ping clofibrate for the second time the EMG and biochemical changes disappeared once more.

This appears to be the first patient reported in which reversible EMG changes are demonstrated after repeated clofibrate administration.

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Asymptomatic autoimmune liver disease in scleroderma

M. M. GUPTA
M.D.

T. W. WARNES
M.R.C.P.

L. WATSON
F.R.A.C.P.

Metabolic Ward, University College Hospital, Gower Street, London

Summary

A case is described of scleroderma with asymptomatic autoimmune liver disease. The patient presented with the features of CRST syndrome (calcinosis, Raynaud's phenomenon, sclerodactyly and telangiectasia) and a raised plasma alkaline phosphatase was found on routine investigation. It is suggested that this latter biochemical finding is likely to indicate associated autoimmune liver disease in patients with scleroderma.

Introduction

There have been sporadic reports dating back to 1934 of liver disease occurring in patients with scleroderma but the association occurs rarely. Thus D'Angelo *et al.* (1969) found more instances of cirrhosis in fifty-eight control patients than in fifty-eight patients with systemic scleroderma, while Bartholomew *et al.* (1964) found only eight examples of chronic liver disease in 727 cases of scleroderma and concluded that there was no relationship between the two diseases. In 1958, Calvert *et al.* described two cases of scleroderma with portal hypertension who bled from oesophageal varices; in the first case, liver biopsy was not performed and in the

second it showed only patchy fibrotic changes. In 1970, Reynolds *et al.* and Murray-Lyon *et al.* independently described the association of primary biliary cirrhosis with scleroderma. All the eight patients described by these workers had evidence of florid liver disease. In this paper we describe a case of CRST syndrome (calcinosis, Raynaud's phenomenon, sclerodactyly and telangiectasia) who had neither symptoms nor signs of liver disease. Elevation of plasma alkaline phosphatase led to further investigations. On fractionation, the isoenzyme was shown to be of hepatic origin whilst the presence of antimitochondrial, antinuclear and smooth muscle antibodies in the serum suggested an associated autoimmune liver disease, which was confirmed by the histological findings on liver biopsy. We shall discuss this in relation to the recent observations of Fox, Scheuer and Sherlock (1973) that primary biliary cirrhosis may now be diagnosed when asymptomatic.

Case report

In 1960, a 41-year-old woman developed sclerodermatous changes in the fingers of the left hand with localized areas of subcutaneous calcification. Similar changes then appeared in the right hand and during the next 4 years calcinosis also developed over the left wrist. She developed Raynaud's phenomenon in

Correspondence: Dr T. W. Warnes, Metabolic Ward, University College Hospital, Gower Street, London WC1 6AU.

1968. She had never noted dysphagia, jaundice or pruritus. Clinical examination in February 1973 revealed bilateral sclerodactyly with calcinosis, typical Raynaud's phenomenon and two small telangiectases on her forehead. She was anicteric and there was no hepatosplenomegaly or any other sign of liver disease. There were no other abnormalities on physical examination. Her blood pressure was 130/70 mmHg.

Investigations. Radiological examination of both hands showed calcinosis circumscripta together with some tapering of the tips of the fingers and some calcinosis in the left wrist joint. Barium swallow showed a slightly dilated oesophagus which did not empty completely when the patient was supine; the motility was also diminished. Barium follow-up showed that the calibre of the proximal small bowel was at the upper limit of normal. Tests of pulmonary function were normal. The ECG showed a Q wave in leads III and aVF consistent with an old inferior myocardial infarct. Plasma urea and creatinine were normal as was the creatinine clearance. Haematology was normal. Tests of liver function showed a plasma bilirubin of 0.9 mg/100 ml; plasma alkaline phosphatase 63 KA units/100 ml; plasma glutamic oxaloacetic transaminase 23 iu/l (normal up to 14 iu/l), plasma glutamic pyruvic transaminase 23 iu/l (normal up to 10 iu/l), albumin 3.9 g/100 ml and globulin 3.8 g/100 ml. Electrophoresis showed moderate elevation of the gamma-globulin. The prothrombin index was normal. Plasma BSP test showed 23% retention at 45 min (normal less than 5%). Separation of the isoenzymes of alkaline phosphatase by electrophoresis on polyacrylamide gel slabs (Anson and

Rowe, 1970) showed that the elevated alkaline phosphatase was of hepatic origin (Fig. 1). Serum IgG was 1880 mg/100 ml, IgM 720 mg/100 ml and IgA 330 mg/100 ml. The serum cholesterol, triglycerides and lipoprotein pattern were all normal. The immunofluorescent technique for antinuclear factor was positive. Antinuclear antibodies were present in a titre exceeding 1/160, smooth muscle antibodies were present at a dilution of 1 in 10 by immunofluorescence and antimitochondrial antibodies were present by immunofluorescence but gave a negative complement fixation titre. Rose Waaler test and rheumatoid slide latex tests were negative.

A needle biopsy (Figs 2 and 3) showed slight cholestasis and inflammatory cell infiltration about the portal system with bile ductule proliferation and reticulin increase which extended into lobules, disrupting the lobular pattern with isolation of groups of liver cells and possibly nodular regeneration. No definite liver cell necrosis was seen. No granulomata were observed. The histological appearances were those of autoimmune liver disease and were thought to be rather more compatible with active chronic hepatitis progressing to cirrhosis than with primary biliary cirrhosis.

Because of the subcutaneous calcification she was started on long-term treatment with probenecid up to 2 g daily as described by Dent and Stamp (1972). She was not given any treatment for the liver disease.

Discussion

The CRST syndrome (Winterbauer, 1964) is a well recognized variant of scleroderma, which frequently runs a benign course. Although liver disease

FIG. 1. Plasma alkaline phosphatase isoenzyme patterns on polyacrylamide gel slab electrophoresis. A, Patient with Paget's disease showing bone isoenzyme; B, present patient showing liver isoenzyme; C, normal control showing both bone and liver isoenzymes. O marks the origin.

FIG. 2. Liver biopsy showing expansion of portal tracts by a chronic inflammatory infiltrate with some fibrosis and bile ductule proliferation (HE $\times 100$).

FIG. 3. Reticulin stain of the same liver biopsy showing destruction of normal architecture ($\times 100$).

is thought to be rare in scleroderma, its association with primary biliary cirrhosis has been recently described. The two patients described by Murray-Lyon *et al.* (1970) presented with hepatosplenomegaly and one had features of CRST syndrome. All the six cases in the series of Reynolds *et al.* (1971) presented

with pruritus and jaundice; three had hepatomegaly and splenomegaly. In both reports an elevated alkaline phosphatase and positive serum antimitochondrial antibody tests were constant features.

In the original description of primary biliary cirrhosis (Addison and Gull, 1851) the classical features

were pruritus, jaundice, xanthomas, xanthelasmas, hepatosplenomegaly and skin pigmentation. Sherlock (1959) reported that 20% of the patients may not be jaundiced at the time of first diagnosis. Doniach and Walker (1969) have proposed a unified concept of autoimmune liver disease in which primary biliary cirrhosis, chronic active hepatitis and cryptogenic cirrhosis form a spectrum of one disease and may be aetiologically related.

Walker, Doniach and Doniach (1970) on screening a large number of hospital patients for antimitochondrial antibodies, detected thirty-five patients with subclinical liver disease and found minor histological changes in eight who were biopsied. Recently four asymptomatic patients with primary biliary cirrhosis have been reported (Fox *et al.*, 1973). All these patients had elevated alkaline phosphatase levels and antimitochondrial antibodies in the serum together with compatible histological findings on liver biopsy. This latter report highlights the problem of defining the prognosis in primary biliary cirrhosis since the diagnosis can now be made during the asymptomatic or subclinical phase.

The histological findings on liver biopsy may not be diagnostic (Scheuer, 1967) for it is often difficult to distinguish chronic active hepatitis from primary biliary cirrhosis in the early stages. Similarly, the end stages of the condition may be indistinguishable from the end stage of cirrhosis due to other causes (Mackay and Wood, 1962). In the present patient, the same difficulty arose because the specimen on liver biopsy did not contain any medium sized bile ducts or granulomata. However, the presence of ANF, smooth muscle antibodies and antimitochondrial antibodies points to the existence of an autoimmune process in the liver.

Whilst treatment of chronic active hepatitis has been shown to improve the prognosis (British Medical Journal, 1973) there is no evidence for the efficacy of immuno-suppressive therapy in established primary biliary cirrhosis. Similarly, there is no evidence about the value of treatment in asymptomatic autoimmune liver disease and, therefore, we did not consider that therapy with steroids or azathioprine was indicated in this patient.

The true incidence of autoimmune liver disease in scleroderma is unknown and the present report clearly underlines that it may be quite asymptomatic. We suggest that routine measurement of the serum alkaline phosphatase in all patients with scleroderma is indicated as a simple screening procedure which

would enable the true incidence of autoimmune liver disease in scleroderma to be established.

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