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Fibrosing alveolitis and active chronic hepatitis without hyperglobulinaemia

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CASES of fibrosing alveolitis and active chronic hepatitis are rare. The small series reported by Turner-Warwick (1968) all had raised globulins, the range being from 4.0 g/100 ml to 5.8 g/100 ml. We report a case in which the diagnosis was made in life and confirmed at necropsy, in whom the serum globulin level remained persistently normal.

Case report

The patient was a 61-year-old woman who presented in 1965 with a short history of cough and dyspnoea. Her chest X-ray at that time showed fairly widespread diffuse shadowing which was thought at first to be inflammatory, but showed little resolution after courses of treatment with penicillin and tetracycline. Tuberculosis was excluded by repeated sputum cultures. A diagnosis of idiopathic pulmonary fibrosis was made, and she was followed up for a time, but her symptoms did not progress. In 1968 she presented with a single, enlarged supraclavicular lymph node. This was excised and the histological appearance showed caseating granulomata. However, no acid-fast bacilli were seen on the sections. Nevertheless, she received 12-months' treatment with anti-tuberculous therapy. At the end of this time she was referred for review and further investigations of her chest condition, mainly because of the abnormal chest X-ray, though this had changed little over the years. She was fully investigated in July 1969.

Clinical examination revealed clubbing of the fingers, crepitations at the lung bases and a liver

enlarged three fingers. Chest X-ray appearances, spirometry, Pao₂ estimations at rest and after exercise and estimation of transfer factor (Table 1) all pointed clearly to a diagnosis of fibrosing alveolitis, but lung biopsy was not considered justifiable. The finding of hepatic enlargement did not at first suggest lupoid hepatitis; there was no history of jaundice, serum bilirubin was normal, spider naevi were not present and there was no splenomegaly. Liver function tests gave normal results for albumin and globulin, with normal electrophoretic strip and immune globulins, the level for the latter being as follows: IgG, 1300 mg/100 ml; IgA, 170 mg/100 ml; IgM, 100 mg/100 ml. Serum transaminases and alkaline phosphatase were raised (44 KA Units/100 ml) and 5-nucleotidase was grossly raised (148 Units). Tests for the LE phenomenon were positive, anti-nuclear factor was positive, smooth-muscle antibodies were positive at a titre of one in four, but thyroid antibodies, mitochondrial antibodies, tests for rheumatoid factor and Australia antigen were negative. Liver biopsy was carried out, and showed the characteristic appearances of active chronic hepatitis.

Treatment. In August 1969 treatment was started with prednisolone in a dose of 60 mg daily, reducing over the course of the next 4 weeks to 20 mg daily and maintaining this dose thereafter. There was some subjective improvement, though lung function tests did not change, and the ESR, which had previously been moderately raised, fell to normal, alka-

TABLE 1.

	Initial values	After treatment with steroids	After treatment with azathioprine
Vital capacity	1.3 l/min	1.57 l/min	1.55 l/min
FEV ₁	Normal	Normal	Normal
Transfer factor	5.0 ml CO/min/mmHg	Unchanged	Unchanged

line phosphatase fell, 5-nucleotidase fell markedly, and transaminases fell while on the high steroid dose, but rose when this was reduced. In September azathioprine was added, in a dose of 200 mg daily, reducing to 100 mg daily after the first week. Thereafter she deteriorated steadily, subjectively at first, but in October becoming jaundiced. The alkaline phosphatase rose, and 5-nucleotidase rose to very high levels (248 Units). Towards the end of October, she developed abdominal pain and vomiting, the jaundice deepened and she died.

Necropsy. Deep jaundice was present, the liver was reduced in size (950 g) deeply bile-stained, with areas of external nodularity. Microscopic appearances showed persistent inflammatory-cell infiltration of the portal tracts which was much less marked than in the biopsy specimen. There was distortion of the lobular pattern, but regenerating nodules were not seen. The lungs were reddish-grey in colour, rubbery in consistency and showed generalized 'honey-comb' appearances (Fig. 1). Microscopically, there was widespread reticular thickening and destruction of the alveolar walls, with fibrosis, and in places a mononuclear exudate, the appearances being those of fibrosing alveolitis. Acute duodenal ulceration was present and death was due to a perforated gastric ulcer, undoubtedly the result of steroid treatment.

Discussion

The diagnosis in this case was made during life. The absence of jaundice and the asymptomatic

FIG. 1. Macroscopic appearance of lungs.

nature of the hepatic disease was noted, as in Turner-Warwick's cases. Jaundice, together with the presence of spider naevi and splenomegaly, is considered to be frequent in lupoid hepatitis (Sherlock, 1968). In each of Turner-Warwick's cases, there was an abnormality of at least one of the immune globulins. The globulin levels in this patient varied between 2.3 g/100 ml and 3.2 g/100 ml on seven occasions during the period of observation and treatment; immune globulins were normal. Apart from the absence of hyperglobulinaemia, there was good evidence of an auto-immune process, with several positive tests for auto-antibodies, the presence of lymphoid infiltration, multi-system involvement and response to steroids. Comparison of the necropsy histology with the biopsy specimen of liver suggested that some improvement had occurred in this case. It seems unlikely that the lungs improved at all. The use of azathioprine in the treatment of lupoid hepatitis has been reported on a number of occasions (Mackay, Weiden & Ungar, 1964; Rastogi, Deodhar & Brown, 1967; Mackay, 1968) but there was no convincing evidence that the treatment was more effective than prednisolone. Deterioration in this patient coincided with the use of azathioprine. When on the steroids alone, she improved subjectively and in respect of the alkaline phosphatase, transaminases and 5-nucleotidase. Following the exhibition of azathioprine, she developed jaundice, the alkaline phosphatase rose, and 5-nucleotidase rose to a dramatically high level. It is not at all clear why this occurred. Bearing in mind the theory that azathioprine, along with other immunosuppressives, exerts its action by selectively removing the clone of abnormal lymphocytes responsible for the auto-immune process, our experience would tend to support the view that the drug is best avoided in cases in which the globulins are normal.

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