Case Report

Low-dose cyclosporin therapy for recombinant erythropoietin-induced pure red-cell aplasia

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Introduction

Pure red-cell aplasia (PRCA) is an uncommon condition. It has been reported to occur in dialysis patients following recombinant erythropoietin therapy, initiated for treatment of anaemia of chronic renal failure [1–3]. In those patients, anti-erythropoietin antibodies have been recorded. Little is known of the natural history of this disease or the safest, most efficacious therapy. Here we describe a patient with only moderate renal impairment, who also developed epoetin-induced PRCA. Initial bone marrow histology failed to make a clear diagnosis. There was no spontaneous remission, but the patient was managed successfully with low-dose cyclosporin alone without compromising renal function.

Case

A 46-year-old woman with a 28 year history of type I diabetes mellitus, diabetic nephropathy and hypertension attended the nephrology services with slowly declining chronic renal impairment. Her previous medical history was remarkable for diabetic microvascular disease (retinopathy, peripheral neuropathy), left below-knee amputation (1997) for Charcot joint, and uncomplicated deep venous thrombosis (1991).

She suffered anaemia, controlled at between 95 and 105 g/l on oral iron for 4 years. Her haemoglobin (Hb) fell to 78 g/l, with a normochromic, normocytic blood film. Her glomerular filtration rate (GFR) was 37 ml/min. Iron stores were depleted [ferritin 26, transferrin saturation (Tsat) 28%]. Following a course of i.v. iron (1 g), her Hb was 82 g/l. Subcutaneous epoetin-α was commenced (6000 U/week). During 8 weeks, her Hb rose to 111 g/l. Epoetin-α was reduced to 3000 U/week and further i.v. iron was given (ferritin 56, Tsat 23%). Hb was stable at 100 g/l.

Four weeks later, her Hb fell to 87 g/l. Epoetin-α was increased to 6000 U/week. The patient presented with lethargy and exertional dyspnoea. Hb was 61 g/l, reticulocytes 3 × 10⁹/l (25–85) and platelets 116 × 10⁹/l (150–350). Epoetin-α was increased to 9000 U/week; 3 U of red-cell concentrate (RCC) were given and bone marrow aspiration with trephine was performed. The trephine was generally hypocellular, with relative reduction in mature erythroid islands. No abnormal cells were seen; iron stores were adequate. The histological conclusion was of anaemia of chronic disease.

This diagnosis did not tally with the clinical picture. Epoetin-α was curtailed. Further investigations were carried out: vitamin B₁₂ and folate were normal, haemolysis screen negative, Ham’s test negative, C-reactive protein and autoantibody screen normal, immunoglobulins and electrophoresis normal, parvovirus B19 titres over 3 months showed no evidence of infection; hepatitis virology, cytomegalovirus (CMV) and Epstein–Bar virus (EBV) titres repeatedly showed no evidence of disease. A CT scan of the thorax, abdomen and pelvis was normal. Anti-microbials, clindamycin and clarithromycin for low-grade amputation stump infection were stopped. Anti-hypertensives, metoprolol and lisinopril were discontinued. No benefit was observed. Despite regular RCC transfusions, Hb fell to 41 g/l; reticulocytes were 1 × 10⁹/l (Figure 1). Platelets remained depressed at 89–138 × 10⁹/l. In addition to increased frequency of RCC transfusion, epoetin-α was recommenced at 6000 U/week. A repeat marrow aspirate with trephine was performed, but was inadequate. A third aspirate was successful: erythroid precursors were rarely seen, with a markedly increased myeloid to erythroid ratio. Haemoglobinization was normal. No dysplastic cells were seen. Marrow cytogenetic studies were negative. Other lineages were normally represented, confirming the histological
diagnosis of PRCA. A working diagnosis of idiopathic
PRCA was made.

In view of diabetes mellitus, it was decided to avoid
corticosteroids [4,5]. Cyclosporin A (CyA) [6] was
introduced, with careful monitoring of blood pressure
(BP) and renal function. Initially a low dose of 50 mg
b.d. (1.6 mg/kg/day) was commenced. Once its toler-
ability was determined, the dose was increased to 75 mg
b.d., then 100 mg b.d. (3.3 mg/kg/day) to achieve a
target 12 h trough level of ≤100 nmol/l. GFR and BP
remained stable. After therapy had been commenced,
serum was analysed using a bioassay for anti-erythro-
poietin antibodies. The bioassay utilized a red-cell
precursor cell line. A 1 ml aliquot of the patient’s serum
neutralized 19.5 U of epoetin; control serum did not
neutralize epoetin. The patient’s serum was strongly
positive. Thus the patient did not have idiopathic
PRCA but erythropoietin-induced PRCA. In light of
this result, epoetin-α, which had been re-introduced as
part of the therapy for management of idiopathic
PRCA, was withdrawn. Five weeks later, reticulocytes
were 25 × 10⁹/l. Twelve weeks after commencing CyA,
and 7 weeks after increasing the dose to 100 mg b.d.,
the patient was independent of RCC transfusion.
Reticulocytes stabilized at >30 × 10⁹/l with Hb
between 80 and 90 g/l. Platelets returned to the
normal range. The bioassay for anti-erythropoietin
antibodies was repeated 16 weeks after commencing
CyA. A 1 ml aliquot of the patient’s serum now
neutralized only 5.0 U of epoetin. Whilst the result
remained positive, it was dramatically reduced. Thirty-
two weeks after commencing CyA, no neutralizing
antibodies were detectable in the serum.

Discussion

PRCA, though rare, is well recognized. Many cases are
idiopathic. A proportion of these subsequently manif-
est myelodysplasia or leukaemias. Many idiopathic
cases have antibodies circulating that inhibit growth of
erthyroid progenitors cultured in vitro. In others,
erthyroid suppression appears to be T cell dependent.
Only rarely have antibodies to endogenous erythro-
poietin been described in idiopathic PRCA [7,8], and
only on one occasion have they been demonstrated to
be functional [7].

Our case of PRCA had anti-erythropoietin antibo-
dies in the serum. Combined with onset 4 months
after the successful introduction of epoetin-α, it was
likely that the development of autoantibodies was a
direct consequence of administration of recombinant
protein. This association was first suggested in 1993 [9],
and again in case reports in 1996, and 1997 [2,3]. In
none, however, was the association as clearly char-
acterized. Recently, 13 patients with epoetin-induced
PRCA have been reported [1]. Twelve had end-stage
renal failure and received regular haemodialysis. They
had a variety of renal lesions, though none had diabetic
glomerulonephropathy. The latency between introduc-
tion of epoetin and onset of PRCA varied from 3 to 67
months. None had a precipitating event and none
showed spontaneous recovery after withdrawal of
epoetin. Thus our case shares some features with
those in the case series [1]. In none of the epoetin-
induced PRCA cases reported to date, however, has
there been an association with thrombocytopenia, as
was found here. This association has been recognized

Fig. 1. Chart showing haemoglobin (circles, g/l) and reticulocyte count (squares, ×10⁹/l) against time. Therapies with i.v. iron (dose/treatment period), epoetin (U/week), CyA (mg/day) and RCC transfusions (# per unit) are demonstrated.
previously in idiopathic PRCA [10]. Our case emphasizes that it is not exclusively dialysis patients who are at risk, but anyone taking epoetin. Further, it serves to heighten awareness of PRCA in patients receiving epoetin who experience an unexplained fall in Hb. Importantly, if epoetin-induced PRCA is diagnosed, epoetin should be withdrawn, which, in other circumstances of falling Hb, would be counter-intuitive.

Successful management of idiopathic PRCA has been reported using prednisolone with cyclophosphamide or CyA [6,11,12]. As a second line agent, CyA alone has been reported to induce remission in up to 65% of idiopathic cases [13]. In those case series of idiopathic PRCA, the dose of CyA was 12 mg/kg/day, a dose which might be precluded in patients with chronic renal failure and hypertension. There are no reports of CyA monotherapy as a treatment for epoetin-induced PRCA.

Although the mechanism of epoetin-induced PRCA appears to be antibody mediated whereas in idiopathic PRCA only rarely is this the case, our patient was treated with CyA. She rapidly went into remission with relatively low doses of CyA (1.6–3.3 g/kg/day), without the need for concomitant prednisolone. Despite having a reduced GFR, renal function has been stable for 4 months whilst on treatment (creatinine 200–240 µmol/l prior to epoetin-α, currently 237). BP has remained well controlled without additional anti-hypertensives. To date, the only other therapeutic strategies reported to induce remission in epoetin-induced PRCA are corticosteroids alone, steroids combined with cyclophosphamide, or steroids with plasmapheresis and i.v. immunoglobulin [1].

In the series of idiopathic PRCA managed with immunosuppression, therapy was slowly tapered 3 months after achieving remission [13]. The relapse rate has been reported at 80%, 24 months after inducing remission [10]. In the series of epoetin-induced PRCA [1], no information was presented about immunosuppressive withdrawal but, following withdrawal of epoetin, the titre of anti-erythropoietin antibodies slowly declined. This was hastened by immunosuppressives. Unfortunately, the decline in titre did not necessarily correlate with clinical remission. If one can extrapolate from the management of other immunologically mediated diseases, it would appear logical to attempt slow withdrawal of immunosuppressive therapy once antibodies are no longer detectable.

Conclusion

This case emphasizes the need to consider the diagnosis of epoetin-induced PRCA in any patient developing transfusion-dependent anaemia following the introduction of epoetin. In the absence of spontaneous remission following withdrawal of epoetin, trial of low-dose CyA should be considered.

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Conflict of interest statement. None declared.

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