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Erythropoietin-Resistant Therapy in Routine Hemodialysis Patients: A Case Report

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ABSTRACT

Background: Anemia in chronic kidney disease can be caused by erythropoietin deficiency. Erythropoietin stimulating agent (ESA) is the treatment of choice for anemia in patients with chronic kidney disease. Some patients for some reason fail to reach target hemoglobin levels despite maximal ESA doses.
Case illustration: We reported a 58-year-old man suffering from CKD with recurrent anemia despite the maximum dose of ESA. The investigations showed secondary hyperparathyroidism due to complications of chronic kidney disorders.
Discussion: Our patient's resistance to erythropoietin therapy was caused by inadequate dialysis and secondary hyperparathyroidism. The management is focused on the adequacy of hemodialysis and the management of secondary hyperparathyroidism with nutrition and medication.

Keywords: anemia, kidney failure, hemodialysis, hyperparathyroidism.

INTRODUCTION

Anemia occurs in 80-90% of chronic kidney disease (CKD) patients. Hemoglobin (Hb) generally begins to fall when the patient's glomerular filtration rate (GFR) decreases as the glomerular filtration rate decreases.[1] Relative deficiency of erythropoietin (EPO) is the main cause of anemia in kidney disease. Therefore, ESA is the main therapy for anemia in CKD patients. ESA resistance is the failure to achieve a Hb increase of 0.5-1.5 g/dl in four consecutive weeks for 12 weeks or failure to maintain Hb within the maintenance target range.[2] Several factors might cause resistance to erythropoietin therapy, such as iron deficiency, chronic blood loss, malnutrition, inadequate dialysis, secondary hyperparathyroidism, inflammation, and acute blood loss. [3,4] This case report aims to learn about the stages of diagnosis and treatment of anemia in hemodialysis patients with suspected ESA resistance.

CASE ILLUSTRATION

Male, 58 years old, with a history of stage V renal failure as a complication of uncontrolled hypertension, routine hemodialysis two times a week since four years ago, complaining of feeling weak for the last two weeks. The patient complains of not having energy and getting tired quickly when doing activities. Complaints accompanied by palpitations and frequent dizziness.

On physical examination, he was conscious and vital signs were within normal limits. The conjunctiva was anemic, other physical examinations were within normal limits. Complete blood count results showed severe normochromic normocytic anemia with hemoglobin level was 4.81 g/dL, hematocrit level was 14.3%, MCV level was 81.42 fl, and MCH level was 27.9 pg. Kidney and liver function markers are within normal limit. Sodium level was 135 mmol/L, potassium level was 3.67 mmol/L, uric acid level was 2.7 g/dl, reticulocytes level was 0.4%, reticulocyte production index (RPI) level was 0.05, serum iron level was 187.84 gram/dl, total iron binding capacity (TIBC) level was 200 gram/dl, transferrin saturation level was 93.5% and ferritin level was 2308 ng/ml, calcium level was 8.7 mg/dl, inorganic phosphate level was 6.13 mg/dl , ESR value was 96 mm/hour, IL-6 level was 44.28 pg/ml, IL-2 level was 12.385 pg/ml, hs-CRP level was 4.1 mg/dl. Parathyroid hormone examination showed an increased intact PTH result of 715.2 pg/ml. The results of the vitamin D examination were decrease 10.1 ng/ml. The terminal FGF23c examination increase showed 5997 pg/ml.

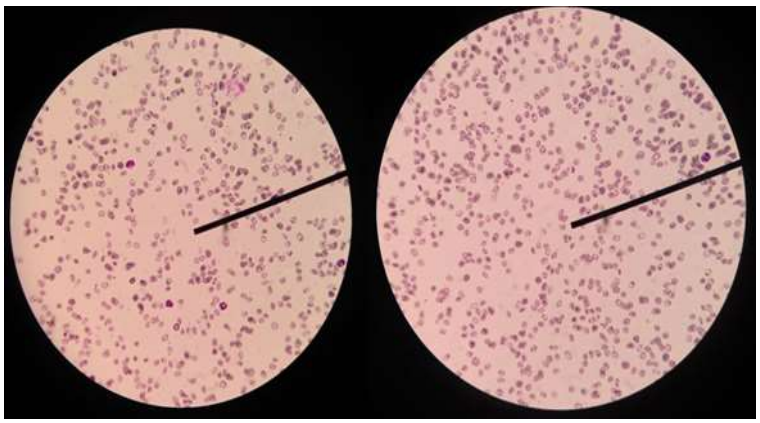

Figure 1. Peripheral blood smear showed that the erythrocyte population was normochromic normocytic with poikilocytosis, normal leukocyte count without immature cell, normal platelet count without giant thrombocytes with the impression of normochromic normocytic anemia.

The peripheral blood smear examination showed normochromic normocytic anemia (Figure 1). The bone marrow aspiration results found that the morphology of the myeloid series was dominant, decreased erythroid series and without blast cell was found in the preparation (Figure 2). The results of the chest X-ray examination with the impression of the heart and lungs did not show any abnormalities.

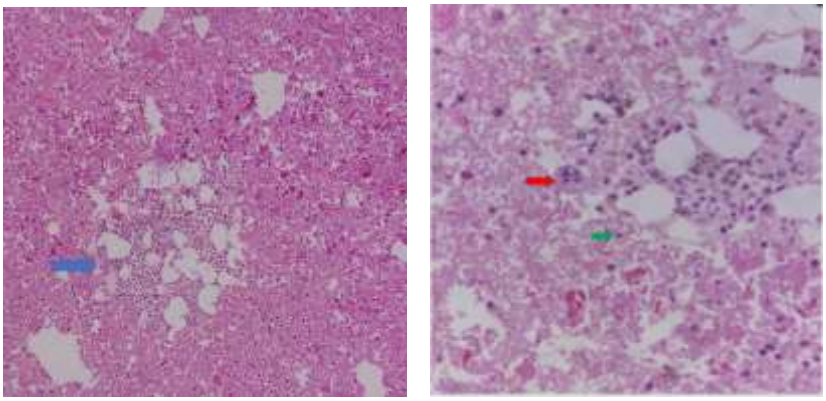

Figure 2. In bone marrow aspiration, the morphology of the myeloid series (➡) was dominant, the erythroid series (➡) is decreased and few megakaryocytes (➡)without blast cell was found in the preparation.

DISCUSSION

Anemia in CKD generally begins in the third stage of CKD and is always found in end-stage CKD. The pathogenesis of anemia in CKD is multifactorial, mainly due to an erythropoietin (EPO) deficiency.[5] EPO is mainly produced in the kidneys and then circulates and acts on tissue receptors throughout the body, especially in the bone marrow. EPO stimulates red blood cell production by binding to and activating the high-affinity receptor (EpoR), which is expressed primarily on the surface of immature erythroid cells to stimulate erythropoiesis.[6] The contribution of EPO deficiency increases as the GFR decreases. Iron deficiency is the second important factor as a cause of anemia in CKD. Studies have demonstrated the role of chronic inflammation and hepcidin as major mediators of impaired iron utilization in CKD patients.[7]

In this case, a patient with end-stage kidney disease has undergone hemodialysis routinely for two years. The laboratory test showed normochromic-normocytic anemia due to chronic disease. The normochromic-normocytic anemia is the most common in CKD. Although some patients also have microcytic hypochromic and megaloblastic anemia.[8] There were no signs of bleeding from the gastrointestinal tract or other source that might be a source of blood loss apart from the hemodialysis process. The results of the patient's fecal occult blood test (FOBT) were within normal limits. The results of the BMP examination did not support a condition of aplastic anemia or hematological malignancy in the patient. The results of the bilirubin examination were also normal, with a low RPI value excluding a condition of hemolytic anemia.

The condition of anemia with serum iron levels that tend to increase in cases characterized by high transferrin saturations and ferritin but must be interpreted with caution because they are influenced by inflammatory conditions through uremic toxin, underlying diseases, hemodialysis process. Soluble transferrin receptor (sTfR) and the ratio of sTfR/log ferritin (TfR-F index) can be used as parameter iron deficiency anemia that not influenced by concurrent chronic disease as well as inflammation but the examination is currently only for research.[9] Indications for ESA therapy are when Hb <10 g/dl and other causes of anemia have been ruled out, provided that there is no absolute iron deficiency anemia and no severe infection. ESA therapy is divided into a correction phase and a maintenance phase. The dose for erythropoietin is 80-120U/kg/week subcutaneously or 120-180U/kg/week intravenous (IV).[7] This patient was given epoetin in stages starting at 4000 IU/week. This dose was increased because the response to the increase in Hb was inadequate to 8000 IU per week (120 IU/kg/week). But patient still suffers from severe anemia and requires transfusion.

Inadequate response to ESA therapy is characterized by failure to achieve the target Hb increase of 0.5-1.5 g/dl during correction phase at a dose of 80-120 IU/kg/week subcutaneously or failure to maintain Hb within the maintenance target range. Suspicion of resistance to ESA therapy through calculating the Erythropoietin resistance index (ERI), an alternative method to measure the level of resistance to ESA therapy.[10] The patient had an ERI value of 18 IU/kg/week/g hemoglobin, ERI value >15 IU/kg/week/g hemoglobin indicate resistance to ESA therapy.

Several conditions that must be evaluated regarding suspected ESA resistance conditions are nutritional conditions, adequacy of dialysis, inflammation, and possible secondary hyperparathyroidism conditions.[11] In this case, the patient had adequate nutrition (BMI 24.8 kg/m2) but the patient's dialysis adequacy was lacking, marked by the calculation Kt/V is 1.56. According to The Kidney Disease Outcomes Quality Initiative (KDOQI), the adequacy of dialysis twice a week must reach Kt/V 1.8. Dialysis inadequacy can lead to chronic inflammatory conditions characterized by increased inflammatory

parameters in these patients and high levels of urea can reduce the response to ESA therapy. In this case, secondary hyperparathyroidism was also found, which was characterized by increased levels of intact PTH, hyperphosphatemia and vitamin D deficiency.

Treatments for patient include controlling the amount of phosphate-containing diet, vitamin D supplementation with or without addition of calcimimetics agent, and choosing the type of dialysis and adequate dialysis.[12] In patients with end-stage renal disease, hyperphosphatemia will occur, leading to secondary hyperpara-thyroidism. Secondary hyperparathyroidism stimulates PTH secretion, thus inhibiting bone marrow burst-forming erythroid units and shortening erythrocytes' life span. There is also an increase in FGF-23 levels, inhibiting erythropoiesis by suppressing EPO production, suppressing EPO receptor expression, and causing chronic inflammation. Administration of vitamin D analogs can reduce PTH hormone levels. Vitamin D supplementation therapy can be administered orally daily or intravenously in dialysis patients. During therapy with vitamin D, it is very important to ensure that serum phosphate and calcium are kept in controlled amounts to prevent calcification. In this patient, the administration of vitamin D supplementation was delayed due to the patient's high phosphate condition.

Beside increasing the frequency and length of dialysis sessions, the choice of dialysis strategy for this patient also plays a potential role in improving anemia control. [13] Uremic substances can suppress the erythropoiesis process, and it is believed that substances with large molecular weights, such as β2-microglobulin, play a role in inhibiting the erythropoiesis process. Compared to conventional dialysis, hemodiafiltration with endogenous reabsorption (HFR) has high solute and cytokine elimination but little adsorption of phosphate. Combination of conventional dialysis and HFR is expected to be able to remove uremic substances and remove excess phosphate effectively.[14] Definitive treatment of secondary hyperparathyroidism is surgical parathyroidectomy, if parathyroid hormone levels persist >800 pg/ml for >6 months, despite complete medical intervention.[15]

CONCLUSION

Resistance to erythropoietin therapy in this patient caused by chronic inflammatory conditions, inadequate dialysis, and secondary hyperparathyroidism. The management includes controlling the amount of phosphate-containing diet, medication for secondary hyperpara-thyroidism conditions, choosing the type of hemodialysis, and adequate dialysis. In this patient, the administration of vitamin D supplementation was delayed due to the patient's high phosphate condition, so a low-phosphate diet accompanied by the administration of a phosphate binder was prioritized in line with the selection and improvement of HD adequacy.

Conflict of Interest: None

REFERENCES

1. Portolés, J., Martín, L., Broseta, J. J., & Cases, A. Anemia in Chronic Kidney Disease: From Pathophysiology and Current Treatments, to Future Agents. Frontiers in Medicine. 2021. Available in https://doi.org/10.3389/fmed.2021.642296.
2. Kidney International Supplements. Clinical Practice Guideline for Anemia in Chronic Kidney Disease. 2012: 2. 282. Available in doi:10.1038/kisup.2012.40.
3. Perhimpunan Nefrologi Indonesia. Konsensus Manajemen Anemia pada Penyakit Ginjal Kronik ke-2. Jakarta. Pernefri. 2011:11-9.
4. Josef, Z., Pavel, H. Pathophysiology of anemia in chronic kidney diseases: A review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2015 Jun; 159(2):197-202.
5. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, classification and stratification. *Am J Kidney Dis* (39). 2012: 1.

6. Watowich, S.S. The erythropoietin receptor: molecular structure and hematopoietic signaling pathways. Journal of Investigative Medicine. 2011;59(7):1067-72.
7. Kandarini, Yenny. Mekanisme Anemia pada PGK dalam Anemia pada Penyakit Ginjal Kronik. Udayana University Press. 2021: 13-16.
8. Suega, Ketut., Bakta, Made., et al. Profile of Anemia in Chronic Renal Failure Patients: Comparision Between Predialyzed and Dialyzed Patients at The Division of Nephrology, Department of Internal Medicine, Sanglah Hospital, Denpasar, Bali, Indonesia. Acta Med Indonesia. 2005: 37.4.
9. Kandarini, Yenny., Mahadita, G.W., Herawati, S., Lestari, A.A.W., Suega, Ketut., Widiana, I.G.R. Soluble Transferrin Receptor and Soluble Transferrin Receptor/Log Ferritin Ratio are Correlated with Iron Status in Regular Hemodialysis Patients. The Indonesian Biomedical Journal. 2021; 13(2):106-220.
10. Kristina, P., Edita, Z., Vytautas, K., Irena, N., Inga, A B. Hepcidin serum levels and resistance to recombinant human erythropoietin therapy in hemodialysis patients. Medicina. 2017; 171:11.
11. Kamalas, A., Nattachai, S., Kitsada, W. et al. Factors associated with erythropoiesis-stimulating agent hyporesponsiveness anemia in chronic kidney disease patients. Hematology Reports. 2019; 11:8183.
12. Emanuel, Z., Ulrich, N. Management of Secondary Hyperparathyroidism in Hemodialysis Patients. In Progress in Hemodialysis - From Emergent Biotechnology to Clinical Practice. 2011: 331-48. Available in www.intechopen.com
13. Kevin, J., Martin, J. F., Markus, Ketteler. Bone and Mineral Disorders in Chronic Kidney Disease. Comprehensive Clinical Nephrology. Sixth edition. 2019: pp. 985-8.
14. Kandarini, Yenny. Manajemen GMT-PGK dalam : Gangguan Mineral dan Tulang pada PGK. Udayana University Press. 2021: 67-70.
15. Lau, W.L., Obi, Y., Zadeh, K.K. Parathyroidectomy in the Management of Secondary Hyperparathyroidism. Clin J Am Soc Nephrol. 2018; 13(6): 952–961.

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