Case Report

Uraemic pericarditis: a reversible inflammatory state of resistance to recombinant human erythropoietin in haemodialysis patients

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Introduction

In the era of recombinant human erythropoietin (rHuEpo), anaemia can be effectively alleviated or corrected in patients with end-stage renal disease (ESRD) [1–3]. The increases in effective erythropoiesis by rHuEpo are dose-dependent over doses ranging between 15 and 500 U/kg body weight [2,3]. Although 95% of patients will respond to high doses of rHuEpo, individual response is variable with doses ranging from 40 to 50 U/kg. Though the efficacy of rHuEpo treatment is impressive, poor responses have been reported [4,5]. Factors known to cause resistance to rHuEpo include chronic inflammations, iron deficiency, aluminium overload, hyperparathyroidism with myelofibrosis, occult blood loss, haemolysis, and haemoglobinopathy. The reason for the variation in response and the mechanism for suppression of the effect of rHuEpo remain obscure. Inflammation and infection represent additional causes of anaemia and resistance to rHuEpo in patients with chronic renal failure [6–9]. We report a case on regular haemodialysis who developed transitory resistance to rHuEpo treatment with temporal association with uraemic pericarditis.

Case report

A 47-year-old Chinese man presented in 1993 with end-stage renal failure as a consequence of chronic glomerulonephritis. He started regular haemodialysis thrice weekly at an outpatient haemodialysis facilities in Taipei. Because of frequent attack of dialysis hypotension, he was referred to our institution in September 1994. rHuEpo cannot be used if the haematocrit level is above 30% according to the National Health Insurance Bureau’s payment policy of rHuEpo in Taiwan. The patient’s haematocrit remained in the range of 31–33% without rHuEpo treatment from the inception of haemodialysis. The interdialysis weight gain was always up to 5.5–7.5 kg at our institution. Dialysis hypotension frequently occurred and resulted in the shortening of dialysis time (from 4 to 3.0–3.5 h per session) and a decrease in blood flow (from 300 to 200–250 ml/min) in each event of hypotension. Inadequate dialysis with Kt/Vurea [10] of 0.8–1.0 was inevitable.

The haematocrit level and iron status were stationary during 1 year of follow-up (Figure 1). In September 1995 the haematocrit suddenly declined to a level of 27% and rHuEpo treatment was initiated for symptomatic anaemia. rHuEpo (Eprex®, Cilag, Switzerland) was administered subcutaneously twice weekly after dialysis. Therapy started with a monthly dose of 8000 U and later increased to 12 000 U. Intravenous iron therapy (total dose 600 mg) was prescribed using a protocol from our previous study [11] due to serum ferritin level of 44 μg/l. Briefly, 100 mg of 2% ferric hydroxide sucrose (Ferrum hausmann®, Switzerland) was administered intravenously postdialysis twice weekly. Serum ferritin rose to the level of 296 μg/l 2 months after iron supplementation. The haematocrit remained below 27% despite increasing doses of rHuEpo and replenishing the iron reserves. In January 1996, the patient suffered from chest pain and exertional dyspnoea. A pericardial friction rub was heard on chest auscultation. Chest X-ray disclosed a sudden increase in the size of cardiac silhouette with the water-bottle contour compared with the previous films. Pericarditis with pericardial effusion was suspected, and confirmed by echocardiography, which demonstrated a massive pericardial effusion with impending tamponade (Figure 2a). Five hundred millilitres of non-bloody effusion was aspirated via echo-guided pericardiocentesis, and a series of investigations showed the following: cell count, WBC 2800/mm³ with...
neutrophils 46%, lymphocytes 48%, and monocytes 6%, and RBC 2070/mm³; protein 6000 mg/dl and sugar 39 mg/dl; no bacterial or mycobacterial growth was seen on effusion culture, and no malignant cells on cytological examination.

The haematocrit further declined to 23% in spite of a stepwise increase in the rHuEpo doses to 20000 U monthly. Plasma C-reactive protein (CRP) rapidly elevated to 15 mg/dl with a parallel rise in serum ferritin to 481 µg/l and a decline in transferrin saturation to 15% (Figure 1). In another aspect the concentration of endogenous serum erythropoietin, measured in duplicate using radioimmunoassay (Incstar®, MN, USA), decreased from baseline of 93 to 54 U/l. We hypothesized that the inflammatory state in uraemic pericarditis was contributing to the patient’s poor response to rHuEpo, and immediately began the intensified haemodialysis. In the period 2 February to 1 March 1996, he was treated by non-heparinized haemodialysis 5 times a week for 4–4.5 h/session using a cellulose acetate hollow-fibre changed from FB 130T (Nipro®, Nissho, Japan) to CA-170 (CA®, Baxter, USA). During the intensive dialysis, Kt/V increased to 1.6–1.7 and the symptoms were dramatically relieved. Treatment protocol then returned to haemodialysis with regional heparinization thrice weekly and continued with a CA-170 dialyser.

The follow-up echocardiography disclosed the resolution of pericardial effusion on 1 April, 1996 (Figure 2b). Plasma CRP and serum ferritin simultaneously reduced to the respective values of 1.1 mg/dl and 51 mg/l. Impressively, the serum erythropoietin level increased to 267 U/l with a concomitant rise in haematocrit level to 33% (Figure 1). The physical performance and quality of life improved significantly. rHuEpo treatment was then stopped while the haematocrit rose to the level of 34–36%. In the 6 months follow-up after intensive dialysis, plasma CRP, serum ferritin, and transferrin saturation were in the range of 1.0–1.1 mg/dl, 78–95 mg/l, and 38–42% respectively. The serum erythropoietin concentration gradually returned to baseline level (95–97.6 U/l).

Discussion

Initially our patient did not require rHuEpo treatment to maintain haematocrit level above 30%. Baseline

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**Fig. 1.** Changes in levels of haematocrit, plasma C-reactive protein, serum ferritin, and endogenous serum erythropoietin before, during, and after the occurrence of uraemic pericarditis.

**Fig. 2.** a, Parasternal long-axis views of echocardiography showing a massive pericardial effusion with right ventricular diastolic collapse before echo-guided pericardiocentesis, and b, the resolution of pericardial effusion 1 month after intensive haemodialysis. Abbreviations: Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle; and PE, pericardial effusion.
erythropoietin level was high and acquired cystic kidney disease was shown on the sonography. In the absence of other well-established states associated with increased erythropoietin production and erythropoiesis, it is assumed that acquired cystic kidney disease is the most likely cause of the phenomenon [12].

In the absence of any obvious cause for blood loss, haemolysis, or iron deficiency, the sudden drop in haematocrit level and the development of resistance to rHuEpo raised the suspicion of the existence of an unrecognized condition. Patients with acute or chronic inflammatory disease frequently exhibit remarkable resistance to the effect of rHuEpo. The inflammatory state may be obvious after surgery or tuberculous arthritis [6], or indolent in perinephric abscess [7], vasculitis [8], and occult rejection in a failed graft [9].

Unless the physician keeps alert, diagnosis of a subclinical inflammation may be difficult, and further impeded in the presence of end-stage renal failure. Plasma CRP is a useful marker for confirming and quantitating the severity of inflammation in patients undergoing dialysis [9,13]. An increase in plasma CRP probably best reflects the inflammatory state of uraemic pericarditis in our patient. An abrupt onset of resistance to rHuEpo preceded the prevailing symptoms of uraemic pericarditis for 3 months. It is typical for this type of rather occult condition. Therefore, when confronted with a patient with unexplained resistance to rHuEpo, it is prudent to determine plasma CRP to rule out the presence of an underlying inflammation.

The mechanism of inflammation-induced inhibition on the effect of rHuEpo has remained unclear. Investigators postulated that specific cytokines such as interleukins (IL-1, IL-6), tumour necrosis factor \( \alpha \) (TNF\( \alpha \)), and \( \gamma \)-interferon (\( \gamma \)INF) may play a pivotal role in the pathogenesis of the anaemia of chronic inflammations [4,5,14]. These inhibitory cytokines not only suppress erythroid progenitor cells but also inhibit reticuloendothelial iron release. Our patient developed rHuEpo-resistant anaemia accompanied by an elevation of serum ferritin. Serum iron and percentage of transferrin saturation were low during the period of uraemic pericarditis despite intravenous iron supplementation. Alvarez-Hernandez et al. [15] proposed that TNF induces hypoferaemia by alteration in the ability of macrophage to handle iron. Rogers et al. [16] reported that IL-1 enhances hepatic ferritin production. Accordingly, we speculated that high levels of inhibitory cytokines may generate ineffective erythropoiesis by interfering with iron availability in our patient of pericarditis.

The normal feedback mechanism that stimulates erythropoietin response to anaemia is absent in patients with chronic renal failure. The blunted erythropoietin response in ESRD patients worsened with inflammation. Investigators advocated that altered concentration of inhibitory cytokines connected with inflammation can inhibit synthesis and secretion of endogenous erythropoietin [14]. Serum erythropoietin level declined in the occurrence of uraemic pericarditis and dramatically rose above baseline during intensive dialysis in our patient. His haematocrit paralleled the erythropoietin fluctuations. This relative erythropoietin deficiency, while not the primary mechanism for decreased erythropoiesis, may contribute to the development of this form of anaemia.

Before the era of rHuEpo, Silverberg et al. [17] reported a case who had a sharp decline in the haemoglobin concentration during a prolonged course of haemorrhagic pericarditis with recurrent tamponade. This phenomenon may reflect blood loss into the pericardial sac and breakdown of red cells. Pericarditis in our case was not haemorrhagic and the relative contribution of haemorrhage to rHuEpo resistance is unlikely. Pericarditis may develop in patients being treated with chronic intermittent dialysis and has been attributed to inadequate control of uraemia [18,19]. Inadequate dialysis initially was a major problem in our patient. Moreover, inadequate dialysis not only led to uraemic pericarditis but also was of course another potential reason for a suboptimal response to rHuEpo therapy [20].

We suggested that echo-guided pericardiocentesis was effective for saving life in patients with uraemic pericarditis with circulatory compromise, and useful for diagnostic purpose in those without tamponade. Intensive haemodialysis [18,19] was successful in resolution of pericardial effusion in our patient. Increasing the intensity of dialysis and resolution of the inflammatory condition resulted in a significant increase in the haematocrit. Our report corroborated the findings of Ifudu et al. [20]. The haematocrit regained stable in the range of 34–36% despite cessation of rHuEpo treatment and the clinical condition improved significantly. The advantage and lack of adverse event, from a clinical and economical point of view, justified the treatment option. Up to now it is the first report of uraemic pericarditis as a cause of resistance to rHuEpo treatment in haemodialysis patients. Inadequate dialysis may be one cause of poor response to rHuEpo, and additional occurrence of an inflammatory state may aggravate this condition. Early detection and prompt management of the underlying disease, if possible, can restore the responsiveness to rHuEpo and reduce the dose requirements.

References


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