Erythro-myeloid aplasia following D-penicillamine treatment in primary biliary cirrhosis

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Summary
A woman with primary biliary cirrhosis and a high liver copper concentration was treated with D-penicillamine as a participant in a controlled trial of the drug. After 14 weeks she developed a Pseudomonas septicaemia and was found to have erythro-myeloid aplasia. Similar, but not identical blood dyscrasias have previously been reported as complications of D-penicillamine therapy. She survived after treatment with antibiotics and granulocyte transfusions, and bone marrow function returned to normal.

Introduction
Copper chelation is the established treatment of Wilson's disease. Primary biliary cirrhosis (PBC) is associated with high liver copper concentrations (Hunt et al., 1963) and assessment of D-penicillamine therapy is under trial. Early results are encouraging and indicate that life expectancy may be prolonged by treatment (Dickson et al., 1977), but side effects are more frequent than in the treatment of Wilson's disease, and the drug has had to be withdrawn in 26% of patients (Jain et al., 1977). A case of erythromyeloid aplasia induced by D-penicillamine therapy is now reported.

Case report
A diagnosis of PBC was made in a 34-year-old woman after a one-month history of right upper quadrant pain. She had been pigmented for 2 years and had hepatomegaly, splenomegaly, raised serum alkaline phosphatase (518-4 i.u./l, normal 20-95 i.u./l) high titre serum mitochondrial antibodies and a liver biopsy compatible with late PBC. Liver copper concentration was 9-5 μmol/g dry liver (normal less than 0-9 μmol/g). Haemoglobin (Hb) was 13-1 g/dl with a peripheral white cell count (WCC) of 7-7 x 10^9/l, and a platelet count of 230 x 10^9/l.

She entered a controlled trial of D-penicillamine and received 300 mg/day of the active drug. After a week of treatment she developed a papular and erythematous rash and also impairment of taste sensation. D-penicillamine was continued and prednisolone 30 mg/day was commenced. The rash quickly faded and the dose of prednisolone was gradually reduced and stopped after 4 weeks. One month later the dose of D-penicillamine was increased to 600 mg/day.

Five weeks later she was admitted to hospital in septicaemic shock with dyspnoea, pyrexia, hypertension and tender cervical adenopathy. Blood culture grew Pseudomonas aeruginosa sensitive to carbenicillin and gentamicin. Hb on admission was 12-5 g/dl and fell to 9-9 g/dl. The reticulocyte count was less than 1%. WCC was 1-5 x 10^9/l and fell to 0-45 x 10^9/l, with only 4% neutrophils. The platelet count was 160 x 10^9/l. She had taken no other drugs in the preceding month, and the D-penicillamine was discontinued on admission. Bone marrow aspiration showed a marked reduction in the erythroid and myeloid series, but megakaryocyte numbers and morphology were normal.

A diagnosis of D-penicillamine-induced erythromyeloid aplasia was made. Treatment consisted of reverse barrier nursing, intravenous carbenicillin and gentamicin, oral metronidazole, sterile food, and gut sterilization with frhamycetin, colistin and nystatin. Granulocyte transfusions, each prepared from buffy coat residues derived from fifty units of donated blood, were given daily for 6 days while the patient remained neutropenic. The average number of granulocytes per transfusion was in excess of 1 x 10^10 cells, they were given within 12 hr of collection, and were not irradiated.

During this time a parapharyngeal abscess developed, and the pus grew P. aeruginosa after the abscess was drained. Ten days after the onset of septicaemia, the peripheral blood film showed a reticulocyte response of 6% and total WCC was 17-5 x 10^9/l with 51% neutrophils. Bone marrow aspiration revealed substantial recovery of erythroid and myeloid series and the patient eventually recovered completely.
Discussion

Initiation of d-penicillamine therapy is frequently followed by moderate degrees of thrombocytopenia, neutropenia and taste impairment, although rarely severe enough to warrant withdrawal of treatment. Skin eruptions, particularly urticaria, are also common, but de-sensitization can usually be achieved by re-introduction of d-penicillamine with a short course of corticosteroid drugs (Walshe, 1963).

Total marrow aplasia is a well recognized complication of d-penicillamine therapy in rheumatoid arthritis (Bourke et al., 1976). Agranulocytosis, though rare, is more common in the first year of therapy and is usually reversible on stopping the drug (Golding, Wilson and Day, 1970). Selective red cell aplasia has occurred after prolonged treatment of a patient with Wilson’s disease with d-penicillamine (Gollan et al., 1976). The occurrence of erythro-myeloid aplasia with preservation of platelet production confirms that d-penicillamine-induced blood dyscrasias can selectively involve any of the haemopoietic cell lines. The mechanism of action is not known, but appears to be idiosyncratic rather than cytotoxic.

Granulocyte transfusions have been used in the treatment of granulopenic patients with infections (Vallejos, McCredie and Bodley, 1975), and the cells can be conveniently obtained as a by-product from the preparation of platelet transfusions. In a randomized trial in granulopenic patients with Gram-negative septicaemia, the transfusions were shown to complement the appropriate antibiotic treatment and significantly improve survival (Herzig et al., 1977). This form of treatment should therefore be considered in the treatment of septicaemia in patients with granulopenia.

References


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