

References

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Acquired pure red cell aplasia due to anti-erythropoietin antibodies in a patient with end stage chronic kidney disease

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Introduction

Anaemia is a common problem in end stage kidney disease. Recombinant human erythropoietin (rHuEPO) is commonly used in management of such patients to maintain optimal hemoglobin levels and to minimise transfusion requirements. Acquired pure red cell aplasia (PRCA) is a rare complication of erythropoietin therapy due to development of anti-erythropoietin antibodies (anti-EPOabs). We report a patient with end stage kidney disease who developed pure red cell aplasia following rHuEPO treatment.

Case report

A 57-year old man with end stage kidney disease due to diabetic nephropathy, presented with fatigue and exertional breathlessness worsening over six weeks duration. He was on subcutaneous injections of rHuEPO (EPIAO® – Shenyang sunshine pharmaceutical co. China,) 4000 units biweekly over one year for anaemia associated with chronic renal failure. He had never been transfused with red cells. On examination he was pale and his hemoglobin level was 3.9 g/dl. His white cell and platelet

counts were normal. Blood film showed normochromic normocytic red cells. The hemoglobin level was maintained around 10 g/dl with above rHuEPO dose until two months back when it dropped rapidly. Figure 1 shows variation of the hemoglobin level with time.

The reticulocyte count was very low (2760/ mm³) and serum ferritin was elevated (571.4 ng/ml). Bone marrow aspiration biopsy showed markedly suppressed erythropoiesis with absent normoblasts and proerythroblasts (Figure 2). Granulocytic and megakaryocytic elements were normal. Anti-erythropoietin antibodies (56.6% – normal up to 4.7% binding) were detected by radioimmunoprecipitation (RIPA) assay. A diagnosis of acquired pure red cell aplasia due to anti-EPOabs was made. Recombinant erythropoietin therapy was discontinued. Patient was given packed red cell transfusions and started on immunosuppressive therapy with prednisolone 1 mg/ kg/ daily. After six weeks of steroid therapy the reticulocyte count rose to 5400/ mm³. Currently he is on regular follow up with top up blood transfusions and is undergoing preliminary investigations for kidney transplantation.

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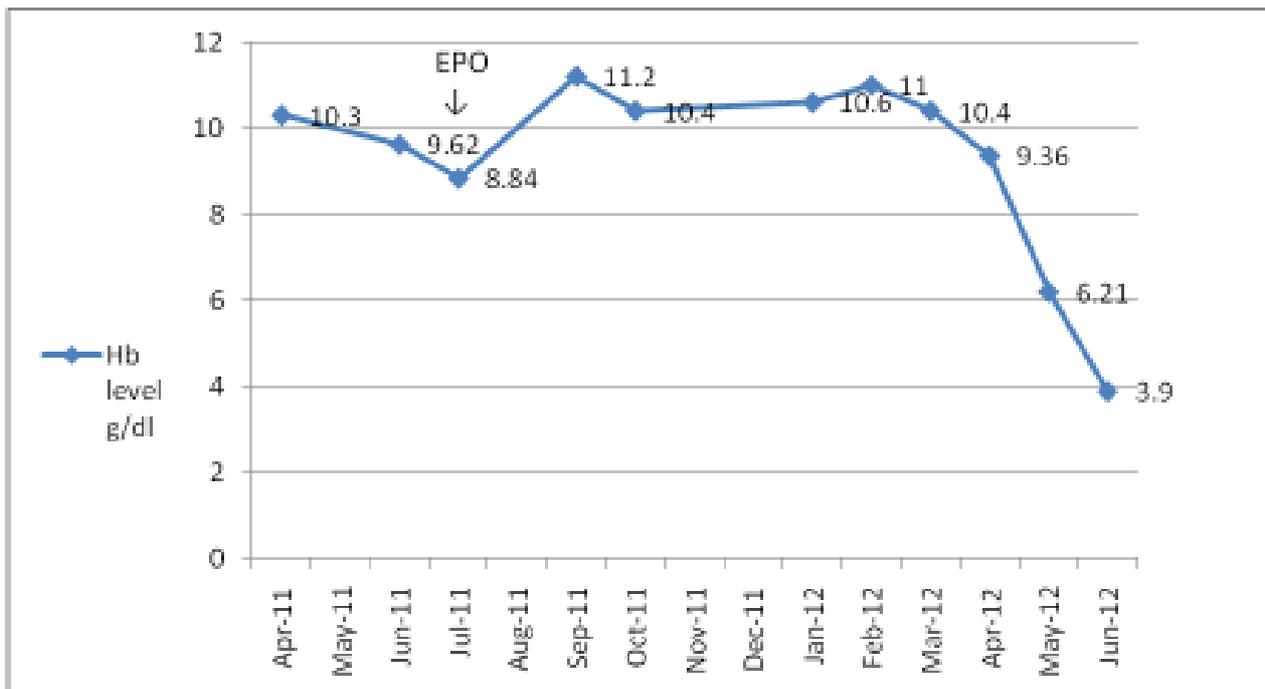


Figure 1. Change in hemoglobin level with time (from April 2011 to June 2012).

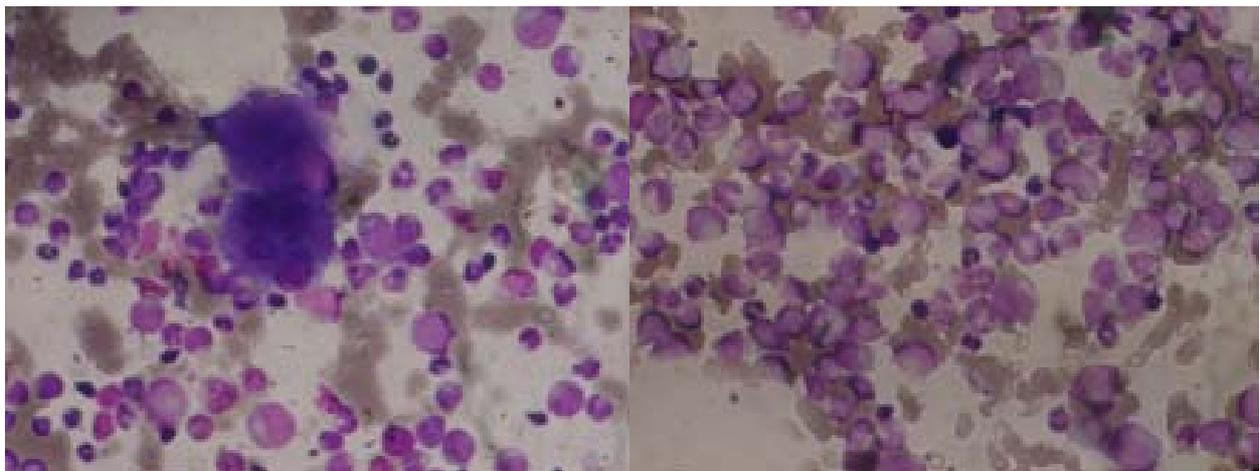


Figure 2. Bone marrow aspirate showing severe erythroid hypoplasia (Leishman stain $\times 400$).

Discussion

Acquired PRCA in patients who are treated with rHuEPO was first described in 1990, ten years after starting its use as a therapeutic agent [1]. It is a rare complication with an exposure adjusted incidence rate of 0.02-0.03 per 10,000 patient-years, and occurs mainly in patients with renal failure who are on long term erythropoietin therapy [2]. Majority of such cases were reported during 1998 - 2002 and there was a steady decline since 2003 [3]. Currently there are concerns about a surge in PRCA in

certain countries (eg. Thailand) due to availability and use of many biosimilar non-patented erythropoietin products at a lower cost [2, 3].

Erythropoietin induced PRCA occurs due to formation of anti-EPOab of IgG (IgG₁ and IgG₄) class which are capable of neutralising recombinant as well as endogenous erythropoietin [4]. The average time to develop PRCA is 9-11 months after starting rHuEPO therapy [2, 5]. It should be suspected when rapidly progressive erythropoietin resistant anemia develops in

patients who are on long term rHuEPO therapy. It reflects almost complete cessation of red cell production characterised by very low reticulocyte count (<10,000 mm³) and a rapid decline of haemoglobin concentration at a rate of 1 g/dl/week, reflecting a decay corresponding to normal red cell life span [1,5]. There should not be a major drop in white cells or platelets. Diagnosis is confirmed by demonstration of complete absence of red cell precursors in bone marrow with normal white cell and platelet precursors and by isolation of anti-erythropoietin antibodies in serum [1, 5]. Anti-EPO antibodies can be demonstrated by radioimmuno-precipitation (RIPA) or ELISA techniques [1, 2, 5]. Additionally rapid increase in serum ferritin and transferrin saturation is noted in PRCA, reflecting cessation of erythropoiesis and interruption of iron utilisation [1].

Anti-EPO antibody induced PRCA is usually reversible after discontinuation of erythropoietin therapy and treatment with immunosuppressive drugs [3, 5]. Patients should not be switched to another recombinant erythropoietin product since antibodies cross react [1, 5]. Cessation of erythropoietin therapy alone without immunosuppressive therapy does not reverse PRCA [5, 6]. Immunosuppressives such as corticosteroids, cyclophosphamide, cyclosporine, mycophenolate mofetil and rituximab have all been used in treatment of anti-EPO antibody induced PRCA with variable success rates [2, 3]. Kidney transplantation is the most effective treatment with complete recovery [1, 2, 5]. Patients need multiple red cell transfusions until normal red cell production resumes. Recently a synthetic erythropoietin receptor agonist, peginesatide, has been successfully used in the treatment of PRCA due to anti-EPO antibodies [2, 3, 4]. Recovery is diagnosed when the reticulocyte count rises >10,000 mm³ and anti-EPO antibodies are no longer detected [7].

Although anti-EPO antibody induced PRCA is a rare complication, physicians need to be aware of the clinical features and diagnostic procedures when managing patient with anemia due to renal failure. At present there are no reports available regarding the antigenicity of this particular brand of rHuEPO. Continuous vigilance is mandatory as a rise in anti-EPO antibody induced PRCA can be expected due to the epidemic of chronic kidney disease as well as wide availability and use of rHuEPO products at an affordable price in Sri Lanka.

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