Scleroderma and Primary Biliary Cirrhosis

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British Medical Journal, 1970, 3, 258-259

Summary: Two cases of scleroderma and primary biliary cirrhosis are described. One had systemic sclerosis with primary biliary cirrhosis of six years' duration at the stage of ductular proliferation. The other had the C.R.S.T. syndrome (calcinosis, Raynaud's phenomenon, sclerodactyly, and telangiectases) with primary biliary cirrhosis at the florid stage. Several similar cases were found in a review of other reports, and it is suggested that the association may be due to a common "autoimmune" process.

Introduction

Though there are reports, dating from 1934, of liver disease occurring in patients with scleroderma few are given in sufficient detail to allow a valid assessment of the type of involvement. Two of the cases described by Bartholomew *et al.* (1964), however, had features suggestive of primary biliary cirrhosis and Reynolds *et al.* (1970) drew attention to this association. In this paper we describe the cases of two patients with scleroderma who have the distinctive immunological and histological picture of primary biliary cirrhosis, and discuss the possible mechanisms involved.

Case 1

In 1963 a 64-year-old woman with mild Raynaud's phenomenon was found to have hepatosplenomegaly. In 1965 she complained of generalized itching, and telangiectases of face and arms were noted. In 1966 bone radiographs revealed an unusual patchy osteoporosis, but a biopsy specimen from the right radius showed normal histology. It was followed by a fracture, and the skin of the right hand and arm later became typically sclerodermatous—the left less so. Macular telangiectases were present on the face, arms, tongue, and lips. They were bluish red and blanched on pressure, but had no central arteriole. No bleeding occurred, and there was no family history of bleeding or telangiectases.

Investigations.—Barium swallow showed dilatation of the oesophagus with absence of peristalsis, and radiographs of the hands showed acrolysis of the terminal phalangeal bones. Liver function tests fluctuated, but changed little overall in three years: plasma bilirubin 1.6-3.5 mg./100 ml., alkaline phosphatase 43-115 K.A. units/100 ml., serum aspartate transaminase 35-113 units/100 ml., serum cholesterol 225-370 mg./100 ml. Serum IgA immunoglobulin (300 mg./100 ml.) was raised and IgM (185) and IgG (1,300) fractions were normal. Immunofluorescent and complement fixing antibodies to mitochondria had been present in low titre since 1966 and smooth muscle antibodies and antinuclear factor had developed in the past year (Dr. Deborah Doniach).

Needle liver biopsy specimens taken in 1966 and 1969 were similar and showed considerable ductular proliferation together with portal fibrosis and early septum formation in the later biopsy (Fig. 1). Portal tracts contained a moderate infiltrate of lymphocytes, neutrophil polymorphs, and plasma cells and there was piecemeal necrosis, pronounced in the second biopsy specimen. The features were those of primary biliary cirrhosis at the stage of ductular proliferation.

FIG. 1.—Case 1. Portal tract with ductular proliferation and piecemeal necrosis. (haematoxylin and eosin. $\times 122$)

Case 2

A 62-year-old woman with Raynaud's phenomenon had noted telangiectases for 10 years. There were sclerodermatous changes in the fingers with small pitted scars and areas of calcinosis. Telangiectases were present on the hands, lips, tongue, and feet, and there was pronounced hepatosplenomegaly. There was no relevant family history and examination of two siblings was negative.

Investigations.—Serum bilirubin 0.7 mg./100 ml., aspartate transaminase 190 units/100 ml. (normal up to 110 units/100 ml.), alkaline phosphatase 44 K.A. units/100 ml., serum cholesterol 236 mg./100 ml. Serum IgG (1,850 mg./100 ml.) and IgM (560 mg./100 ml.) were raised and IgA was normal. Mitochondrial antibodies and the sensitized sheep cell test were positive at a titre of 1/256, and smooth muscle antibodies and antinuclear factor were weakly positive. (Dr. Deborah Doniach). Radiographs of the hands showed acrolysis of the terminal phalanges with soft tissue calcification and the barium swallow diminished peristalsis.

A needle liver biopsy specimen showed retention of normal

FIG. 2.—Case 2. Portal tract showing dense infiltrate of lymphocytes and plasma cells near a damaged bile duct. Surrounding hepatic parenchyma is normal. (H. & E. $\times 170$)

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architecture apart from a minor degree of septal fibrosis and irregularity of the limiting cell plates with piecemeal necrosis. Larger portal tracts contained focal deposits of lymphocytes and plasma cells in association with damaged bile ducts (Fig. 2). There was no ductular proliferation or cholestasis and the histological features were those of primary biliary cirrhosis at the florid duct stage.

Discussion

The first patient has systemic sclerosis with oesophageal involvement. The skin changes became more pronounced in the right arm after the fracture, as they did in the patient of Copeman and Medd (1967) after a fracture of the humerus. The second patient has the characteristic C.R.S.T. syndrome (calcinosis, Raynaud's phenomenon, sclerodactyly, and telangiectases), which is a well-recognized and often benign variant of scleroderma. The telangiectases of scleroderma are microscopically and macroscopically identical with those of the Osler-Weber-Rendu syndrome, though they are said to occur later in life and are less likely to bleed (Winterbauer, 1964). There was, however, no family history in our cases, nor apparently in the cases described by Reynolds *et al.* (1970), to suggest that the Osler-Weber-Rendu syndrome coexisted with scleroderma and primary biliary cirrhosis though these authors put forward this view. Four of the five patients they described with chronic intrahepatic cholestasis and skin telangiectasis had sclerodactyly, and three of these the C.R.S.T. syndrome. All five patients had mitochondrial antibodies in high titre and in four the liver histology was compatible with primary biliary cirrhosis.

The histological appearances in the two present cases are also typical of primary biliary cirrhosis, in Case 1 at the stage of ductular proliferation (stage II) and in Case 2 at the florid duct stage (stage I) (Rubin *et al.*, 1965). Mitochondrial antibodies were present in the serum of both cases and are almost invariable in primary biliary cirrhosis (Doniach *et al.*, 1966). Antinuclear factor and rheumatoid factor are commonly present in the serum in both primary biliary cirrhosis and scleroderma (Bouchier *et al.*, 1964; McGiven *et al.*, 1968). Though the pattern of immunoglobulin disturbance is not constant enough to be of great diagnostic help, a high IgM is often found in primary biliary cirrhosis as in Case 2.

Several reports of liver disease in scleroderma have appeared in the literature. Hepatomegaly (Rivelis, 1963) and hepatosplenomegaly (Milbradt, 1934; Boyd *et al.*, 1954; Massimo, 1954) have been noted, as well as cirrhosis (Piper and Helwig, 1955; Calvert *et al.*, 1958; Pérez and Barbieri, 1959) and "chronic biliary cirrhosis" (Goetz, 1945). Striking calcification of the liver and spleen has been recorded once (Harvier and Bonduelle, 1947). Disturbed liver function with raised levels of plasma bilirubin, alkaline phosphatase, and serum aspartate transaminase were noted in some cases by Barnett and Coventry (1969) and in one case of the C.R.S.T. syndrome (Dellipiani and George, 1967), but no histological details were given. Involvement of the extrahepatic biliary tree with fibrosis of the gall bladder (Copeman and Medd, 1967) and mucosal ulceration causing extrahepatic obstructive jaundice has also been found (Wildenthal *et al.*, 1968). Brief reports on hepatic histology include focal necrosis (Piper and Helwig, 1955), lymphoid cell infiltration (Ormea and Aprà, 1955), capsular thickening (Rivelis, 1963), and concentric fibrosis of the portal tracts with round-cell infiltration (Batsakis and Johnson, 1960; Copeman and Medd, 1967).

More detailed histological and biochemical data are available in a few cases. In the descriptions and photographs of the hepatic histology in five cases reported by Bartholomew *et al.* (1964) infiltration with lymphocytes, disruption of the limiting cell plates, and ductular proliferation were prominent features. In two patients the histological description of the

interlobular bile duct damage and the high serum alkaline phosphatase levels are very suggestive of primary biliary cirrhosis, and this diagnosis also closely fits the description of a case by Grilliat *et al.* (1967). The five cases described by Reynolds *et al.* (1970) have already been mentioned. MacKay and Wood (1962) found that one of their 22 patients with lupoid hepatitis also had scleroderma. It may be difficult, however, to distinguish the early stages of primary biliary cirrhosis from lupoid (or chronic aggressive hepatitis), particularly on a needle biopsy specimen, and the later stage of the condition may be indistinguishable from the end stages of cirrhosis from other causes.

Though these two cases have been seen over a three-year period, liver disease of all varieties would appear to be rare in systemic sclerosis. From the records of 727 cases only seven with cirrhosis were found (Tuffanelli and Winkelmann, 1961). The aetiology of scleroderma is unknown, but because of the presence of antinuclear factor and other antibodies in the serum it is often considered to have an autoimmune basis. It may also occur in association with other "auto-immune diseases" such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome (Tuffanelli and Winkelmann, 1962). Similarly, the histological appearances and serological abnormalities in primary biliary cirrhosis also suggest an autoimmune aetiology. There seems to be little doubt, from the literature reviewed and the present two cases, of a link between scleroderma and primary biliary cirrhosis, and it is hoped that this report will stimulate study of possible common immunological abnormalities.

We are grateful to Professor J. Anderson for details of the early history of the first patient and to Dr. J. R. R. Spurrell for permission to publish the second case.

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