Successful reintroduction of a different erythropoiesis-stimulating agent after pure red cell aplasia: relapse after successful therapy with prednisone

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Abstract

We report a 3-year case history that describes a 78-year-old woman with recurrent transfusion-dependent pure red cell aplasia (PRCA) secondary to recombinant epoetin use that was responsive to immunosuppressant therapy. The patient had kidney disease of unknown aetiology (estimated glomerular filtration rate of 13 ml/min/1.73 m²) and was not on dialysis. After 16 months of therapy with subcutaneous Eprex, she developed anti-erythropoietin antibody-confirmed PRCA and was started on high dose prednisone (50 mg per day). Within 5 months, the patient’s serum was clear of antibodies and, under the cover of low dose prednisone (5–7.5 mg per day), therapy with a different erythropoiesis-stimulating compound (Aranesp) was initiated due to persistent fatigue and anaemia. At 3 months of therapy, the serum anti-erythropoietin antibodies remained negative and, due to the patient’s requests, and after discussion, prednisone therapy was discontinued. Unfortunately, 3 months after cessation of prednisone, a recurrence of PRCA was confirmed by the development of profound anaemia and reappearance of anti-erythropoietin antibodies in the patient’s serum. High dose prednisone (50 mg per day) was reinstituted, whereupon, 2 months later, antibodies were again confirmed to be negative. This case report demonstrates the responsiveness of PRCA to simple immunosuppressive therapy, and the ability to introduce different erythropoiesis-stimulating agents in the presence of such therapy. It appears that there may be problems associated with discontinuation of immunosuppressive therapy in the presence of sustained erythropoiesis-stimulating agent therapy in those in whom the condition has occurred previously.

Keywords: darbepoetin; erythropoietin; pure red cell aplasia; steroids

Introduction

Pure red cell aplasia (PRCA) is a well documented but rare complication of epoetin therapy. Approximately 200 confirmed cases have been reported over the past 25 years, with the vast majority of cases occurring after 1996 secondary to the changes in the Eprex formulation [1–5]. Once PRCA has occurred, various immunosuppressive therapeutic modalities have been suggested with variable success [1,2,6,7]. Our case is unique in that we were able to demonstrate the effectiveness of high-dose prednisone therapy at terminating the initial episode of PRCA and, at a low dose, protecting against recurrence during reintroduction of erythropoiesis-stimulating agent therapy (darbepoetin). Although our patient relapsed after successful treatment of her PRCA, it was only after she had been weaned off the prednisone, that we were able to again achieve remission with prednisone therapy alone.

Case

On May 22, 2002 a 78-year-old lady was started on therapy with pre-filled syringes of Eprex 3000 U subcutaneously (s.c.) weekly (erythropoietin-a; Ortho Biotech/Janssen-Ortho Inc.) after being diagnosed with chronic kidney dysfunction [creatinine 296 µmol/l; estimated glomerular filtration rate (eGFR) 13 ml/min/1.73 m²]. At the time of initiation of epoetin therapy, her haemoglobin was 77 g/l and it rose steadily to 122 g/l by December 2002 (reticulocyte count of 40 × 10⁹/l). She did well until the spring of 2003 when she was found to have a haemoglobin persistently below 120 g/l. Despite progressive increases in her Eprex dose (4000 U weekly to 6000 U biweekly), her
haemoglobin and reticulocyte count continued to fall between May and August 2003. On August 20, 2003, her haemoglobin had decreased to 61 g/l with an unmeasurable reticulocyte count. She was subsequently admitted to hospital for red cell transfusion and investigation of her anaemia with reticulocytopenia. Bone marrow biopsy done on August 29, 2003 revealed normal myeloid and megakaryocyte lines with absent red cell lines, consistent with the diagnosis of PRCA. Investigations in hospital, including an autoimmune screen, infectious serology and total body computed tomography, did not reveal any secondary cause of her PRCA. A serum sample was sent to PPD Development, CLIA Immunochemistry Laboratory in Richmond, Virginia for evaluation of serum erythropoietin levels and the presence of anti-erythropoietin antibodies. Tests performed on September 9, 2003 revealed an inappropriately normal serum erythropoietin level of 23.7 mU/ml (normal range 10–30 mU/ml) and positive serum erythropoietin antibody levels by anti-erythropoietin radioimmunoprecipitation at 1.7% c.p.m. at 1:100 dilution (positive ≥0.9% c.p.m. at 1:20 dilution) [8].

On September 25, 2003, 16 months after starting epoetin therapy, Eprex was discontinued and immunosuppressive therapy was initiated with prednisone 60 mg daily and cyclophosphamide 100 mg per os daily; the latter was discontinued after 5 days secondary to intolerance. At initiation of immunosuppressive therapy, her haemoglobin remained low at 73 g/l with persistent absence of reticulocytes (0/μl). She remained transfusion dependent between September 25 and October 28, 2003, requiring 3 units every 2 weeks (total 15 units transfused), see Figure 1.

By October 22, 2003, our patient started to report a worsening of her underlying anxiety and depression on prednisone therapy. Unfortunately, she found these side effects quite intolerable and an effort was made to wean her off the steroids. Even though the prednisone dose was being reduced by 5 mg/week, her transfusion requirements decreased to 3 units every 2 weeks with a corresponding rise in her reticulocyte count. At the time of her last transfusion, January 27, 2004, her reticulocytes were 52×10⁹/l on 20 mg per day of prednisone, with a corresponding haemoglobin of 78 g/l. By February 25, 2004, on 10 mg of prednisone, she had maintained a haemoglobin of 103 g/l. Her creatinine remained steady at 246 μmol/l (eGFR 17 ml/min/1.73 m²) without dialysis. Tests performed

| Antibody Status | + | - | - | + |
| Prednisone      |   |   |   |   |
| Epoetin Therapy | EPREX |   | ARANESP | |
| Blood Transfusion |   |   |   |   |

**Fig. 1.** Changes in haematological variables correlated to epoetin and prednisone therapy. The time course of the two episodes of PRCA in this patient, demonstrated the increase in epoetin therapy dose (represented by ↑) coincident with the drop in haemoglobin, reticulocyte count and development of anti-erythropoietin antibodies (represented by +). It is followed by the subsequent response of the haemoglobin, reticulocyte count and cessation of anti-erythropoietin antibodies (represented by –), to the initiation, weaning (represented by ↓) and eventual cessation of prednisone therapy. Blood transfusion frequency is represented as 3 units transfused per value, except for September 15 and September 29, 2004 where 2 units were transfused per value.
at the CLIA Laboratory on March 2, 2004 revealed negative serum erythropoietin antibody levels at 0.2% c.p.m. at 1:20 dilution (negative ≤0.6% c.p.m. at 1:20 dilution) [8].

Given the negative antibody status and the continued slow decline in haemoglobin, the decision was made to reinitiate erythropoietin therapy with Aranesp 20 µg s.c. every 14 days (darbepoetin-α; Amgen) under the cover of 7.5 mg per day of prednisone on March 19, 2003. Tests performed on June 24 revealed persistently negative serum erythropoietin antibody levels at 0.3% c.p.m. at 1:20 dilution (negative ≤0.6% c.p.m.) while on Aranesp 20 µg s.c. every 7 days and prednisone 5 mg per day. At this time, her haemoglobin peaked at 110 g/l (reticulocyte count of 27×10⁹/l) and was maintained at 110 g/l (reticulocyte count of 15×10⁹/l) 1 month later. On July 20, 2004, due to intolerable side effects and at the patient’s insistence, prednisone therapy was halted.

Blood work-up over the next 2 months revealed a continued decline in her haemoglobin to 74 g/l and a persistent reticulocytopenia at 5×10⁹/l. Given the possibility of PRCA, Aranesp therapy was discontinued and prednisone reinitiated at 50 mg per day. Blood transfusions were reinitiated at a rate of 2 units every 2 weeks. On November 12, 2004, anti-erythropoietin antibodies were again found to be positive at 1.2% c.p.m. at 1:100 dilution (positive ≥0.9% c.p.m. at 1:20 dilution) [8], see Figure 1.

While on 50 mg of prednisone per day, her transfusion requirements decreased, requiring 3 units of packed red cells on November 12, 2004 and December 1, 2004. Subsequent blood work-up revealed a rising reticulocyte count with concurrent reduction of her prednisone dose, reaching a peak of 90×10⁹/l on January 10, 2005 while on 35 mg of prednisone daily. Testing done on January 19, 2005 revealed negative anti-erythropoietin antibodies (0.1% c.p.m. at 1:20 dilution; negative ≤0.6% c.p.m. at 1:20 dilution) [8].

At the time of writing, she is not taking any erythropoiesis-stimulating agent. Given her intolerance to prednisone, imuran 50 mg per day (azathioprine) was introduced for its steroid-sparing effect. Unfortunately, medication intolerance has forced her physicians to reduce the dosage of both prednisone (10 mg per day) and imuran (25 mg every other day). Transfusions are now required at a rate of 3 units every 4 weeks, although the interval is increasing. Reticulocyte count is currently 34×10⁹/l with a haemoglobin of 103 g/l. The patient remains depressed but is otherwise clinically stable.

Discussion

We present an atypical clinical course of a rare but well described complication of erythropoietin therapy. Our case is unique in that we were able to demonstrate clearly resolution of PRCA and successful reintroduction of a different erythropoiesis-stimulating agent with prednisone therapy alone. Although our patient relapsed after successful treatment of her PRCA, it was only after she had been weaned off the prednisone, and we were able to again achieve remission with prednisone therapy alone.

PRCA is a rare syndrome of anaemia associated with low reticulocyte count, absent bone marrow erythroblasts, resistance to epoetin therapy and anti-erythropoietin antibodies [2,4,7]. It has been attributed to the induction of an IgG antibody directed against the protein moiety of the glycosylated erythropoietin polypeptide [1,4,9,10]. Typically, PRCA occurs after 3–67 months of therapy with recombinant epoetin [1,7], with a median occurrence after ~9 months of therapy for Eprex [2,6]. As a phenomenon, PRCA markedly increased after 1998, peaked in 2001 and then slowly declined thereafter [2–5,7,9,11]. Although rarely described before 1996 (four cases), ~200 cases were described between January 1998 and March 2003 [4].

The dramatic rise in incidence after 1998 has been attributed to various changes in the Eprex formulation, handling and delivery that are thought to have conferred an increase in immunogenicity [2,7,9]. The changes included the substitution of polysorbate 80 and glycine for human serum albumin as stabilizer, the use of exposed rubber plungers and silicone oil lubricant in pre-filled syringes, the shift from the intravenous (i.v.) to the s.c. route of administration, and ‘self-administration’ which is associated with problems in storage (i.e. >8°C) and handling [1,6,7,9].

Our patient developed PRCA in the context of all these changes, having started therapy with pre-filled syringes of Eprex administered by the s.c. route in May of 2002. Although diagnosis was confirmed in September 2003, it is likely that she started to manifest the effects of PRCA as early as December 2002, 7 months after the initiation of Eprex therapy, as indicated by the need for increasing doses without effect. Her clinical course post-development of PRCA was typical of previously described cases. After her haemoglobin peaked in December 2002–January 2003, she demonstrated a progressive decline in haemoglobin values over the subsequent 8 months, eventually becoming transfusion dependent.

To our knowledge, this is the first reported case of PRCA relapse in a patient with negative anti-erythropoietin antibodies documented during rechallenge with a different erythropoiesis-stimulating agent.

While previous reviews have suggested variable effectiveness of immunosuppressant therapy, our patient demonstrated complete resolution of previously demonstrated anti-erythropoietin antibodies with prednisone therapy alone [1,2,6,7,11]. Her transfusion requirements decreased from 1 unit per week to 1 unit every 2 weeks after only 6 weeks of therapy. After only 19 weeks of progressively weaning her off prednisone therapy, she received her last unit of transfusion, maintained a haemoglobin in the high 80s to low 90s g/l, and demonstrated a negative serum erythropoietin antibody.

Subsequently, while on low dose therapy, antibody-negative status was maintained by the chronic
immunosuppression. This allowed us successfully to reintroduce erythropoiesis-stimulating agent therapy with therapeutic effect. As demonstrated by our patient, darbopoietin therapy with concomitant low dose prednisone successfully increased our patient’s haemoglobin from 90 to 110 g/l. Unfortunately, cessation of prednisone therapy resulted in a recurrence of PRCA, which to our knowledge is one of the first reported cases of PRCA relapse in a patient with negative anti-erythropoietin antibodies documented during rechallenge with a different erythropoiesis-stimulating agent.

Mandreoli et al., in their report demonstrating the effectiveness of rituximab at terminating PRCA and allowing for successful reintroduction of therapy [12], postulated that the beneficial effect of rituximab was maintained at 1 year via suppression of B-cell regeneration and, by extension, antibody production. It is possible that the high dose prednisone therapy was able to terminate anti-erythropoietin antibody production and/or secretion in our patient through non-specific mechanisms. The subsequent low dose prednisone maintained this B-cell suppression and allowed successful reintroduction of therapy with a different erythropoiesis-stimulating agent by inhibiting new antibody production and/or secretion. Under this cover of low dose prednisone, our patient was able to increase her haemoglobin successfully, demonstrating that the therapy was in fact successful for a period of time. It is postulated that only when we ceased the chronic immunosuppression therapy were the primed memory cells able to re-secrete antibodies, causing a delayed recurrence of her previous PRCA. This assertion of the immunoprotective effects of prednisone is substantiated by both the absence of anti-erythropoietin antibodies on testing 3 months post re-introduction of darbopoietin and the almost immediate recurrence of PRCA post-prednisone discontinuation.

The importance of this clinical course is implied from the previous case reports and reviews present in the literature. Previous reviews and case reports have offered renal transplant as a potential alternative to exogenous erythropoiesis-stimulating agent therapy, and the debate as to whether renal transplantation itself or the use of immunosuppressive agents accounts for the success of this therapy continues [2,6,11,13]. For those who are not transplant candidates, treatment of the persistent anaemia has been limited to transfusions, given the recommendation to avoid any re-introduction of erythropoietin therapy [1,7]. This case demonstrates that erythropoiesis-stimulating agent therapy may be successfully re-instituted if combined with chronic low dose prednisone therapy. It also demonstrates that cessation of the immunotherapy may result in recurrence. Unfortunately, due to patient intolerance, we were not able to test our hypothesis that steroid-sparing agents, such as azathioprine, would have similar effects to prednisone. More work is needed to understand the mechanism of PRCA in individuals with CKD.

Conflict of interest statement. Dr Levin is a member of the speaker’s bureau and advisory board, she also conducts research with Janssen-Cilag, OrthoBiotech, Roche and Amgen. All other authors declare no conflict of interest.

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