Cholestatic hepatitis: a rare hepatic manifestation of systemic lupus erythematosus

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Systemic lupus erythematosus is a multi-system inflammatory disease. The clinical manifestations are diverse. Hepatic manifestation is a rarely seen complication of systemic lupus erythematosus. We report a case of complication of systemic lupus erythematosus presenting as cholestatic hepatitis in a 56-year-old Chinese woman. The cholestatic hepatitis progressed as part of the lupus activity and responded to steroid therapy.

HKMJ 1997;3:331-4

Key words: Hepatitis; Cholestasis; Lupus erythematosus, systemic; Liver

Introduction

Systemic lupus erythematosus (SLE) is a multi-system inflammatory disease associated with the development of auto-antibodies to a variety of self-antigens. The clinical manifestations of SLE are diverse. In 1982, the American Rheumatism Association (ARA) published revised criteria for the classification of SLE.[1] For a diagnosis of SLE, individuals should have four or more of the following features: malar rash, discoid rash, photosensitivity, oral ulcers, non-erosive arthritis, pleuritis or pericarditis, renal disorder, seizures or psychosis, haematological disorder, immunological disorder, or positive anti-nuclear antibodies. Liver disease is not one of the common manifestations of SLE. In classical descriptions of SLE, it is stated that clinically important liver disease is infrequent.[2] We report a case of SLE that first presented as cholestatic hepatitis.

Case report

The patient was a 56-year-old Chinese woman who had an unremarkable past medical history. She presented with a one-day history of fever and had a productive cough with purulent sputum. For the two preceding months, she had lost more than 10 pounds of body weight and had had a poor appetite. She was a non-drinker and had no long term drug history.

A general examination showed her to be jaundiced, pale, and dyspnoeic with an elevated body temperature of 38.2°C. Chest examination demonstrated coarse crackles heard over both lung fields. Other parts of the examination were unremarkable. There was 2+ proteinuria in the mid-stream urine but the culture for organisms was negative. Investigations revealed a normochromic, normocytic anaemia (haemoglobin 9.4 g/dL [normal range, 11.5-15.5 g/dL]) with normal white cell and differential counts. The renal function test showed normal functioning. The liver function test (LFT) was deranged, with bilirubin at 38 μmol/L (normal range, 2-18 μmol/L), alkaline phosphatase, 304 U/L (normal range, 30-120 U/L) and alanine transaminase, 71 U/L (normal range, 0-35 U/L). The chest X-ray showed bilateral lower zone haziness and pleural effusion. The sputum culture grew a *Klebsiella* species. Ultrasonography of the upper abdomen revealed a normal biliary tree.

The patient was treated for bronchopneumonia with a possible sepsis-associated cholestasis. Despite a course of antibiotics, her fever did not subside and her condition deteriorated with accompanying increasing jaundice. Repeated blood tests showed pancytopenia and a further deranged LFT showed a total bilirubin of 147 μmol/L, alkaline phosphatase, 319 U/L, and alanine transaminase, 58 U/L. The anti-nuclear factor titre was markedly elevated (1:1280 [normal range, <1:80]). Autoimmune markers, including anti-nDNA and rheumatoid factor, were all positive but tests for anti-mitochondrial antibody and anti-smooth muscle

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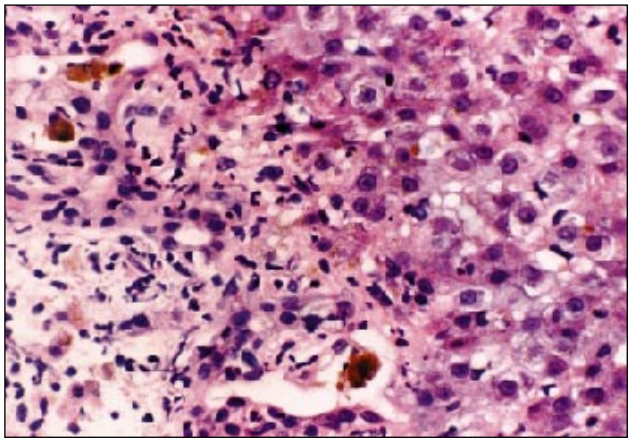

Fig 1. Portal area (left lower corner) and acinar zone 1 of the liver showing bile ductular proliferation, ductular cholestasis, and polymorph exudate in the porto-parenchymal junction. (H&E, x 250)

antibody were negative. Viral hepatitis serological tests including screening for hepatitis A, B, and C, were also negative. Other bacterial investigations were negative and a diagnosis of SLE was made.

A liver biopsy was performed because of her progressive jaundice and deteriorating LFT results. Microscopic examination of the liver tissue showed that the hepatic architecture was preserved. The portal area showed peripheral ductular proliferation with bile plug and polymorph exudate (Fig 1). Swollen liver cells with marked canalicular development and liver cell cholestasis were noted in acinar zone 3 (Fig 2); occasional cholestatic liver cell rosettes were seen. Some acidophilic bodies and focal liver cell necrosis marked by clusters of lymphocytes were also noted. Kupffer cells were prominent with ingested diastase resistant periodic-acid-schiff reaction positive and Perls' stain positive material. No piecemeal necrosis and eosinophils were found. The combination of acinar zone 3 hepatocellular and canalicular cholestasis with peripheral bile ductular cholestasis was consistent with the presence of septicaemia.

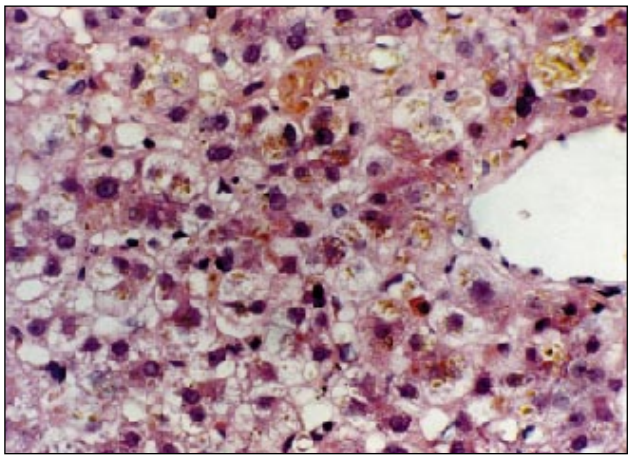

Fig 2. Acinar zone 3 area with central vein on left showing swollen and foamy hepatocytes with marked hepatocellular and canalicular cholestasis. (H&E, x 250)

The patient's condition deteriorated and was complicated by heart failure and renal failure (proteinuria of 2.77 g/24 hours [normal range, <0.15 g/24 hours]). Echocardiography showed dilated cardiomyopathy with pericardial effusion and she subsequently had a generalised convulsion. High dose steroid (oral prednisolone, 1 mg/kg body weight daily) was introduced together with anti-heart failure treatment (diuretic, digitalis, inotropic agent, ACE inhibitor). Serial measurement of her renal and liver function showed that these were improving. At this juncture, a renal biopsy was performed, which revealed features of a resolving diffuse proliferative glomerulonephritis, WHO class IVa. Prednisolone was gradually reduced to a dose of 10 mg daily.

Along with her clinical improvement, her renal and liver function returned to normal with the following values found: urea 6.9 mmol/L (normal range, 3.0-6.5 mmol/L), creatinine 72 μmol/L (normal range, 50-110 μmol/L), total bilirubin 6 μmol/L (normal range, 2-18 μmol/L), alkaline phosphatase 82 U/L (normal range, 30-120 U/L) and alanine transaminase 27 U/L (normal range, 0-35 U/L). The lung congestion and infiltration resolved. Her autoimmune markers also regressed with negative anti-nDNA and anti-nuclear factor (homogenous pattern) decreasing to 1:160 in titre (normal range, <1:80).

Discussion

Systemic lupus erythematosus is an immunologically-mediated disease characterised by flares and remissions, and abnormalities in many systems. Early reports suggested that clinical liver disease was uncommon in SLE.[3]

There is no characteristic histological feature present in the liver of patients with the condition.[4] A variety of histological lesions have been observed on liver biopsy in patients with SLE, including cholestasis with prominent bile plugs, steatosis, acute or chronic hepatitis, granulomatous hepatitis, and cirrhosis. A form of cholestasis described as 'canalicular cast' of bile was reported to be peculiar to SLE patients with liver disease.[5] The canalicular cast of bile represents pseudoglandular or cholestatic liver cell rosettes

and is observed in any long-standing canalicular cholestasis.

Matsumoto et al[6] presented pathological findings for 52 livers from patients with SLE. Hepatic congestion was the most common condition (40), followed by fatty liver (38), arteritis (11), cholestasis (9), peliosis hepatis (6), chronic persistent hepatitis (6), non-specific reactive hepatitis (5), cholangiolitis (4), nodular regenerative hyperplasia of the liver (3), and haemangioma (3). Although congestion and cholestasis may be acute terminal illnesses, fatty change is considered to be specific to the SLE liver. In addition, some of the liver injury found in patients with SLE may be the result of drug treatment.[7] There are reports indicating that exposure to a large dosage of steroids is a significant factor in the aetiology of severe fatty change.[8]

Gibson and Myers[9] studied liver enzyme patterns in 81 patients with SLE. Fifty-five per cent had abnormal values and 29% had no cause for these changes other than SLE. Miller et al[10] assessed 260 SLE patients and found that elevations in serum aspartate transaminase, alanine transaminase, and alkaline phosphatase were common and tend to reflect the level of activity of the patient's SLE more than histological abnormalities do.

Runyon et al[5] reviewed 238 SLE patients with liver disease. In his study, prednisone was most often used to treat other manifestations of SLE, which also improved the liver function tests. Follow-up liver biopsy specimens, however, showed varying responses to therapy. They believe that it is advisable to treat patients with SLE and active liver disease. Decisions to initiate, increase or decrease steroid therapy should take into account the degree of liver disease activity as well as the other manifestations of SLE present.

In this patient, although the initial clinical and biopsy features were compatible with cholestatic hepatitis as a complication of sepsis, the subsequent course and other features proved that the hepatitis was part of the disease activity related to SLE. Firstly, the fever and possible sepsis associated with bronchopneumonia were not responsive to antibiotics and cultures were persistently negative. Secondly, the prolonged duration and marked elevation of the bilirubin level (up to seven times the normal value) were not consistent with liver dysfunction associated with septicaemia. In a prospective study on liver dysfunction in adult patients with septicaemia, up to 65% of patients had at least one elevated liver function test (including aspartate aminotransferase, alanine minotransferase, alkaline phosphatase, and bilirubin) on day 2 after the onset of fever.[11] On day 5, the percentage of patients with such abnormality dropped markedly. The elevated liver enzymes rarely exceeded three times the upper limit of normal. In this patient, the cholestatic hepatitis persisted for approximately two months and elevation of bilirubin was up to seven times the upper limit of the normal value. The cholestatic hepatitis worsened simultaneously, with the progressive multisystem involvement of SLE. Finally, the hepatitis and the other manifestations of SLE responded to corticosteroid therapy. As to the biopsy results, although peripheral ductular proliferation and ductular cholestasis are characteristic of septicaemia, a similar picture occurs in cases of acute, severe, cholestatic hepatitis.[12] Thus, the combined clinicopathological features are consistent with acute cholestatic hepatitis as the presenting feature of the SLE. It progressed as part of the disease activity and responded to immunosuppressive therapy.

In summary, we report a case of an SLE patient with hepatic, renal, cardiac, pulmonary, haematological, and neurological involvement with jaundice as the initial manifestation of the disease. Her liver derangement and other manifestations of the disease responded well to steroid therapy.

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