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An Interesting Case of Erythropoietin-Resistant Anaemia

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ABSTRACT

Hyporesponsiveness to Erythropoiesis Stimulating Agents (ESA) or Erythropoietin(EPO), resistance occurs when the patient cannot reach normal haemoglobin levels even with the administration of ESA at higher-than-normal doses. We report a case of severe and persistent anaemia despite high doses of EPO and a trial of Desidustat (Prolyl Hydroxylase Inhibitor), while on conservative management for Chronic Kidney Disease. Bone marrow biopsy showed Pure Red Cell Aplasia and was managed with intravenous immunoglobulin (IVIG) for Parvovirus B19-induced PRCA. This case report emphasises the importance of bone marrow biopsy in EPO refractory anaemia in CKD patients and the role of IVIG and prolyl hydroxylase (PHD) hypoxia-inducible factor (HIF) inhibitors in the management of such patients.

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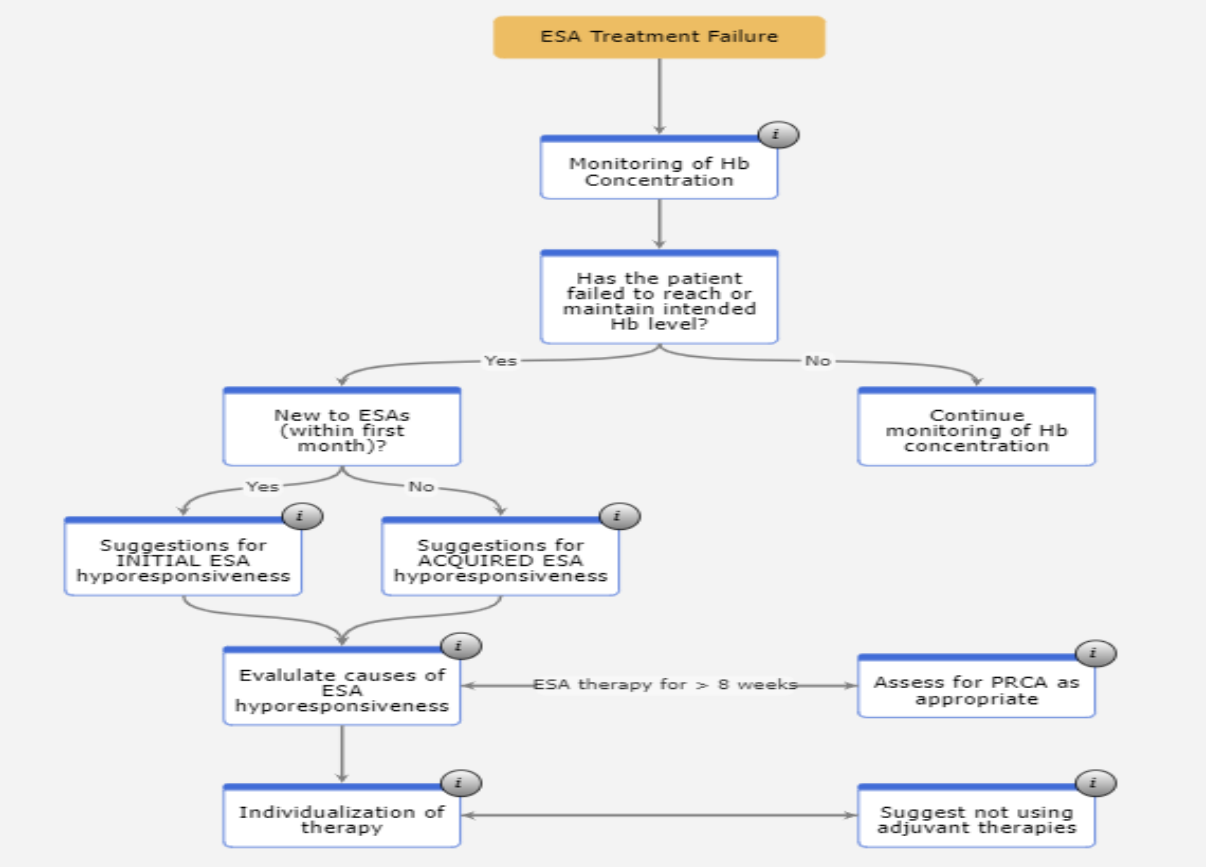
INTRODUCTION

EPO-resistant anaemia has been defined as the inability to maintain a desired haemoglobin level despite a dose of 450 U/kg/week of intravenous (IV) EPO, which is about 300 U/kg/week of subcutaneous EPO or 1.5 µg/kg/week of darbepoetin alfa using the Kidney Disease Outcomes Quality Initiative (KDOQI) criteria. [(1)] Patients with chronic kidney disease (CKD) have a relatively deficient erythropoietin (EPO) production, and this is the main cause of anaemia in this group. There is a marked variability in the response to EPO therapy and 5-10% of patients develop resistance to rhEPO therapy. Resistance to rhEPO therapy has been associated with inflammation, oxidative stress and functional iron deficiency, as major causes. [(2)]

Erythropoietin gene expression and EPO synthesis in the peritubular cells in the kidney are stimulated by hypoxia under the regulatory control of tissue Hypoxia Inducible Factor-1 (HIF-1). Prolyl hydroxylase (PHD) inhibitors offer a potential treatment alternative in CKD-induced anaemia by stabilising HIF, which improves erythropoiesis by increasing EPO generation and decreasing hepcidin. Desidustat is a novel PHD inhibitor to treat anaemia of CKD. Desidustat inhibited EPO resistance caused by rhEPO treatment, decreased hepcidin, IL-6 and IL-1β, and increased iron and liver ferroportin.[(3)] Patients on stable ESA therapy who experience a sudden rapid decrease in Hb should be evaluated for pure red cell aplasia.



Anaemia in CKD: ESA Failure[4]

Pure red cell aplasia (PRCA) is an uncommon condition characterised by normochromic-normocytic or normochromic-macrocytic anaemia, significantly low reticulocyte count, and a near absence of erythroid precursor cells in the bone marrow. [5] Acquired PRCA can be associated with factors such as neoplasms, thymoma, autoimmune disorders, pregnancy, or chronic infection with human parvovirus B19 in individuals with compromised immune systems. [6] Arrest of erythropoiesis leading to PRCA can be induced by cellular inhibition of the differentiation and survival of erythroid progenitor cells and erythroblasts or by soluble inhibitors (e.g. antibodies) directed against the erythroid progenitor and erythroblast or very rarely against the EPO molecule.[7] The diagnosis of PRCA requires a bone marrow examination and is based on the absence or near absence of erythroblasts.

In immunodeficient individuals, chronic anaemia caused by Parvovirus B19 infection is attributed to the specific suppression of erythropoiesis, resulting in low reticulocyte counts while maintaining normal platelet and granulocyte levels. [8] CKD-associated immune dysfunction, including impaired humoral and cellular immune responses exacerbates the susceptibility to Parvovirus-induced PRCA.

CASE REPORT

A 61-year-old lady with a history of Type 2 Diabetes Mellitus, hypertension, coronary artery disease and cerebrovascular accident, was under follow-up for chronic kidney disease from diabetic nephropathy. There was a drop in her haemoglobin levels corresponding to her drop in eGFR and she was started on EPO 4000 units once weekly. Her haemoglobin initially improved and stayed stable for 3 months. Later her haemoglobin dropped despite increasing her EPO dose to 14000 units per week. Her haemoglobin levels dropped to as low as 4.5 gm/dL and required multiple blood transfusions. EPO was stopped and she was started on an HFI inhibitor, Desidustat 100 mg thrice weekly. She was evaluated for other causes of anaemia including gastrointestinal blood loss and multiple myeloma. Her transferrin saturation and ferritin levels were normal with her peripheral smear showing normocytic normochromic anaemia with reticulocytopenia. Since her anaemia was not improving with haemoglobin remaining around 6 gm/dL, a bone marrow biopsy was done. The biopsy showed a mildly hypocellular marrow with marked erythroid hypoplasia, normal granulopoiesis, adequate megakaryocytes, and no increase in immature cells or blasts. The patient tested positive for Parvovirus B19 antibodies, and based on the severe anaemia and bone marrow findings she was diagnosed to have Parvovirus B19-related pure red cell aplasia.

The patient was started on intravenous immunoglobulin (IVIG) infusion, 100g in total over the course of 5 days. Her haemoglobin stabilised at 7.3 gm/dL at the time of discharge and was restarted on Desidustat 100mg thrice weekly to aid endogenous EPO production. Over the next 4 months after the IVIg administration she remained transfusion free with the haemoglobin level improving to 9.4 gm/dL at the last outpatient follow-up.

DISCUSSION

CKD is a chronic inflammatory state where persistent inflammation may contribute to the variability in Hb levels and hyporesponsiveness to erythropoietin stimulating agents (ESA) that precipitate into severe anaemia. Many anaemic chronic kidney diseases (CKD) patients are refractory to erythropoietin (EPO) effects due to inflammation, deranged iron utilisation, and generation of EPO antibodies. [9] Once EPO resistance sets in, increasing the EPO dosage will not have a significant effect on haemoglobin levels, rather might exacerbate EPO resistance due to EPO antibodies. Discontinuation of EPO treatment and blood transfusion

will be needed for EPO-resistant cases. Patients receiving ESA therapy and encountering a sudden decline in haemoglobin levels should undergo an evaluation to assess the possibility of pure red cell aplasia. PRCA may be linked to various factors, including neoplasms, thymoma, autoantibodies, pregnancy, or chronic infection with human parvovirus B19, especially in individuals with weakened immune systems.[6]

In our case of EPO hyporesponsiveness, the patient was initially managed by increasing rhEPO dose but due to persistent drop in haemoglobin, multiple blood transfusions were needed. The rhEPO treatment was stopped, suspecting ESA resistance. Other causes of persistent anaemia were investigated and her bone marrow biopsy confirmed PRCA. Further evaluation of PRCA, showed that her IgG antibody for parvovirus was positive, suggesting the diagnosis of Parvovirus B19 induced PRCA and hence IVIG treatment was initiated. Intravenous immunoglobulin (IVIG), which contains a large amount of anti–HPV-B19 IgG, is the treatment of choice for HPV-B19 PRCA.[3]. In patients with B19V-induced anaemia, treatment with IVIG is associated with favourable outcomes. The patient described here responded well to treatment with a total of 100 grams of intravenous immunoglobulin (IVIG) over a period of 5 days. Her reticulocyte levels normalised at the end of the IVIG therapy period, and haemoglobin levels gradually increased.

In addition to the IVIG therapy, the patient was provided with a desidustat, hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitor, used in the treatment of anaemia associated with chronic kidney disease (CKD). It inhibits prolyl hydroxylase domain enzymes, resulting in the stabilisation of hypoxia-inducible factor which stimulates erythropoietin production and erythropoiesis.[10] In patients switching from an ESA the recommended dosage of Desidustat is 100, 125 or 150 mg three times weekly, depending on the previous dose of epoetin, darbepoetin or methoxy polyethylene glycol-epoetin beta. The patient discussed here was given Desidustat 100mg thrice weekly. This case report highlights the importance of desidustat in the regular management of anaemia in CKD and in specific clinical settings like EPO resistance. With the above management, her haemoglobin levels improved over the next few months and is remaining transfusion-independent without the need for erythropoietin.

CONCLUSION

Our case highlights the clinical presentation of pure red cell aplasia, the role of IVIG in the treatment of Parvovirus B19-related PRCA and the usefulness of desidustat in the

management of PRCA. Prolyl hydroxylase inhibitor, Desidustat has the potential to address EPO resistance in CKD by enhancing endogenous erythropoietin synthesis and reducing hepcidin levels. Desidustat shows promise in the regular management of anaemia in the CKD population and in specific clinical settings like EPO resistance.

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CONFLICT OF INTEREST

There is no conflict of interest.

ABBREVIATIONS

CKD- Chronic Kidney Disease

PRCA- Pure Red Cell Aplasia

ESA- Erythropoiesis Stimulating Agents

EPO- Erythropoietin

PHD- Prolyl Hydroxylase

HIF- Hypoxia-Inducible Factor

KDOQI- Kidney Disease Outcomes Quality Initiative

IVIG- Intravenous Immunoglobulin

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