Case report

Systemic lupus erythematosus and nodular regenerative hyperplasia of the liver

P KLEMP,¹ A H TIMME,² AND G M SAYERS³

From the ¹Rheumatic Disease Unit, Department of Medicine, and the Departments of ²Pathology and ³Haematology, Groote Schuur Hospital, University of Cape Town, Observatory 7925, Republic of South Africa

SUMMARY A patient with systemic lupus erythematosus and nodular regenerative hyperplasia of the liver is presented.

Key words: liver function tests, hepatomegaly.

Nodular regenerative hyperplasia (NRH) of the liver in association with rheumatoid arthritis, Felty's syndrome, polyarteritis nodosa, CREST syndrome (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia), infective endocarditis, congestive cardiac failure, and neoplasia have been documented in several case reports and reviews.^{1–15} There is only one report documenting three cases of systemic lupus erythematosus (SLE) and NRH of the liver.¹⁶ Of 30 cases of NRH reviewed by Stromeyer and Ishak,¹³ three had positive antinuclear antibodies, two of whom also had positive LE cell preparations, but none had any other clinical or serological evidence of SLE.

We report a further patient with SLE and NRH of the liver.

Case report

A 29-year-old South African black female was seen at the Lupus Clinic, Groote Schuur Hospital in September 1982. She had non-erosive polyarthritis, thrombocytopenia, a strongly positive antinuclear factor (ANF) (homogeneous staining pattern), and a double-stranded DNA antibody (dsADA) level of 26 µg DNA bound per ml serum (normal 0–10 µg/ml). In addition she was malnourished, had generalised shotty lymphadenopathy, a 2 cm non-tender hepatomegaly, and she was 32 weeks

pregnant. There was no history of Raynaud's phenomenon, alopecia, malar rash, serositis, epilepsy, psychosis, photosensitivity, or oral ulceration.

The haemoglobin was 8.4 g% (84 g/l) (hypochromic microcytic), white cell count (WCC) $5.6 \times 10^9/l$, ESR > 150 mm/1st hour, total haemolytic complement (CH₅₀) 200 units/ml (normal 160–220), C3 115 mg/dl (normal 115–150), C4 14 mg/dl (normal 20–40), rheumatoid factor was positive (sheep cell agglutination 2000 (normal <32), latex fixation 20 000 (normal <80)), creatinine clearance 70 ml/minute, a few granular casts with no proteinuria. Initial liver function tests were entirely normal and serum albumin was 25 g/l (normal 35–50).

A lymph node biopsy showed reactive hyperplasia and sinus histiocytosis. She was treated with paracetamol, ferrous gluconate, and folic acid and had a normal vaginal delivery at term. Polyarthritis recurred three months later, and she developed epistaxis and bleeding of the gums. The haemoglobin was 6.1 g% (61 g/l), red cell count $2.86 \times 10^{12}/l$, packed cell volume 0.238, mean corpuscular volume 83 fl, WCC $7.16 \times 10^9/l$, platelet count $128 \times 10^9/l$, dsADA 39 µg DNA bound per ml serum, CH₅₀ 114 units/ml, ANF 2500 (homogeneous), and serum albumin 24 g/l. The total protein was 114 g/l, and immunoelectrophoresis showed two paraproteins (IgA and IgG) in broad bands as part of the polyclonal increase in gammaglobulins. She was treated with naproxen and ferrous sulphate, received three units of antigen reduced packed cells, and was discharged well. She defaulted but returned three months later with a recurrence of epistaxis,

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Correspondence to Dr P Klemp, Rheumatology Unit, Department of Internal Medicine, University of Stellenbosch, PO Box 63, Tygerberg 7505, Republic of South Africa.

bleeding gums, polyarthritis, pyrexia, and confusion. Plasma viscosity ranged from 20.00 to 26.3 cP (normal <1.7), and blood cultures were negative. Because of her clinical state and the high plasma viscosity she was given 60 mg prednisone daily and had three plasma exchanges. The plasma viscosity and the immunoglobulins fell to within normal limits and there was marked clinical improvement.

Ten days later she had two grand mal seizures, became confused, and developed a right hemiplegia and fever. The cerebrospinal fluid was hazy, under normal pressure, with protein 0.2 g/l, globulin 1+, glucose 2.8 mmol/l (blood glucose 6.8 mmol/l), adenosine deaminase normal, and chloride 129 mmol/l. There were moderate red blood cells, 17 polymorphs, 15 lymphocytes, and Gram and Indian ink stains were negative. Plasma viscosity was normal. An electroencephalogram showed a large hemispherical abnormality with intermittent delta waves, and computed tomographic (CT) scan performed initially and three days later showed features strongly suggestive of a cerebral abscess in the left frontoparietal area. However, exploratory needling on two occasions failed to show an abscess. Her condition deteriorated rapidly and she died.

Liver function tests performed regularly during the 13-month illness remained normal except for minor increases of alkaline phosphatase and aspartate transaminase on a few occasions, while hepatomegaly and hypoalbuminaemia were present throughout. The hypoalbuminaemia was ascribed to her poor nutritional state and to disease activity.

AUTOPSY FINDINGS

The body was that of a slightly built, young, black female. Both lungs showed congestion and oedema. The heart and pericardium were normal. The spleen was enlarged (365 g) with marked pallor of the cut surface. The kidneys were of normal size but deeply congested. A peptic ulcer, 0.5 cm in diameter, was present in the stomach. The oesophagus was normal.

The liver was enlarged (2028 g). The external surface was studded with scattered, slightly raised, pale nodules (Fig. 1). These ranged in size from 1 mm to 1.0 cm in diameter. There was no cirrhosis. Similar pale nodules were found throughout the cut surface. No abnormality was noted in the portal or hepatic veins.

In the brain (1350 g) there was an abscess, 5.00 cm in diameter, situated in the region of the left internal capsule.

MICROSCOPIC PATHOLOGY

In the liver the normal structure was replaced by nodular areas which varied considerably in size.

Fig. 1 External surface of liver shows pale nodules projecting from surface. Intervening liver is smooth.

Some were less than a lobule in diameter; others were three to four times larger. This alteration was most clearly seen in reticulin-stained sections (Fig. 2). The nodules were frequently centred around portal tracts and were surrounded by compressed reticulin fibres, while central veins were seen in the

Fig. 2 A reticulin-stained section in which a portal tract occupies the centre of the nodule. A central vein is indicated. ($\times 240$).

Fig. 3 Slightly enlarged pale staining hepatocytes in the nodule are seen on the left side; the atrophic cells at the periphery are indicated. (H&E, $\times 60$).

areas between the nodules. The appearance was therefore one of reversed lobulation. The liver cells within the nodules were enlarged, but outside they were atrophic (Fig. 3). In the latter areas moderate sinusoidal dilatation was noted. No lesions were found in the central or portal veins. There was no evidence of scarring or cirrhosis.

Other findings of note included foci of active inflammatory changes in the kidneys, hyperplasia of the endothelial cells in the splenic pulp, atrophy of the zona fasciculata of the adrenals, and hyperplasia of the bone marrow, in which all elements were involved. In the pancreas a single medium-sized artery showed destruction of the media with old mural thrombus. A limited mononuclear infiltrate surrounded the vessel.

Discussion

We have documented the fourth case of SLE and NRH of the liver. NRH may present with portal hypertension and haemorrhage from oesophageal varices, hepatomegaly with mild disturbances of liver function (as in our case), or it may be asymptomatic. Therefore although the association of SLE and NRH appears to be rare, it is likely that NRH is underdiagnosed, especially in mild cases. Needle biopsy of the liver is unreliable, as the lesion may be missed.⁵

NRH is characterised by the presence of numerous

hyperplastic hepatocellular foci throughout a non-cirrhotic liver.^{12 13} The predominant localisation of the dilatation is at the periphery of the hyperplastic areas.^{5 12 13} No consistent relationship of the smaller nodules to the portal tracts could be discerned. Recently, vascular changes, i.e., necrotising angiitis with thrombotic occlusion, have been reported in NRH in cases of polyarteritis nodosa,¹⁵ but this feature was absent in the present case. In common with the three cases previously reported,¹⁶ atrophy of the adrenals was a significant accompanying feature and appeared to be due to corticosteroid therapy may be an aetiological factor in the development of NRH. Recently, attempts have been made to implicate vascular disturbances in the causation of association was that the majority of cases had been treated with corticosteroids, antineoplastic or immunosuppressive agents. Although largely circumstantial, this evidence suggests that drug therapy may be an aetiological factor in the development of NRH. Recently, attempts have been made to implicate vascular disturbances in the causation of NRH,^{8 15 17} but there is no evidence to suggest that they apply to the majority of cases, including the present one.

It is of interest that, as in the three cases of NRH and SLE described by Kuramochi *et al.*,¹⁶ renal disease was not a particularly significant feature. The only evidence of vasculitis in this case was found in the pancreas.

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