


Anaemia in a Chronic Kidney Disease Patient: The Hidden Clue

Dhanya Mohan*,
Mohammed Railey,
Fakhriya Alalawi and
Amna Khalifa Alhadari

Department of Nephrology, Dubai
Hospital, PO Box 7272, Dubai Health
Authority, Dubai, United Arab Emirates

***Corresponding authors:**

Dr. Dhanya Mohan, MD

 drdhanyapraveen@gmail.com

Department of Nephrology, Dubai Hospital,
PO Box 7272, Dubai Health Authority, Dubai,
United Arab Emirates

Citation: Mohan D, Railey M, Alalawi F,
Alhadari AK (2019) Anaemia in a Chronic
Kidney Disease Patient: The Hidden Clue.
Dual Diagn Open Acc Vol.4 No.2:75.

Abstract

The anaemia of chronic kidney disease is associated with cardiovascular disease, decreased quality of life, and mortality. The introduction of recombinant human erythropoietin (rHuEPO) has transformed the management of this condition. However, a significant proportion of patients fail to respond to even high doses of rHuEPO. We report a patient, known to have thalassemia trait, with Chronic Kidney Disease Stage 5, secondary to hypertensive nephrosclerosis, on conservative therapy, who had progressively increasing EPO requirement. Anaemia persisted despite IV iron supplementation and large EPO doses. Persistent anaemia was initially attributed to the thalassemia trait and recurrent bleeding per rectum, which were actually red herrings. Further evaluation including a bone marrow aspirate, led us to the diagnosis of myeloma (light chain disease). The only clue to the diagnosis of myeloma in this patient was refractory anaemia and erythropoietin hyporesponsiveness.

Keywords: Anaemia; Chronic Kidney Disease; Recombinant human erythropoietin; Thalassemia

Received: August 21, 2019; **Accepted:** September 04, 2019; **Published:** September 10, 2019

Introduction

It is important to recognise refractory anaemia in Chronic kidney disease patients. When anaemia persists despite administration of adequate doses of Erythropoetin, one needs to evaluate the patient for Erythropoetin hyporesponsiveness. Among the causes, hematologic abnormalities need to be considered, where a bone marrow examination can clinch the diagnosis as in this case. Here, refractory anaemia in the setting of CKD was the clue that led us to the diagnosis of myeloma.

Hence, we wrote this up to highlight this important clinical lesson.

Case Presentation

A male in his mid 60's had been diagnosed to have hypertension, ischemic heart disease, and residual right hemiparesis following an ischemic cerebrovascular accident over the last ten years. In addition, he had history of pulmonary tuberculosis and completed anti-tuberculous treatment.

He had been on follow-up in our Nephrology clinic for evaluation and management of chronic kidney disease. The aetiology of chronic kidney disease was presumed to be hypertensive nephrosclerosis. From 2005-10, serum creatinine ranged from

5 to 6 mg/dl, with estimated GFR: 10 ml/min. He did not have uremic symptoms or features of fluid overload, hence was not commenced on Renal Replacement Therapy (RRT).

One particular problem we encountered during his treatment was anaemia. He was known to have Thalassemia trait. In 2004, haemoglobin was 7.2 mg/dl, MCV 67. fL, Fe Sa: 10%, Ferritin: 154 ng/ml. He was given treatment for iron deficiency anemia with intravenous Iron saccharate and then oral iron. He was subsequently lost for follow up. In 2006, Hb was again detected to be low with reduced iron saturation (Hb 9.1 gm/dl, Fe Sa: 15%). IV and oral iron replacement were prescribed, and he was also commenced on Erythropoetin 4000 units twice per week. During subsequent follow up visits, haemoglobin and MCV remained persistently low. Iron studies were adequate. During these years, he complained of recurrent episodes of bleeding per rectum. A surgical evaluation revealed third degree haemorrhoids and he was on medical therapy for the same. He also underwent upper GI endoscopy and colonoscopy on two separate occasions in 2006 and 2010, to evaluate anaemia and recurrent bleeding PR. UGI scopy on both occasion revealed gastroduodenitis, CLO test was negative. Colonoscopy in 2006 revealed two sessile polyps, which were benign on histopathology and in 2010 was reported as normal. In 2009, he underwent umbilical hernia repair

elsewhere, which was complicated by severe intra-operative bleeding, necessitating ICU care for one month and multiple blood transfusions.

The erythropoietin requirement was noted to be progressively increasing. The haemoglobin profile and erythropoietin dose at various time periods are charted in **Figure 1**.

The persistent anaemia was initially thought to be due to his recurrent bleeding episodes, thalassaemia trait and intercurrent illness. However, after the hernia surgery in 2009, despite the high erythropoietin dose, haemoglobin remained persistently below 7.5 gm/dl. His medications included Ferrous sulphate, erythropoietin, Clopidogrel, atorvastatin, allopurinol, pantoprazole, calcium carbonate, neurobion and folic acid. Considering the large erythropoietin requirements and low haemoglobin, we evaluated him for erythropoietin hyporesponsiveness.

A detailed gastroenterology evaluation had conclusively ruled out any possible GI bleed. Considering functional iron deficiency, he was treated with a course of vitamin C, but haemoglobin remained the same. The serum PTH was within the recommended target for CKD stage 5, hence hyperparathyroidism was unlikely. Though chronic inflammation could not be conclusively ruled out, there was no obvious source of infection. Pure red cell aplasia was ruled out in the presence of a normal reticulocyte count.

A blood film was repeated and showed microcytic hypochromic anemia with tear drop cells, elliptocytosis and occasional normoblast-suggestive of leucoerythroblastic picture. Clinical examination was unremarkable except for the anaemia and right hemiparesis. There was no lymphadenopathy or hepatosplenomegaly.

Considering his persistent microcytic hypochromic anaemia with high serum ferritin, we thought of the possibility of myelodysplastic syndrome (Sideroblastic anaemia) and referred

him to haematology for further evaluation. Bone marrow aspirate and biopsy were done and surprisingly revealed 61% plasma cells with atypia and vacuolation, clinching the diagnosis of myeloma (**Figure 2**). Further myeloma work up revealed low levels of IgG, IgM, and IgA. The serum free light chain assay revealed markedly elevated kappa chains of 1215 ng/ml (normal: 3.3-19.4 ng/ml), with high kappa/lambda ratio of 87 (Normal: 0.26-1.65). No lytic lesions were seen on skeletal X-rays. The diagnosis of kappa light chain secreting myeloma was made, and this explained the anaemia. In fact, the only clue to the diagnosis of myeloma in this patient was refractory anaemia and erythropoietin hyporesponsiveness.

Investigations

Hb: 7 g/dl

MCV: 72.2 fL

WBC: 6100/cc

Platelets: 256000/cc

Retics: 2.8%

LDH: 255 U/L

Iron saturation: 34.7%

Ferritin: 1569 ng/mL

Serum Creatinine: 5.3 mg/dl

Urea: 126 mg/dl

Serum albumin: 4.2 mg/dl

Globulins: 2 g/dl

ALP: 130 U/L

ALT: 7 U/L

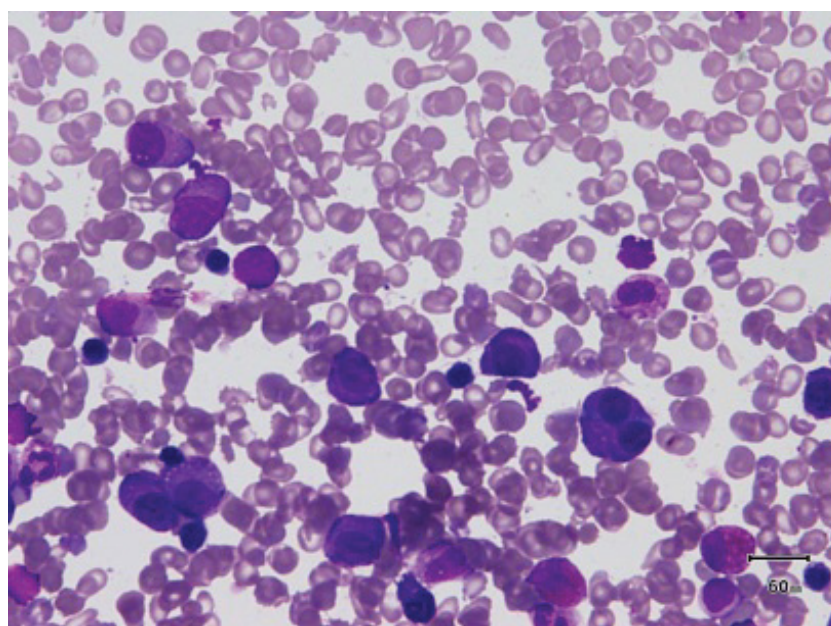


Figure 1 Haemoglobin profile and Erythropoietin requirement over time.

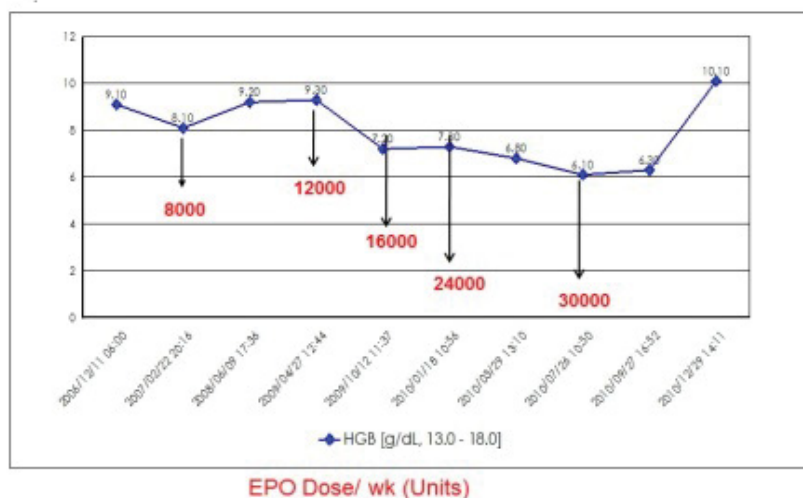


Figure 2 Bone Marrow Aspirate showing plasma cells (61%) with atypia and vacuolation, typical of myeloma.

Serum bilirubin: 0.8 mg/dl

Calcium: 8.7 mg/dl

Phosphate: 3 mg/dl

PTH: 96 pg/ml (Normal: 5-30 pg/ml)

Differential Diagnosis

The possibilities for anaemia we considered were:

1. Chronic Inflammation
2. Thalessemia Trait
3. Haematological disorder

Treatment

He received treatment for myeloma which included IV Bortezomib; however, he succumbed to the illness nine months after the initial diagnosis.

Outcome and Follow-Up

He succumbed to the illness nine months after the initial diagnosis.

Discussion

The anaemia of chronic kidney disease is associated with cardiovascular disease, decreased quality of life, and mortality. The introduction of recombinant human erythropoietin (rHuEPO) has transformed the management of this condition. Nevertheless, a significant number of patients fail to respond, even to high doses of rHuEPO. In patients with chronic kidney disease, erythropoietin resistance is common, costly, and has implications beyond the management of anaemia because the presence of erythropoietin resistance portends mortal outcomes.

Various renal organisations have come up with the definition of large EPO requirement. According to European Best Practice Guidelines, a continued need for >300 IU/kg per week when

administered subcutaneously is defined as an inadequate response to rHuEPO, while a somewhat higher threshold of 400 IU/kg per week is suggested if Epoetin is administered intravenously [1]. US guidelines define hyporesponsiveness as a failure, in the presence of adequate iron stores, to achieve and maintain the target haemoglobin (Hb) level at a rHuEPO dose of 450 IU/kg per week when administered intravenously or 300 IU/kg per week when administered subcutaneously [2].

It is not always easy to identify the cause of rHuEPO hyporesponsiveness. Thus, a stepwise approach is needed to investigate patients with a poor response to rHuEPO. The patients are stratified into three group anaemia by checking the mean corpuscular volume: microcytic, normocytic, and macrocytic. When the survey for folate or vitamin B12 deficiency reveals no abnormality in macrocytic anaemia, iron status should be assessed in the three groups [3].

There are many different possible causes of inadequate response to epoetin. Iron deficiency, whether absolute or functional, is considered to be the most important, and it is widely accepted that maintaining adequate iron levels reduces rh-Epo dosage requirement and improves efficacy in haemodialysis patients. Infection and inflammation have been shown to influence responsiveness to rh-Epo by disrupting iron metabolism and eliciting the release of cytokines that inhibit erythropoiesis. Another factor for consideration is severe hyperparathyroidism, which can lead to a reduced number of responsive erythroid progenitor cells. Inadequate dialysis can also negatively impact on rh-EPO therapy, and aluminium overload interferes with iron metabolism and reduces the efficacy of rh-EPO. Deficiencies in vitamin B12, folic acid and potentially vitamin C can all reduce the efficacy of treatment with rHuEPO. These have been summarised in **Table 1** [4].

Chronic infections, chronic non-infectious inflammatory states, and chronic blood loss need to be ruled out while evaluating erythropoietin hyporesponsiveness. Unsuspected malignancies and haematological disorders need to be considered in the iron replete patient with rHuEPO hyporesponsiveness. Although

Table 1 Potential causes of inadequate response to rHuEPO [4].

Major factors
Iron deficiency
Infection
Non- infectious inflammatory state
Chronic Blood loss
Minor factors
Hyperparathyroidism
Inadequate dialysis
Aluminium overload
Folic acid or vitamin B12 deficiency
Vitamin C deficiency
Malignancy
Drug intake (ACE Inhibitor)
Haemolysis and bone marrow disorders

most disorders associated with hyporesponsiveness are readily apparent, a review of available information on patients with coexisting hematologic or oncological disorders may be worthwhile. In our patient, other classical signs of myeloma like hypercalcemia, albumin/globulin reversal or skeletal involvement were absent, and the only clue to the diagnosis of light chain secreting myeloma was EPO resistance.

The patient with anaemia, chronic kidney disease, and a preexisting hematologic disorder represents an uncommon, but challenging, cause of ESA hyporesponsiveness and deserves special consideration. Studies have shown that patients with

thalassemia have a poor response to ESA and need higher doses of ESA to achieve target haemoglobin levels [5-8].

In myeloma patients with CKD on haemodialysis, higher doses of rHuEPO were required to achieve target haemoglobin levels [9]. Therapy with rHuEPO reduces transfusions and improves quality of life in myeloma patients with anaemia, with or without chronic kidney disease [10].

One could speculate whether the high doses of rHuEPO caused or worsened the myeloma in our patient, considering its oncogenic potential. It would be difficult to prove this. However, there have been many reports of successful use of rHuEPO in haemodialysis patients, to treat anaemia related to myeloma, especially after commencing chemotherapy [11].

Learning Points/Take Home Messages

Hyporesponsiveness to rHuEPO is an important issue in the treatment of anaemia of CKD. Among the many causes, iron deficiency is the most common and easily correctable one.

In the iron replete patient, a careful and systematic approach must be adopted to evaluate the inadequate response.

Conclusion

Once other common causes like inflammation and hyperparathyroidism have been ruled out, the physician should keep an open eye to look for unsuspected haematological disorders including marrow disorders and malignancy, for which the only clue could sometimes be the refractory anaemia.

References

- 1 Cameron JS (1999) European Best Practice Guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant* 14: 1-50.
- 2 National Kidney Foundation anemia working group (1997) NKF-K/DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. *Am J Kidney Dis* 30: S192-240.
- 3 Tarng DC, Huang TP, Chen TW, Yang WC (1999) Erythropoietin hyporesponsiveness: from iron deficiency to iron overload. *Kidney Int Suppl* 69: S107-118.
- 4 Druke T (2001) Hyporesponsiveness to recombinant human erythropoietin. *Nephrol Dial Transplant* 16: 25-28.
- 5 Cheng IK, Lu HB, Wei DC, Cheng SW, Chan CY, et al. (1993) Influence of thalassemia on the response to recombinant human erythropoietin in dialysis patients. *Am J Nephrol* 13: 142-148.
- 6 Di Iorio B, Guastaferrò P, Bellizzi V (2003) Relationship between resistance to erythropoietin and high anomalous hemoglobin levels in hemodialysis patients with beta-thalassemia minor. *Blood Purif* 21: 376-380.
- 7 Lai KN, Wong KC, Li PK, Lui SF (1992) Use of recombinant erythropoietin in thalassaemic patients on dialysis. *Am J Kidney Dis* 19: 239-245.
- 8 Di Iorio B, De Nicola L, Bellizzi V, Minutolo R, Zamboli P, et al. (2004) Efficacy of erythropoietin on dialysis in patients with beta thalassemia minor. *Blood Purif* 22: 453-460.
- 9 Powe NR, Griffiths RI, Greer JW, Watson AJ, Anderson GF, et al. (1993) Early dosing practices and effectiveness of recombinant human erythropoietin. *Kidney Int* 43: 1125-1133.
- 10 Dammacco F, Luccarelli G, Prete M, Silvestris F (2002) The role of recombinant human erythropoietin alpha in the treatment of chronic anemia in multiple myeloma. *Rev Clin Exp Hematol Suppl* 1: 32-38.
- 11 Ruedin P, Pechère Bertschi A, Chapuis B, Benedet P, Leski M (1993) Safety and efficacy of recombinant human erythropoietin treatment of anaemia associated with multiple myeloma in haemodialysed patients. *Nephrol Dial Transplant* 8: 315-318.