Medical Memoranda

Diffuse Systemic Sclerosis with Abnormal Liver and Gall Bladder

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A case of diffuse systemic sclerosis is described in which the gall bladder was involved in the sclerotic process, an occurrence not previously noted.

Case History

A woman aged 51 was seen at St. Thomas's Hospital by Dr. H. J. Wallace in 1963 with a five-year history of generalized pruritus. One year previously she had suffered an impacted fracture of the neck of the right humerus with separation of the greater tuberosity. This healed satisfactorily, but despite physiotherapy the arm lost much of its usefulness because of the rapid development of tightness of the skin of that arm and hand. She had had Raynaud's phenomenon in both hands and feet. On examination advanced scleroderma of the right forearm and hand and widespread guttate scleroderma, mainly of the upper arms and shoulders, were present, along with a generalized increase of pigmentation. There were many telangiectases of face, lips, buccal mucosa, tongue, and both hands—important physical signs of diffuse systemic sclerosis (Johnston *et al.*, 1965).

She had had infectious hepatitis at age 17, being jaundiced for two weeks. Stasis eczema of the leg had occurred at age 35 after an operation for varicose veins. Later she had developed contact eczema due to hypersensitivity to an antihistamine cream. She did not drink alcohol and had had no drugs known to cause liver damage.

Haemoglobin was 82% and E.S.R. (Westergren) 105 mg. in one hour. No L.E. cells were seen in the peripheral blood. Serum antinuclear factor was negative. Serum protein electrophoresis showed raised alpha-2, beta, and gammaglobulins. Serum creatine was 1 mg./100 ml. The blood urea and creatinine clearance were normal. The formiminoglutamic acid test was slightly positive. Fatty-acid excretion in a five-day stool save averaged 6.7 g./24 hours. E.C.G. and chest *x*-ray picture were normal. A supine barium swallow and meal showed normal oesophageal peristalsis and no oesophageal varices, but a hiatus hernia was present with free gastro-oesophageal reflux.

In October 1964 she was admitted to Kingston Hospital with shortness of breath and anginal pain on exertion. She had had melaena for the previous week and had recently had heartburn associated with regurgitation of bitter fluid. On examination she was very pale, with a raised jugular venous pressure, sacral oedema, and bilateral basal crepitations. The liver was enlarged and firm.

Her haemoglobin was 33% and M.C.H.C. 24%. The red cells showed extreme hypochromia. The E.S.R. was 149 mm. in one hour. Sternal marrow showed normoblastic hyperplasia and no free iron could be demonstrated. No L.E. cells were seen in the peripheral blood. Serum calcium was 9.8 and phosphate 4.2 mg./100 ml. The serum vitamin B_{12} was 600 $\mu\mu$g./ml. Liver-function tests showed bilirubin conjugated and total 0.75 mg./100 ml., thymol turbidity 6.0 units, serum cholesterol 270 mg./100 ml., alkaline phosphatase 95 units, aspartate transaminase 68 units, alanine transaminase 57 units, and total serum proteins 8 g./100 ml. (albumin 4 g., globulin 4 g.). Electrophoresis showed increased gammaglobulin. Prothrombin index was 100%. Electrophoresis of the alkaline phosphate enzyme suggested an origin from liver rather than bone. The histidine loading test was figlu-positive. Four specimens of stool were positive for occult blood, and two separate three-day collections of stool showed an average fatty-acid excretion of 3 and 4.8 g./day respectively. Barium-meal examination showed no dilatation or delay in the oesophagus, but free oesophageal reflux and a sliding hiatus hernia were present. No oesophageal varices were seen. The stomach, duodenum, and small bowel were normal.

A diagnosis of bleeding from the hiatus hernia was made and oral iron and folic acid were given. Six weeks later the haemoglobin was 75%.

In view of the abnormal liver-function tests a cholecystogram was taken; this showed poor concentration of the contrast medium in spite of a double dose. Good contraction of the gall bladder occurred after a fatty meal. No opaque calculi were seen, but some small non-opaque stones were suspected in the fundus. Aspiration liver biopsy: serial histological sections showed diffuse infiltration of the portal tract by moderate numbers of mixed inflammatory cells; to a small extent this exudate involved the adjacent parenchyma, which was otherwise normal. Because of the possibility of extrahepatic biliary obstruction laparotomy was performed by Mr. W. J. D. Bradfield. The liver was very nodular and the spleen enlarged. The gall bladder was yellowish but contained no calculi. The common bile duct was normal and a cholangiogram via the cystic duct was normal. Cholecystectomy and liver biopsy were performed. The gall bladder was 9 cm. long and its wall was thickened and oedematous. Microscopy showed an intact mucous membrane, but there was a considerable degree of fibrosis of the serosa without obliterative endarteritis, suggesting that the fibrosis was more likely to be part of a diffuse systemic sclerosis than to be due to chronic cholecystitis. The liver biopsy revealed the histological appearances of an early but uniform fibrosis, most pronounced in the portal tracts but also spreading out into the parenchymal tissue (Figs. 1 and 2).

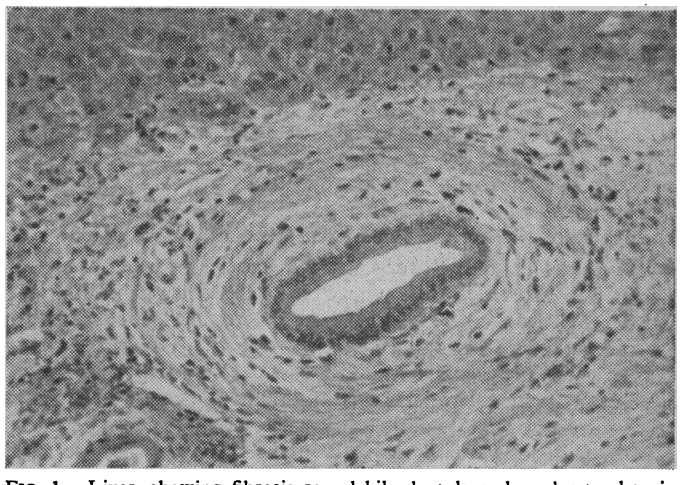

FIG. 1.—Liver, showing fibrosis round bile ductule and moderate chronic inflammatory changes. (H. and E. ×80.)

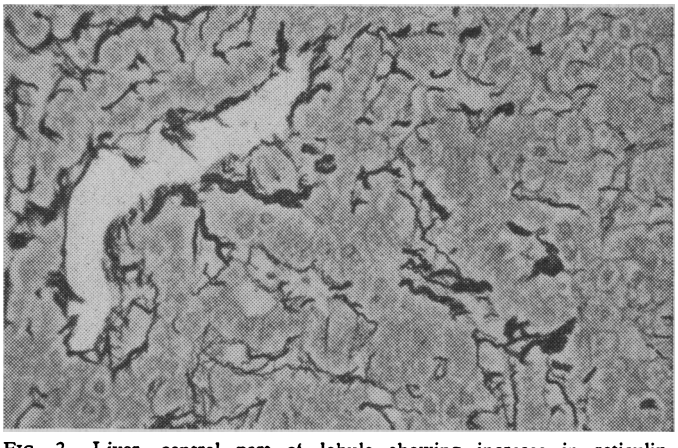

FIG. 2.—Liver, central part of lobule showing increase in reticulin. (Silver impregnation. ×90.)

The patient made a good recovery from the laparotomy. However, during the next year her spleen became intermittently palpable and she was slightly jaundiced. Liver-function tests on 8 October 1965 resulted as follows: bilirubin conjugated 1.3 mg./100 ml., total 1.5 mg., thymol turbidity 4.0 units, serum cholesterol 335 mg./100 ml., alkaline phosphatase 110 units, aspartate transaminase 88 units, alanine transaminase 96 units, total serum proteins 7.3 g./100 ml. (albumin 3.8 g., globulin 3.5 g.). Electrophoresis showed increased gammaglobulin.

Discussion

The two unusual features in this patient were the rapid progression of the scleroderma of the arm after fracture of the humerus and the involvement of the liver and gall bladder. The only other reference we have found to trauma apparently influencing scleroderma is made by Zarafonetis (1964). In that case scleroderma of the left arm developed after a cut on the hand.

In view of the histological appearances there is little doubt that the abnormal gall bladder in the present case was due to involvement by the sclerotic process. Such involvement has not to our knowledge been previously described, though acute arteritis and periarteritis in the gall bladder were mentioned in one case by Leinwand *et al.* (1954). The liver involvement in the present case seems also to be related to the scleroderma, but it is impossible totally to exclude its being a sequel of the previous hepatitis. The histological features, however, are atypical for this, and the involvement of the gall bladder further diminishes this possibility.

Some previous accounts of liver abnormalities in scleroderma were summarized by Tuffanelli and Winkelmann (1961) and by Bartholomew *et al.* (1964), and in the latter series of 727 cases of scleroderma a "severe non-specific cirrhosis of unknown aetiology" was present in four. Other references include three examples of "focal necrosis" and one of portal cirrhosis (Piper and Helwig, 1955) and one of chronic biliary cirrhosis (Goetz, 1945), but histological details are insufficient to compare these with the present case. The histological changes in the case described by Batsakis and Johnson (1960), however, are very similar to those in the case we describe. But in two cases reported by Beigelman *et al.* (1953) the changes affected the centre of the hepatic lobule and were dissimilar.

Calvert *et al.* (1958) reported two cases of systemic scleroderma and hepatic fibrosis which bled from oesophageal varices. Treacy (1960) recorded hepatic failure as the cause of death in one patient. Though involvement of the hollow viscera in some degree is probable in most cases (Haubrich, 1965), liver involvement in scleroderma is undoubtedly rare. No cases were seen among 150 patients investigated by Leinwand *et al.* (1954), and none was discovered in the review of the literature by Goldgraber and Kirsner (1957). In addition, it is not mentioned in standard textbooks on liver disease (Kleckner, 1960 ; Popper and Shaffner, 1961 ; Sherlock, 1963 ; Schwartz, 1964) or in books on connective-tissue disorders (Richardson, 1963) or on skin pathology (Allen, 1954 ; Lever, 1961). It is therefore essential that detailed histology should be reported in all future cases, so that an attempt may be made to establish finally whether such involvement is aetiologically related, and, if so, what is the characteristic macroscopic and microscopical pattern.

Similarly, a catalogue of liver-function tests in future cases might reveal a diagnostic spectrum. The present case showed a striking pattern with a grossly raised serum alkaline phosphatase, a moderate rise in serum transaminases, and very slight rises in the thymol turbidity and bilirubin. It is known that scleroderma alone does not produce abnormal liver-function findings, though the serum gammaglobulin is often increased (Štáva, 1958).

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P. W. Monckton Copeman, M.B., M.R.C.P.,
Senior Registrar, Skin Department, Westminster Hospital, London S.W.1.

W. E. Medd, M.D., M.R.C.P.,
Physician, Kingston Hospital Group, Kingston-upon-Thames, Surrey.

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