Pure red cell aplasia associated with recombinant erythropoietin: a case report and brief review of the literature

M Atif Mohd Slim, Riaz Shaik

Abstract

Pure red cell aplasia (PRCA) is a rare adverse effect of recombinant erythropoietin (rEPO). Affected patients rapidly become transfusion-dependent, with many requiring immunosuppressive therapy for remission. We report a confirmed case in an elderly female, possibly the first of its kind in New Zealand, who was started on rEPO for anaemia of chronic kidney disease. We also briefly review current literature on rEPO-associated PRCA.

Pure red cell aplasia (PRCA) is a rare adverse effect of recombinant erythropoietin (rEPO), and first came to worldwide attention following a flurry of reports in the early 2000s.\(^1\) Due to the exclusive loss of erythroid precursor cells in the marrow, patients rapidly become transfusion-dependent, with some requiring intensive immunosuppressive therapy for remission.\(^2\)

We report the case of an elderly female who was admitted under General Medicine at Waikato Hospital for erythropoietin-resistant anaemia of chronic kidney disease (CKD), later diagnosed with PRCA. To our knowledge, this is the first report of confirmed rEPO-associated PRCA in New Zealand.

Case report

Mrs A was an 89-year old New Zealand European woman who presented to our hospital in April 2013 for the second time in 2 months with erythropoietin-resistant, transfusion-dependent chronic symptomatic anaemia of Stage IV CKD secondary to renovascular disease.

She denied pain, symptoms of gastrointestinal bleeding, or regular use of non-steroidal anti-inflammatory drugs apart from aspirin. Her background included double-mastectomy for non-metastatic breast cancer, and partial pelvic clearance with formation of an ileal conduit urostomy for transitional cell cancer. She was otherwise well and active, with no significant active comorbidities. She was not on dialysis.

In August 2012, Mrs A was started on NeoRecormon® (Roche, Germany), a recombinant erythropoietin (rEPO) product, at 6000 U subcutaneously once weekly. However, her haemoglobin continued to deteriorate from 92 g/L pre-treatment, to 52 g/L in February 2013, which led to the first hospital admission.

Despite increasing the dose to thrice weekly at the time, she experienced minimal symptomatic improvement, and was again referred to the hospital in April 2013. On presentation this time, her haemoglobin was 46 g/L, 7 months after commencing rEPO.
Physical examination was unremarkable save for marked pallor. She was haemodynamically stable. Blood tests showed normocytic normochromic anaemia and isolated reticulocytopenia (2x10^9/L) with an unremarkable blood film. Iron studies showed elevated ferritin (909 ng/mL) and increased transferrin saturation (98%). Her creatinine was 261 micromol/L, with an estimated glomerular filtration rate of 13 mL/min.

Further tests, including B12, folate, and a screen for myeloma and haemolysis, were negative for other causes of rEPO-resistant anaemia of CKD. Subsequent bone marrow trephine revealed complete absence of erythroid precursors, but normal findings for other cell lineages, and normal marrow iron stores.

A provisional diagnosis of pure red cell aplasia (PRCA) secondary to rEPO was made, and administration of the drug was ceased. She was discharged on two weeks of high dose corticosteroids for haematological follow-up, where this was discontinued and weekly doses of rituximab were started for a month.

However, Mrs A continued to be transfusion-dependent. In June 2013, we sent a blood sample to Germany (MicroCoat Biotechnologie GmbH, Bernried) for anti-EPO testing. Enzyme-linked immunoabsorbent assay confirmed circulating anti-EPO at a titre of 16,282 ng/mL, 3 months following cessation of NeoRecormon®, effectively establishing the diagnosis of rEPO-associated PRCA. Sadly, Mrs A died in August 2013 due to unrelated urosepsis.

**Discussion**

The pathogenesis of anaemia in CKD is multifactorial, reflecting dysfunction in erythropoiesis and iron regulation. Features include decreased erythropoietin production, marrow hyporesponsiveness to erythropoietin, decreased red blood cell (RBC) lifespan, increased hepcidin levels, and impaired reticuloendothelial release of iron. Treatment options where other causes for anaemia have been excluded include iron supplementation, rEPO, blood transfusions and renal transplantation.

rEPO resistance occurs in up to 10% of CKD patients treated for anaemia. Common causes for rEPO-resistance that should be considered include chronic occult bleeding, iron deficiency, nutritional deficiency (specifically folate and B12), inflammation, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, hyperparathyroidism, haemolysis, malignancy (especially haematological), and aluminium toxicity.

PRCA is a rare blood disorder typified by severe, sudden-onset normocytic normochromic anaemia with isolated reticulocytopenia. Bone marrow examination by trephine or aspirate characteristically show exclusive absence of erythroid precursor cells with preservation of other lineages. Iron studies may show markedly elevated ferritin and high transferrin saturation due to the arrest of erythropoiesis and subsequent build-up of iron stores.

Clinical progression of the disease may be rapid with loss of haemoglobin up to 1g/L/day, reflecting RBC lifespan. Virtually all patients become transfusion-dependent. PRCA is more commonly a primary disorder, but acquired forms have also been recognised as secondary to infection (particularly parvovirus B19), malignancy, haemolytic syndromes, autoimmune disease, seropositive arthritides, and
medication, including rEPO. PRCA can also be the early manifestation of some forms of leukaemia.

With an estimated incidence of 0.02 to 0.03 per 10000 patient-years, rEPO-associated PRCA is a rare but nevertheless significant adverse effect. First coming to worldwide attention following a case series published in 2002, it presents clinically as rEPO-resistant anaemia up to 25 months following commencement of regular treatment. Initially associated with epoietin-α (Eprex®; Johnson & Johnson, Puerto Rico), it is now a recognised adverse effect in other forms of rEPO available in the market, including epoietin-β (NeoRecormon®).

Subcutaneous preparations have been implicated in the vast majority of rEPO-associated PRCA, theorized to be due to a greater immunogenic response via this route compared to intravenous. However, rEPO-associated PRCA has also been reported with exclusive intravenous administration. Additional hypotheses as to possible causes include immunogenic non-active constituents of the preparation (such as polysorbate-80), and the use of rubber plungers. Eprex® and NeoRecormon®, in subcutaneous and intravenous preparations, are funded in New Zealand.

Given the rarity of rEPO-associated PRCA, its diagnosis in the setting of rEPO-resistant anaemia of CKD remains primarily that of exclusion. An international working group in 2004 recommended both a bone marrow biopsy (trephine or aspirate) and an anti-EPO titre to establish diagnosis.

As of the time of writing, standardized and commercially available assays for the antibody have not yet been developed. Nonetheless, evidence is lacking as to how diagnosis will necessarily influence management. Certainly the cessation of rEPO is mandatory in the management of rEPO-associated PRCA. However, recovery is seldom spontaneous, and in many patients, significant anti-EPO titres can still be detected months after cessation, necessitating repeated blood transfusions.

Although there have been isolated reports of spontaneous remission in rEPO-associated PRCA, the mainstay in treatment is similar as in primary and acquired PRCA, being immunosuppressive therapy in addition to addressing the underlying cause in acquired forms. The level of evidence for therapy primarily comprise of retrospective analyses of individual case reports due to the rarity of rEPO-associated anaemia. There is subsequently paucity of data to recommend one immunotherapy over another.

In one study of 47 European patients, untreated patients who survived to a 12-month median continued to exhibit reticulocytopenia. Recovery rates were 56% for corticosteroid treatment with or without adjunctive intravenous immunoglobulins, 67% for cyclosporine alone, 87% for corticosteroids plus cyclophosphamide, and 100% for renal transplant.

A separate US-based study of 191 international patients similarly reported only 1 spontaneous recovery out of 62 who received no treatment, whilst 57% of patients treated with one or more immunosuppressive therapy fully recovered. 56% of patients re-challenged with rEPO in the study exhibited returned responsiveness to erythropoietin (the median time post-cessation prior to re-challenge was not reported), and 95% of patients who underwent renal transplantation achieved transfusion-dependence.
Evidence for rituximab is similarly limited, but the literature is promising with reports of remission within a maximum of 4 weeks in some patients with non-rEPO-associated PRCA. Success has also been reported in at two recent cases of PRCA associated with epoietin-α.

Both epoietin-α and epoietin-β are short-acting rEPO and have the same sequence of amino acids as human erythropoietin, with minor variations in the degree of glycosylation. As such, molecular structure is unlikely to account for their antigenecity and there is consequently no evidence as of time of writing for changing to a different brand in the treatment of rEPO-associated PRCA.

In summary, corticosteroid monotherapy is generally considered as first-line in PRCA, but in rEPO-associated PRCA, current evidence appears equivocal for either combination steroid therapy or cyclosporine. Rituximab may be considered. Renal transplant confers the best chance for recovery, although it is not known if the effect is necessarily due to the transplant itself, or the high-dose immunosuppressive therapy routinely used in the post-transplantation period.

A European review recommended intravenous rEPO re-challenge as a viable option in management provided that patients are monitored for anti-EPO titres, reticulocytopenia, and systemic immunological reactions.

Conclusion

At the time of writing, the Centre for Adverse Reactions Monitoring (Dunedin) has not received any reports of drug-induced PRCA in New Zealand when contacted. To our knowledge, Mrs A is the first reported case of rEPO-associated PRCA in the country. She was first diagnosed with CKD about 18 months prior to her presentation, with symptomatic anaemia being the primary feature.

Following the diagnosis of PRCA, her rEPO treatment was ceased. Three months later, Mrs A continued to exhibit reticulocytopenia, although she was minimally symptomatic and was able to cope with normal daily activities. To avoid continued transfusion-dependence, intravenous rEPO rechallenge would have needed to be considered. No further interventions for PRCA were initiated prior to her death.

This case report highlights a very rare adverse effect of rEPO. It is important for New Zealand physicians to consider this diagnosis in patients who develop PRCA whilst on treatment, and to be aware that avenues are available for further investigation.

Author information: M Atif Mohd Slim, Trainee Intern, Waikato Clinical School, University of Auckland, Hamilton; Riaz Shaik, Advanced Registrar, Department of Medicine, Waikato Hospital, Hamilton

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Correspondence: M Atif Mohd Slim, House Surgeon, Waikato Hospital, Pembroke Street, Private Bag 3200, Hamilton 3240, New Zealand. Email: atif.matapena@gmail.com

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