Case report

Cholestatic jaundice caused by D-penicillamine

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SUMMARY D-penicillamine is not generally considered to cause hepatic damage. Cholestatic jaundice developed in a patient with rheumatoid arthritis 4 weeks after penicillamine was added to his treatment regimen, and he died in acute renal failure. The probability that penicillamine caused the cholestasis is discussed.

Cholestatic jaundice is a well-known complication of a growing list of drugs. We report a patient with severe cholestatic jaundice with bilirubin values up to 88 mg/100 ml (1505 μ mol/l), who developed fatal postoperative renal failure. D-penicillamine, which the patient received for rheumatoid arthritis, seems to have been the cause of the cholestasis. We conclude that D-penicillamine should be added to the list of cholestatic drugs.

Case report

A 56-year-old man suffering from seropositive rheumatoid arthritis requiring high doses of salicylates and steroids was started on D-penicillamine 300 mg daily in order to reduce the amount of steroid dosage. Penicillamine was gradually increased to 600 mg/day. Liver function tests at the start of treatment on 26 June 1974 were normal: bilirubin was not raised, SGOT 26 units, SGPT 29 units, alkaline phosphatase 1.7 Bodansky units, cholesterol 264 mg/100 ml (6.8 mmol/l). A routine chest x-ray showed a round lesion in the left lung and the patient was referred to hospital for investigation.

A few days before admission (22 July) he complained of itching, dark urine, and acholic faeces, and jaundice was noted. Laboratory findings showed bilirubin 15 mg/100 ml (257 μ mol/l) (direct 10.1 mg/100 ml; 172.7 μ mol/l), SGOT 95 units, SGPT 203 units, alkaline phosphatase 12 Bodansky units, cholesterol 612 mg/100 ml (15.9 μ mol/l). Treatment with steroids and penicillamine was stopped.

Examination showed a severely jaundiced Cushingoid looking male. Temperature was 37.4°C, pulse rate 92/min, blood pressure 130/80 mmHg. The liver was tender with a total span of 10 cm. The spleen was not palpable. His right wrist and knee showed acute arthritic changes. The rest of the physical examination was negative.

LABORATORY FINDINGS

Hb 10.1 g/dl; leucocytes 2.3×10^9 /l with myelocytes, 2% band forms, 28% segmented polymorphonuclears, 14% eosinophils, 10% monocytes, 42% lymphocytes, thrombocytes 528×10^9 /l, reticulocytes 14.2%; sedimentation rate 131 mm in one hour; urea, glucose, electrolytes, calcium, phosphorus, serum proteins normal. Bilirubin 39.2 mg/100 ml (670.3 μ mol/l), mostly direct; SGOT 100 units, alkaline phosphatase 20.4 Bessey-Lowry units; prothrombin time 55%. Cholesterol 665 mg/100 ml (17.2 mmol/l), fibrinogen 10 g/l, iron 120 μ g/100 ml (21.5 μ mol/l), TIBC 280 μ g/100 ml (21.5 μ mol/l), C-reactive protein negative; Rose-Waaler latex, and rheumatoid arthritis slide test positive; no LE cells found. Coombs's test negative; glucose-6-phosphate dehydrogenase normal; HBsAg positive.

Three days after admission his temperature rose to 39°C. A liver needle biopsy was not attempted as cholangitis could not be excluded. At exploratory laparotomy, no pathology of the pancreas or biliary system was found. The liver was hard and greenish brown. Intraoperative cholangiography showed open bile ducts of normal diameters and normal passage of contrast media into the duodenum. Liver biopsy was performed, after which bilirubin rose to 88.4 mg/100 ml (1512 μ mol/l). Severe acute renal failure developed and despite peritoneal dialysis, the patient died 10 days after laparotomy.

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PATHOLOGICAL FINDINGS

Histological examination of the biopsy specimen of a piece of greenish-brown liver showed a marked degree of fatty infiltration in the hepatocytes, and a moderate amount of bile pigment focally situated in hepatocytes, Kupffer cells, and occasionally in the bile canaliculi (Fig. 1). The bile ducts were normal. There were occasional small foci of hepatocellular necrosis (Fig. 2). Postmortem examination showed a normal biliary system and pancreas. The liver weighed 2000 g, was smooth and greenish yellow. Liver architecture was well preserved. There were numerous mature lymphocytes in the portal spaces. Large amounts of bile pigment were seen in hepatocytes and Kupffer cells and numerous bile plugs in bile canaliculi. A few hepatic cells were moderately enlarged, but there were no signs of individual or massive cell necrosis. The small and large bile ducts were normal. A hard brown nodule was found in the upper lobe of the left lung and proved to be an alveolar cell carcinoma of the lung. The kidneys weighed 350 g and were slightly oedematous and yellowgreen. Histologically, biliary casts were present in the tubules and bile pigment in the tubular epithelium.

Discussion

Our patient fits well into the category of drug-induced cholestatic jaundice. No extrahepatic obstruction was found at operation of post-mortem examination. Cholestatic viral hepatitis can be excluded as there were no signs of inflammation in the surgical and post-mortem liver specimen. The positive HBsAg does not refute this conclusion as

Fig. 2 Small area of liver cell necrosis. *H & E* $\times 150$.

0.89% of Israelis are healthy carriers (Bar-Shani *et al.*, 1972).

The very high bilirubin level is an unusual finding, but has been described in patients with hepatitis with haemolysis and in patients with alcoholic liver disease complicated by renal failure (Fulop *et al.*, 1971). Our patient developed renal failure only after the bilirubin reached 88 mg/100 ml (1505 $\mu\text{mol/l}$), but he had anaemia (Hb 10.1 g/dl) and reticulocytosis (14.2%), which indicate that haemolysis was a contributing factor. The high bilirubin levels in patients with hepatitis and haemolysis have been explained as due to the increased pigment load in patients with impaired excretory capacity due to hepatobiliary disease. This mechanism could explain the high bilirubin in our patient as he did not have hepatocellular damage, but had impaired excretory capacity.

Fig. 1 Bile in canaliculus and Kupffer cells (arrows). *H & E* $\times 250$.

Our patient received prednisone, aspirin, and D-penicillamine. None is known to cause cholestatic jaundice. Prednisone and aspirin are widely used, and thus seem unlikely to be the cause of the cholestasis. Hepatic damage due to aspirin has been reported (Russel *et al.*, 1971; Iancu, 1972; Rich and Johnson, 1973; Seaman *et al.*, 1974; Wolfe *et al.*, 1974; Garber *et al.*, 1975), but the patients reported did not develop jaundice. They had raised transaminases, and some raised alkaline phosphatase. Histological findings were compatible with chronic active hepatitis or acute hepatocellular injury but not with cholestasis. The raised enzyme seems to be dose related as many patients had a blood salicylate level of more than 30 mg/100 ml. The only hepatic damage attributed to steroids is fatty infiltration (Klatskin, 1969), and prednisone is probably the cause of the fatty infiltration of the liver in our patient.

Penicillamine, on the other hand, has only lately been widely used, and this makes it more likely to be the offending drug. Penicillamine is a degradation product of penicillin. Its chemical structure makes it an effective chelator of copper, mercury, zinc, and lead. It has, therefore, been used in Wilson's disease and lead and mercury poisoning, as well as in cystinuria. As these diseases are rare, its use has been limited. Lately, penicillamine has been used in the treatment of rheumatoid arthritis (Multicentre Trial Group, 1973; *British Medical Journal*, 1973) and other collagen diseases. Adverse reactions to the drug have been known for some time and include fever, rashes, leucopenia, eosinophilia, thrombocytopenia, loss of taste, nausea, and proteinuria (Levine, 1970). Recently, side effects such as a lupus-like syndrome (Oliver *et al.*, 1972), a myasthenia-like clinical picture (Bucknall *et al.*, 1975), and Goodpasture's syndrome (Sternlieb *et al.*, 1975) have been reported. Leading articles listing the complications of penicillamine (*British Medical Journal*, 1973, 1975; *Lancet*, 1975) have not mentioned jaundice.

Jaundice associated with penicillamine has been described. Walshe (1968) reported a 9-year-old boy with Wilson's disease in whom penicillamine treatment was discontinued as it caused fever, urticaria, abdominal pain, and jaundice. Rau *et al.* (1972) reported a case of cholestatic jaundice in a patient receiving penicillamine for scleroderma, who developed fever with an itching macular rash after 2 weeks of treatment. Jaundice appeared after a further week. Her bilirubin level was 7.4 mg/100 ml (126.5 μ mol/l), SGOT 76 IU, SGPT 90 IU, and alkaline phosphatase 33.4 Bodansky units; eosinophils 5% on differential blood count. On stopping the drug, liver function tests returned to normal. Skin tests showed hypersensitivity to penicillamine

only. A liver needle biopsy performed before penicillamine was started was normal, but biopsy was not repeated. The sequence of events in this case suggests cholestatic jaundice due to the penicillamine. We believe that these 2 cases and our case make the probability of penicillamine causing cholestatic jaundice reasonable. Cholestatic jaundice, though rare, should therefore be added to the list of adverse reactions to penicillamine.

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