

Pure red cell hypoplasia secondary to isoniazid

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Summary: We describe a 77 year old man who developed pure red cell aplasia while receiving antituberculous therapy including isoniazid. Prompt recovery occurred following cessation of isoniazid. In this paper we also review previously described case reports of isoniazid-induced pure red cell aplasia.

Introduction

Pure red cell aplasia (PRCA) is characterized by a selective reduction or elimination of the erythropoietic cell line in bone marrow;¹ both granulocytic and megakaryocytic production remain normal. Acquired cases of PRCA are often secondary to drug exposure and have been reported in association with dilantin, chlorpropamide, tolbutamide, phenylbutazone, penicillin, cotrimoxazole and isoniazid.^{1–7} Five cases of isoniazid-induced PRCA have previously been reported in the English literature.^{6,7} In this article we report one additional case, and review the literature.

Case history

A 77 year old man with a past history of pulmonary tuberculosis diagnosed in 1940, was admitted in September 1983 with a one month history of malaise, weight loss and dyspnoea. A chest X-ray revealed a left pleural effusion. *Mycobacterium tuberculosis* was subsequently cultured in both sputum and pleural fluid and he was commenced on combination chemotherapy of isoniazid, rifampicin, ethambutol and pyridoxine. At this time the full blood count was normal: haemoglobin 13.3 g/dl, white cell count $5.7 \times 10^9/l$ (normal differential), platelets $256 \times 10^9/l$. Rifampicin was stopped one month later due to anorexia and nausea and streptomycin substituted.

In January 1984 he was re-admitted with an 8-week history of dyspnoea and fatigue. He denied any history of blood loss or jaundice. Physical examination revealed marked pallor. His liver was palpable with a span of 10 cm; the spleen was also palpable 4 cm below the costal margin. At this time his only medication was the anti-tuberculous chemotherapy and this was stop-

ped on admission. Initial haematological evaluation revealed a haemoglobin of 5.0 g/dl, normocytic/normochromic film, and a reticulocyte count of 1%, white cell and platelet counts were both normal at $5.3 \times 10^9/l$ and $201 \times 10^9/l$, respectively. All investigations for haemolysis were normal. A liver-spleen radionuclear study showed mild splenomegaly with slightly increased isotope uptake. Bone marrow aspirate performed 4 days after admission was generally hypocellular with evidence of regenerating erythroid islands. He was then transfused to a haemoglobin of 12.8 g/dl, and his anti-tuberculous medications restarted.

Two weeks later, the haemoglobin was 9.7 g/dl, with a reticulocyte count of 0.1%; white cell count $5.4 \times 10^9/l$, platelets $175 \times 10^9/l$. A repeat bone marrow aspirate revealed hypocellularity, with greatly reduced erythropoiesis; myelopoietic and megakaryocytic cell lines were normal. This confirmed the diagnosis of pure red cell aplasia (PRCA), and ferrokinetic studies, which showed a marked reduction in plasma iron turnover and red cell utilization of iron in the presence of a normal serum iron, supported this. Isoniazid was stopped, the other anti-tuberculous drugs continued, and the patient was transfused to a haemoglobin of 12.2 g/dl. Two weeks later, the haemoglobin was stable at 12.1 g/dl, with a reticulocytosis of 5.4%; white cell count $5 \times 10^9/l$, platelets $188 \times 10^9/l$. He has subsequently maintained a normal haemoglobin level and the reticulocyte count has returned to normal.

Discussion

The diagnosis of PRCA was made in this patient on the basis of severe and selective anaemia, reticulocytopenia and erythroid hypoplasia, the latter documented after an inadvertent re-challenge with

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Table I Previously published cases of isoniazid-induced pure red cell aplasia.

Patient Age Sex	Duration of exposure and re-exposure (months)	Other drugs*	Time until recovery	Reference
1 32/M	6.0/2.0	PAS/Pyr Insulin	6 days	6
2 42/M	4.5	Eth/Pyr Phenobarbitone	11 days	7
3 66/F	4.0	Pred/Pyr	35 days	7
4 53/M	6.0	Pyr	30 days	7
5 81/M	2.0	Eth/Pyr	4 days	7
6 77/M	3.0/2 weeks	Eth/Strep/Pyr	4 days (marrow) /14 days (peripheral blood)	This report

*Eth = ethambutol; Pyr = pyridoxine; Pred = prednisone; PAS = para-amino salicylic acid; Strep = streptomycin.

isoniazid; his initial bone marrow examination performed 4 days after cessation of isoniazid showed early erythroid regeneration.

The duration of exposure to isoniazid before presentation with anaemia ranged from 2 to 6 months in the cases reviewed (Table I). However, in our patient this period was only 2 weeks after the re-administration of the drug; this was confirmed on both the bone marrow aspiration and the reticulocytopenia. This shortened time interval was also noted in Patient 1 (Table I) after his re-exposure to isoniazid. This rapid development of the PRCA may represent increased susceptibility to the toxic agent after re-exposure, or more likely, that the isoniazid-induced PRCA may be generally rapid in onset but is not recognized until the patient becomes symptomatic of his anaemia.

The length of time elapsed following the cessation of the isoniazid until the onset of initial erythroid regeneration varied from 4 days to 35 days. Certainly, in our patient there was evidence of early recovery in the form of erythroid 'islands' on the initial bone

marrow aspirate performed 4 days after ceasing the isoniazid. This rapid recovery was responsible for the early confusion in the diagnosis, and the re-commencement of the isoniazid. This recovery rate is consistent with the relatively short half-life of isoniazid, in which 75% to 95% of the drug is excreted within 24 hours,⁸ except in patients with the 'slow acetylator' phenotype.

Isoniazid has been associated with other red cell dyscrasias such as sideroblastic anaemia, megaloblastosis and auto-immune haemolytic anaemia.⁹ The incidence of isoniazid-induced PRCA is not known, but with only two previous reports in English language publications it is probably rare. The pathogenesis of PRCA is also not known; suggested mechanisms include a direct toxic effect of isoniazid, or its metabolite, on the erythroid precursor cells, or formation of a drug-antibody complex.⁷ Whatever the mechanism, the prompt recovery observed in this and the previously reported cases,^{6,7} suggest that it is a readily reversible toxicity, provided it is recognized.

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