

CHOLESTASIS DUE TO D-PENICILLAMINE TOXICITY

IN ROSS PhD MRCP* AND PK DASS MD**

Summary

A patient with sero-positive rheumatoid arthritis was treated with D-penicillamine (cumulative dose 3.75g). Three weeks after starting therapy she developed a fever, rash and a cholestatic jaundice. Cessation of D-penicillamine resulted in improvement. However, reintroduction of D-penicillamine 10 days later (cumulative dose 2g), was followed by acute hepatic failure and death. Liver biopsy showed widespread centrilobular necrosis and cholestasis. This case represents a hypersensitivity reaction to D-penicillamine.

INTRODUCTION

D-penicillamine (β , β -dimethyl cysteine) is a copper chelating agent and immunosuppressant, used in the treatment of rheumatoid arthritis, Wilson's disease and occasionally primary biliary cirrhosis. Severe side effects are reported in 20 to 50% of patients and the drug is discontinued in about 30% of patients.¹ Common adverse reactions are gastro-intestinal upset, urticaria and rashes, proteinuria and leucopenia. Hepatotoxicity attributed to D-penicillamine therapy is uncommon, but appears to manifest as either an asymptomatic rise in liver transaminases and alkaline phosphatase or as a potentially fatal cholestatic jaundice. We describe a case of fatal hepatic necrosis and cholestasis in a patient treated with D-penicillamine.

CASE REPORT

A forty-year-old Chinese female was admitted for treatment of seropositive rheumatoid arthritis. Her disease first started 4 years previously and she had received several courses of high dose aspirin and non-steroidal anti-inflammatory drugs. She had had no previous jaundice or blood transfusions. Examination showed active arthritis, but no signs of liver disease. Aspirin, 900mg qds, was restarted and in view of her poor response to such therapy in the past, D-penicillamine 250mg daily was prescribed.

After 15 days of therapy she developed an intermittent fever and her white blood cell count fell from $8.9 \times 10^6/l$ to $3.9 \times 10^6/l$. D-penicillamine was discontinued. One day later she complained of pruritus and a rash. Three days later she was jaundiced and had pale stools. A provisional diagnosis of acute viral hepatitis was made. Her SGOT was 135 i.u./l (5-35), SCPT 135 i.u./l (5-35), alkaline phosphatase 181 i.u./l (15-50), bilirubin 118 micromol/l, (< 25), total protein 77g/l (65-79),

albumin 31g/l (35-55) and hepatitis B surface antigen negative. Her jaundice regressed without further treatment.

Ten days after discharge she restarted D-penicillamine and took a further eight 250mg tablets. She promptly developed deep jaundice and was readmitted. Her liver was 2cm enlarged. SGOT was 91 i.u./l, alkaline phosphatase 167 i.u./l and bilirubin 445 micromol/l (conjugated 308, unconjugated 137). Abdominal ultrasound showed no evidence of extra-hepatic obstruction or gallstones. Aspirin was discontinued. Four days after her last dose of D-penicillamine she developed acute hepatic failure and died.

Needle biopsy of the liver showed widespread centrilobular and focal necrosis with cytoplasmic and intracanalicular cholestasis (Fig. 1). The hepatocytes showed fatty change. There was oedema of the portal tracts, which were infiltrated by small numbers of mononuclear cells and occasional polymorphonuclear leukocytes (Fig. 2). However, there were no eosinophils. Ballooning degeneration of the hepatocytes and Councilman bodies were not present in the biopsy.

DISCUSSION

There appear to be two types of liver injury associated with D-penicillamine therapy. In one group of patients there is a hypersensitivity reaction causing a cholestatic jaundice, while in the other group there is an asymptomatic rise in liver transaminases and alkaline phosphatase.¹⁵

Currently 14 cases of cholestasis attributed to D-penicillamine therapy have been reported.²⁻¹⁴ These patients were treated in most cases for rheumatoid arthritis. Signs that may precede the onset of liver disease were fever and a pruritic rash. Jaundice occurred

* Department of Medicine. School of Medical Sciences. Universiti Sains Malaysia, Penang.

** Department of Pathology. School of Medical Sciences. Universiti Sains Malaysia, Penang.

Address for reprint requests: IN Ross, Department of Medicine, Hospital Universiti, Kubang Kerian, Kelantan.

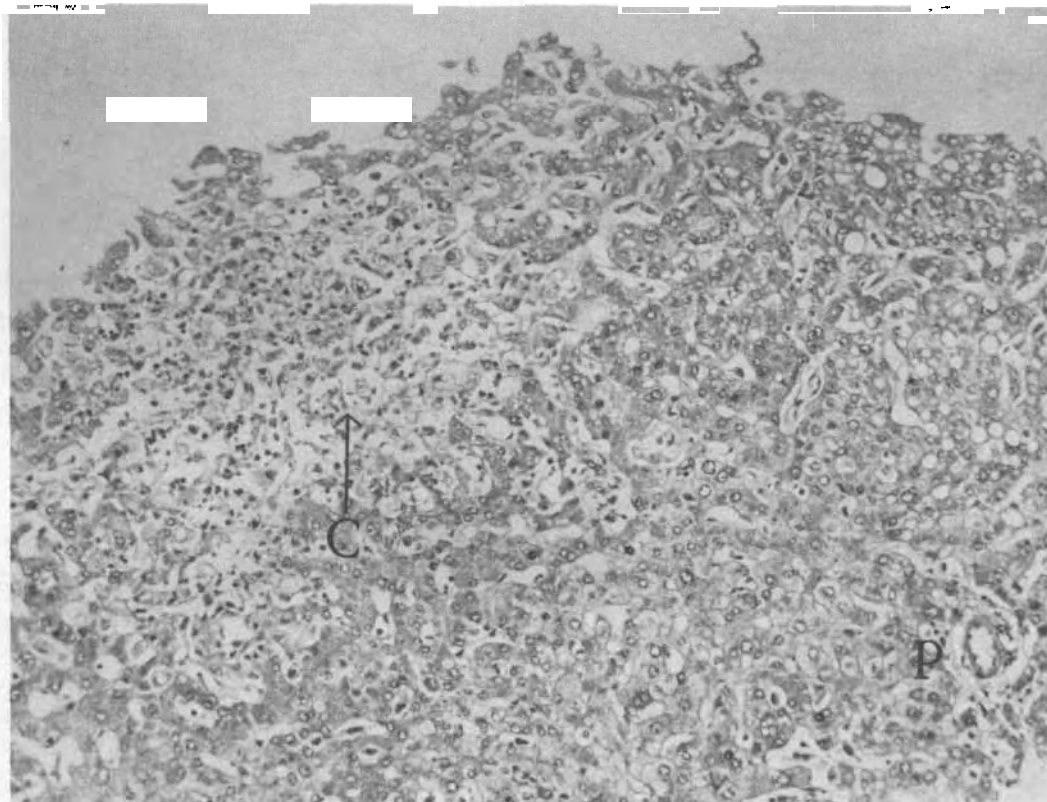


FIG 1 Liver biopsy showing a large area of centrilobular necrosis. The central vein (C) is collapsed and indistinct. P indicates a portal tract. H & E X 600.

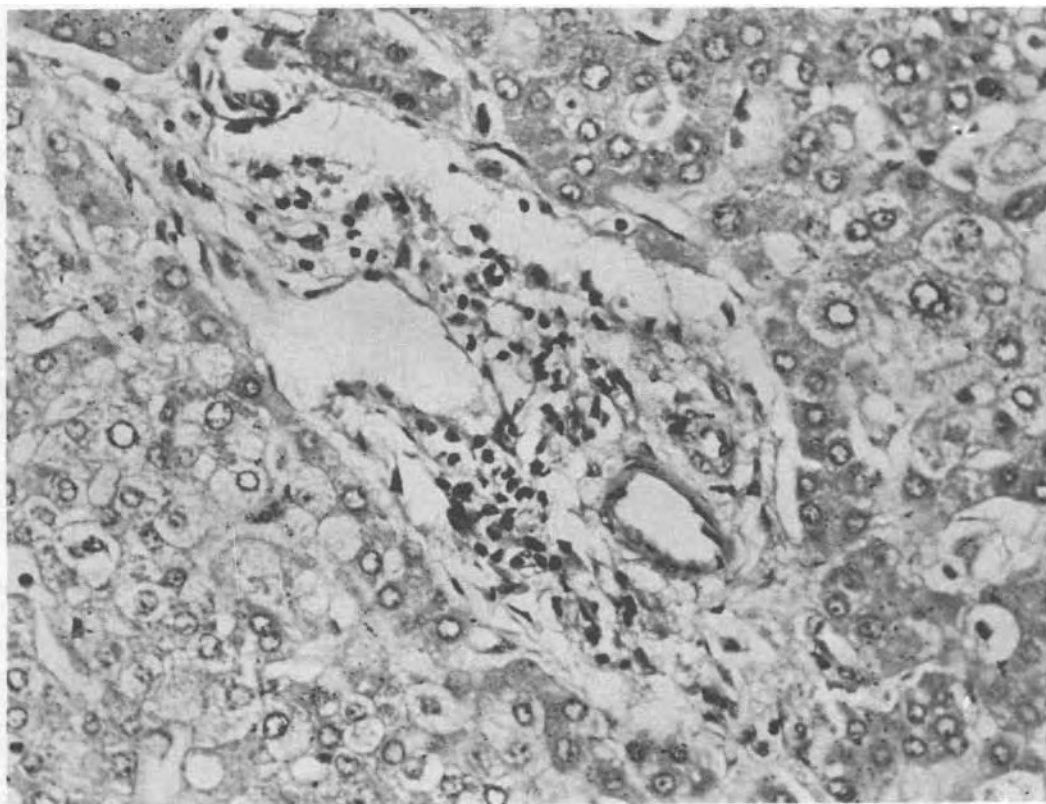


FIG. 2 : Liver biopsy showing oedema of the portal tract with a collection of mononuclear cells and occasional polymorphonuclear leucocytes. H & E X 1200.

approximately 3 weeks after starting D-penicillamine and occurred even 3 to 7 days after the drug had actually been stopped.^{8,12} Hepatomegaly may or may not be present. An eosinophil count was normal in the majority of cases. Clinical and biochemical features of these patients are summarised in Table 1. Liver biopsies in 7 cases showed cholestasis and in 4 patients, focal necrosis.

The majority of patients have a spontaneous recovery on withdrawal of D-penicillamine after approximately 3 weeks.²⁻¹⁶ Apart from the patient described here, 2 other patients have died following D-penicillamine cholestasis, both deaths due to acute renal failure.^{4,7}

D-penicillamine has been used in several large studies and major adverse reactions involving the liver have not been recorded. The point in favour of sensitivity to the drug is that the hepatotoxicity is independent of the cumulative dosage of D-penicillamine, which ranged from 2.8g to 71.8g. The sensitization period was from 1 to 6 weeks in 11 of the 12 patients documented while rash and fever were present in the majority of the patients. Finally there was a prompt recurrence of liver damage in the patients who received the drug a second time.¹² Even though the

clinical features of D-penicillamine cholestasis strongly suggest the occurrence of a hypersensitivity reaction in this patient, the liver histology changes of centrilobular and focal necrosis are not typical of hypersensitivity reactions. Idiosyncratic cholestatic-hepatocellular injury can occur due to a metabolic reaction and has been described with azathioprine.¹⁶ This pattern of liver injury is seen in individuals who have an adverse reaction to halothane. Like the halothane reaction, there is evidence of both a hypersensitivity reaction and metabolic reaction occurring in D-penicillamine associated cholestasis. In the patient reported here, there were no features to suggest viral hepatitis as the cause of the histological lesion; the biochemical and histological features of salicylate hepatitis were also absent.

Eleven patients treated with D-penicillamine have been reported to have developed asymptomatic abnormalities of liver function, as identified by serial testing.^{10,14,17,18,19} The clinical features of these patients are compared to those with cholestasis in Table 1. Essentially these patients have elevation of transaminases and alkaline phosphatase, but not bilirubin.

TABLE 1

COMPARISON OF THE CLINICAL AND BIOCHEMICAL FEATURES FOUND IN D-PENICILLAMINE-ASSOCIATED CHOLESTASIS AND ASYMPTOMATIC LIVER DISEASE.

Values are quoted as the median and range in parenthesis. p values are derived from comparisons using a Wilcoxon rank sum test.

	CHOLESTASIS	ASYMPTOMATIC	P VALUE
Rheumatoid arthritis*	11	11	
Other diseases*	3	0	
Male : female	4 : 9	0 : 8	
Age, years	47 (9-60)	52 (31-77)	> 0.05
Cumulative dosage, grams	10.5 (3-72)	32 (6-196)	< 0.05
Onset of disease, weeks	3 (2-20)	20 (6-76)	< 0.001
SGOT i.u./l	119 (52-390)	264, 440 ⁺	
Alk phos X normal	6 (4-8)	2, 2 ⁺	
Bilirubin micromol/l	118 (38-1505)	Normal	

* Number of patients with that disease

+ Only two values available.

This is reversible on cessation of D-penicillamine administration. These individuals differ from the cholestatic group in that the cumulative dosage required to cause liver damage is significantly higher, while altered liver function could only be detected after a median of 20 weeks therapy. Liver biopsies in 5 such patients showed normality in one, inflammation in two and toxic hepatitis with focal necrosis in the remaining 2 patients. In several patients D-penicillamine had previously been used or was re-introduced at a lower dosage, without adverse reaction. Presumably these patients demonstrated a pure metabolic reaction to D-penicillamine, rather than an hypersensitivity reaction.

In conclusion, liver function tests should be monitored at least during the first six weeks of therapy with D-penicillamine. Jaundice, if it occurs, is an absolute contraindication for further D-penicillamine therapy.

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