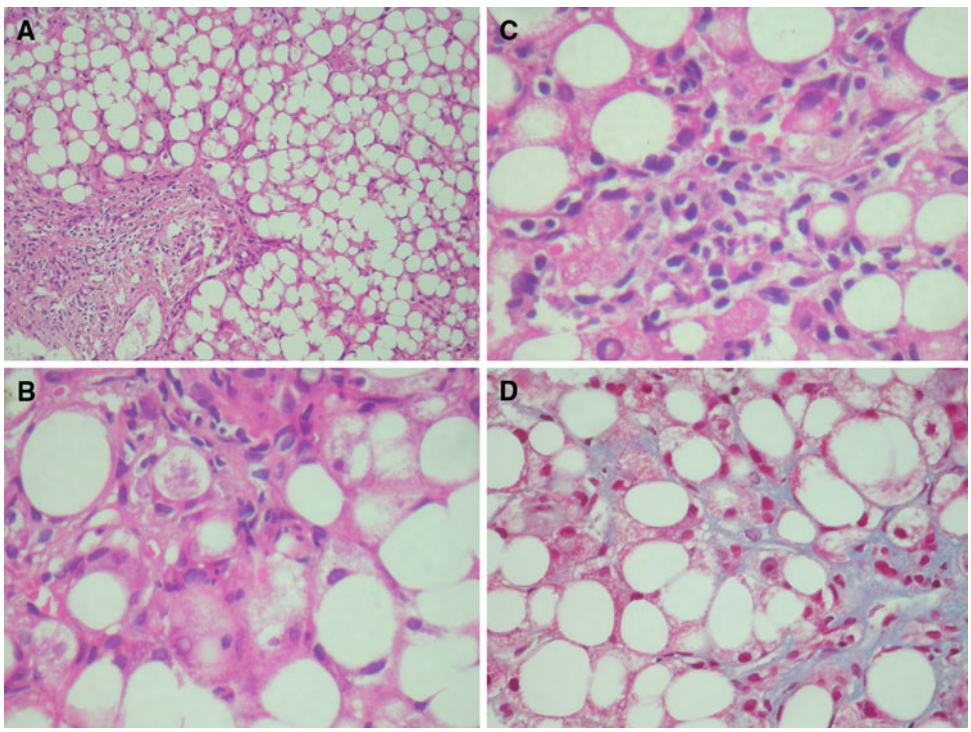

Fig. 1 Liver biopsy showing severe macrovesicular steatosis (**a**), zone 3 hepatocellular ballooning (**b**) with mixed inflammatory infiltrate (**c**), and mild zone 3 perisinusoidal fibrosis (**d**)

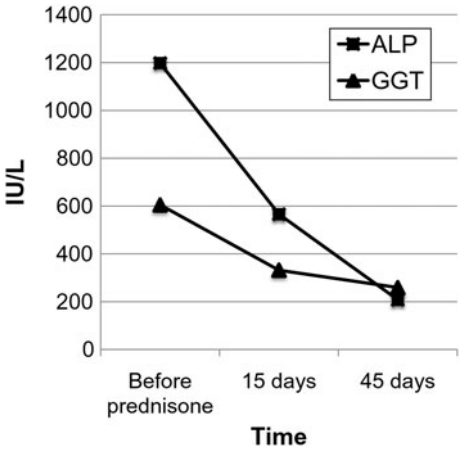

Fig. 3 Serum levels of alkaline phosphatase (*ALP*) and gamma-glutamyl transpeptidase (*GGT*), before and after steroid therapy

biopsy was available in 33 patients, and steatosis was the most common finding (36%). Other abnormalities included chronic active hepatitis, granulomatous hepatitis, cholestasis, and centrilobular necrosis. In contrast, in a 12-month prospective study, published in 1984, 23% of 260 patients with SLE presented with liver tests abnormalities but only 8% of these cases had no identifiable etiology. Liver biopsy, performed in 14 patients, revealed minimal, unspecific lesions in all cases [3]. In both studies, episodes of elevated liver enzymes, especially aminotransferases, were associated with episodes of activity of SLE. Liver disease was also reported to be more common in the late-onset SLE than in the early-onset SLE in two retrospective studies [5, 6].

The differentiation between SLE hepatitis from AIH with extrahepatic manifestations is frequently difficult. Since these disorders share a common pathophysiological background, clinical and biological autoimmune phenomena such as polyarthralgia, hypergammaglobulinemia, antinuclear antibodies, and anti-smooth muscle antibodies can be found in both entities [7]. Nevertheless, this distinction is of major importance because complications and therapy of these conditions are rather different [8–10].

Clinical, laboratory features, and histological analysis of liver tissue can be used for differential diagnosis between AIH and SLE hepatitis. Presence of pleuritis, pericarditis, leukopenia, rash, psychosis, and/or proteinuria are more compatible with SLE [11]. Anti-dsDNA antibodies, as detected by ELISA, are frequently positive in both AIH and SLE. However, the immunofluorescence assay using *Crithidia lucillae* substrate showed to be negative in 98% of patients with AIH and positive in 80–90% of patients with active SLE [4, 12–14]. More recently, in a comparative study, anti-ribosomal P antibody was described to be positive in 68.8% of the patients with SLE-associated hepatitis and none of those with AIH, suggesting that this marker may be useful in differentiating the two conditions, especially in patients without renal dysfunction and central nervous system lupus [15].

Finally, although not fully specific, histological findings can be useful in differentiating AIH from SLE hepatitis. Therefore, liver biopsy should be considered when differential diagnosis is insufficiently certain through clinical and laboratorial grounds. For instance, the presence of cirrhosis or periportal (chronic active) hepatitis suggests AIH, while the presence of only lobular hepatitis is more compatible with SLE. In both conditions, the inflammatory hepatic infiltrate consists mainly of lymphocytes, while in untreated AIH, these are usually mixed with plasma cells [4]. For those patients showing periportal hepatitis and fulfilling both AIH and SLE criteria, the autoantibodies mentioned previously may be helpful in the distinction. Recently, Tojo et al. reported five cases of AIH accompanied by SLE (AIH–SLE overlap). Three of these patients showed chronic hepatitis with severe activity, one had acute and severe hepatitis with submassive necrosis in both portal and lobular areas, and the last one exhibited liver cirrhosis. All patients had no serious extra-hepatic manifestations and showed a rapid response to corticosteroid, achieving complete recovery from both SLE symptoms and liver dysfunction [16].

In the present case, biochemical findings suggested a predominantly cholestatic pattern. A thorough investigation could not identify any alternative explanation for the liver abnormalities found, and a presumptive diagnosis of SLE hepatitis was made. There was no history of exposure to drugs with recognized association with cholestatic toxic liver injury, and other causes of liver disease have been carefully excluded. An overlap with a primary cholestatic liver disease has also been considered as an alternative diagnosis, since the association between SLE and PBC [17–19] or autoimmune cholangiopathy [20] has already been described. However, in the present case, typical features of these disorders such as nonsuppurative destructive cholangitis on liver biopsy and positive AMA were absent. Alternatively, the finding of steatohepatitis in the present report may indicate that nonalcoholic fatty liver disease (NAFLD) may be responsible, at least in part, for the biochemical abnormalities observed. Even though hepatic steatosis has been described as a relatively common histological finding in SLE [2, 21], it is not clear whether this feature represents a direct effect of SLE or a consequence of associated conditions. In addition, the absence of NALFD common risk factors, such as obesity, diabetes, and dyslipidemia, the predominantly cholestatic pattern, and the prompt response to prednisone therapy point to SLE as the probable explanation for the liver abnormalities in this case.

In summary, liver involvement in SLE is frequently unrecognized, and differential diagnosis between SLE hepatitis and AIH, although difficult, must be made in order to avoid potential complications associated with inadequate therapy. Histological analysis of liver tissue is usually helpful, and improvement of liver tests with therapy is typically seen in these cases.

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