Hepatic fibrosis in a child possibly due to prolonged methotrexate

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SYNOPSIS A case is described in which marked hepatic fibrosis probably resulted from the prolonged treatment of acute leukaemia with methotrexate.

Fibrosis of the liver following therapy with folic acid antagonists has been reported by Colsky, Greenspan, and Warren (1955), by Hitzig and Schärer (1960), and by O'Rourke and Eckert (1964). The first paper recorded hepatic fibrosis in five children and the second in three; all had acute leukaemia. O'Rourke and Eckert's patient was an adult given methotrexate for psoriasis.

CASE REPORT

H.R., presented in October 1961 at the age of 7 years with a history of general ill health for three weeks and of spontaneous bruising on the legs for three days. There was no history of radiation either to the mother during pregnancy or to the child, and in particular there was no history of jaundice.

On examination she was pale and there were extensive ecchymoses and petechiae on the legs. There was a 7 cm. enlargement of the spleen and liver but no lymphadenopathy. The haemoglobin was 5.9 g./100 ml., the platelet count 40,000/c.mm., the white cell count 1,200/c.mm. No abnormal cells could be found in the peripheral blood but the marrow showed a uniform replacement by lymphoblasts. The diagnosis was clearly one of acute lymphoblastic leukaemia.

She was entered in an M.R.C. leukaemia trial and treated initially with 6-mercaptopurine alone at a dose of 75 mg. per day (2.5 mg. kg.). She failed to respond to this during 24 days during which three blood transfusions were required; no reaction followed these. Prednisone, 40 mg. a day, was then added and was followed by prompt clinical and haematological remission. The 6-mercaptopurine was continued for nearly 12 months (a total of 27 g.). On several attempts to reduce the dose of prednisone she showed early evidence of relapse so that the 6-mercaptopurine was eventually stopped and methotrexate substituted at a dosage of 2.5 mg. per day (approximately 0.05 mg./kg.). For a short time aminopterin in an equivalent dosage was substituted. Prednisone was continued at first in low dosage and eventually withdrawn.

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She continued in haematological remission until June 1965 with the exception of two possible early relapses which responded promptly to either re-starting or increasing steroids. Latterly the platelet counts were moderately depressed but the haemoglobin and white cell counts were maintained at normal levels. During treatment with methotrexate she had five cerebral episodes associated with increased intracranial pressure and the appearance of leukaemic cells in the cerebrospinal fluid. On reviewing the history there seems no doubt that all the cerebral episodes were due to cerebral leukaemic deposits. These episodes responded promptly to intrathecal methotrexate, the number of injections varied from one to three given at three to five-day intervals. The total dosage on each occasion varied from 13.5 to 42 mg. and in all 149 mg. was given intrathecally. The total oral dosage was approximately 2.5 g. given over rather less than three years; toxicity was not a problem and there were no gastrointestinal complications. She finally relapsed in June 1965 and 3 mg. of Vincristine was given intravenously. This was without effect and she died 192 weeks after starting treatment. The immediate cause of death was massive intrapulmonary haemorrhage.

NECROPSY FINDINGS

The body showed slight Cushingoid appearances but was chiefly remarkable for the extent and severity of the ecchymoses and petechial haemorrhages. The lungs showed massive pulmonary oedema and haemorrhage and both major bronchi contained blood clot. The alimentary tract contained fresh blood but there were no oesophageal varices. The liver weighed 1,200g; it was yellow and of firm consistency. The surface was smooth but showed numerous discrete nodules 5 to 10 mm. in diameter. The spleen was moderately enlarged and weighed 720g.; it was uniformly dark red and firm in consistency. The lymph nodes, which were brownish red, were enlarged. The bone marrow was dark red.

FIG. 1. The extensive fibrotic lesions, particularly in the portal areas ($\times 66$).

The brain showed a number of petechial haemorrhages.

On histological examination the spleen, lymph nodes, and bone marrow showed an intense infiltration with leukaemic cells. The meninges also showed leukaemic infiltration which was quite marked in places. The normal architecture of the liver was distorted by numerous strands of connective tissue, which was mainly present in the portal areas and by their continuity they produced numerous isolated liver nodules. A few fine strands of collagen penetrated into the liver lobules (Fig. 1). Reticulin and Van Gieson stains confirmed that the strands were composed of fibrous tissue and collagen. There was a slight proliferation of bile ductules in the portal tracts and a slight infiltration by lymphocytes in places. The capillary blood vessels were congested. There was no leukaemic infiltration. The liver lobules showed marked fatty change which was mainly central; the sinusoids were congested but Kupffer cells appeared normal. There was no pigment

except in a few cells in the periphery. Some nodules presented the picture of regeneration.

DISCUSSION

The clinical features of this case were typical of acute lymphoblastic leukaemia. The survival time of three years and eight months was, however, rather greater than the average of treated cases which at the present time is about 16 months. During life there was no clinical evidence of the marked fibrosis of the liver which was found at necropsy. There was no history of infectious hepatitis and there was no indication that the hepatic damage might have resulted from the blood transfusions given early in the course of the disease. No drugs likely to produce hepatic damage were given.

The histological appearance of the liver was very similar to that reported by Colsky *et al.* (1955) and by Hitzig, and Schärer (1960) in their leukaemic patients who had been treated with methotrexate. There is no really satisfactory explanation of the occurrence of this type of hepatic fibrosis. It has been suggested that the lesions might be a sequel to the destruction of leukaemic cells in the liver but in the patient described by O'Rourke and Eckert the treatment was given for psoriasis. Such lesions do not appear to occur in the livers of patients treated with drugs other than methotrexate. A possible exception to this is the reported occurrence of a cholangiolitic type of hepatitis (Ellison, Silver, and Engle, 1959) and acute liver damage (Clark, Hsia, and Huntsman, 1960) during treatment with 6-mercaptopurine. At no time, however, was our patient jaundiced or showed any evidence of hepatic failure and we do not know of any cases in which the type of liver damage seen in our case resulted from treatment with 6-mercaptopurine. It seems most likely that the folic acid antagonists interfere with the metabolism of choline and methionine and so eventually produce fibrosis of the periportal type. It has been suggested that the liver in young children may more readily be damaged by drugs, but the type of liver damage seen in our case has been described in an adult and our patient was older than those described previously.

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