

Red Cell Aplasia in Chronic Kidney Disease Patient Treated With Erythropoietin: A Case Report

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ABSTRACT

Kidneys are the major source of erythropoietin production, anemia of chronic kidney disease is mainly caused by erythropoietin deficiency. Chronic kidney disease patients are treated with erythropoiesis stimulating agents (epoietin Alfa, epoietin beta), which is considered the gold standard for treatment of anemia in chronic kidney disease patients. One of rare and serious complication in patients treated by erythropoiesis stimulating agents is pure red cell aplasia, which is characterized by rapid decline in hemoglobin concentration of 5-10g/l per week, with normal count of white blood cells and platelets, and absolute reticulocyte count less than 10,000/ml. Pure red cell aplasia is treated by stopping erythropoiesis stimulating agents, cytotoxic drugs and peginesatide.

Key words: Chronic kidney disease, Erythropoietin, Pure red cell aplasia.

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Introduction

Pure red cell aplasia is very rare hematological disease which causes severe anemia. This disease may be congenital disorder like diamond-black fan syndrome, or an acquired disorder due to viral infections, thymoma, systemic lupus erythromatosus and lymphoproliferative disorders.^(1,2) Patients receiving erythropoietin stimulating agents more than 8 weeks rarely develop antibodies which neutralize both erythropoiesis stimulating agents (ESAs) and endogenous erythropoietin that results in immunological form of red cell aplasia called antibody mediated red cell aplasia, characterized by sudden development of severe transfusion-dependent anemia.⁽³⁾

Case Report

We present A 58 year old Jordanian male

diagnosed to have hypertension for the past ten years, ischemic heart disease for five years, and chronic kidney disease on hemodialysis for eleven years three times per week, presented with easy fatigability and inability to perform his usual activities. Physical examination revealed pallor with vital signs as follows: blood pressure 105/60 mmhg, temperature of 37c, pulse rate 104/min, ejection systolic murmur at the apex and enlarged palpable liver. The rest of the physical exam was unremarkable. His monthly laboratory results, WBC $6.9 \times 10^9/l$, PCV 22.2%, plat $169 \times 10^9/l$, MCV 86.7fl, PT 14 second, PTT 30 seconds, INR 1.0, BUN 57mg/dl, CR 6.9mg/dl, UA 8.0mg/dl, Serum albumin 36g, Total protein 65g, Alkaline phosphatase 156 unit, Serum Potassium 4.2meq/l, Serum calcium 9.3mg/dl, phosphorus 5.6mg/dl, AST 16 unit, ALT 18 unit, Urine analysis normal, Serum

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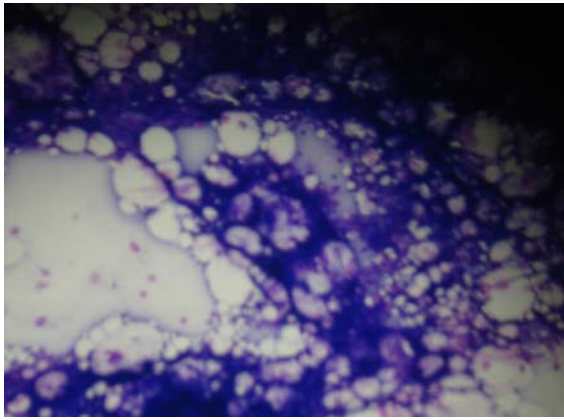


Fig. 1

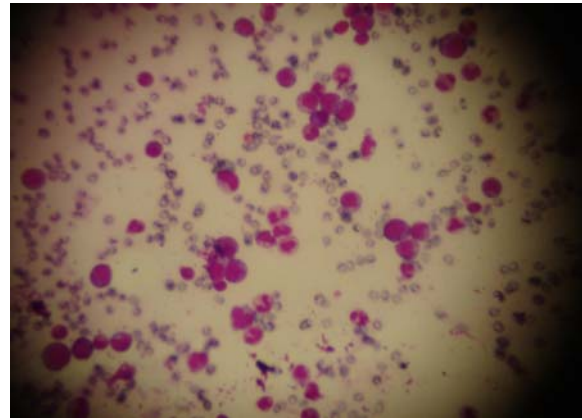


Fig. 2

Fig. 1, 2: Geimsa stained smears showing the bone marrow aspirate of the patient with absent erythroblasts

ferritin: 210mg/dl, transferrin saturation more than 25%, Serum B12: 512. He has been treated by erythropoietin 4000 iu s/c twice weekly, intravenous iron sucrose, and became blood transfusion dependant for last 6 months but his PCV was never over 27%. He was referred for hematology opinion who did for him bone marrow aspirate and biopsy, which showed normocellular bone marrow for age, the estimated cellularity was 45%, the erythroid precursors were absent, the granulocytic precursors are quantitatively normal with normal maturation and differentiation and with adequate megakaryocytes.

Figure 1 and 2 bone marrow aspirate smears showing normal megakaryocytes, absence of erythroid precursors with full maturation of myeloid series and hypocellularity.

The final diagnosis was consistent with pure red cell aplasia. Chest computed tomography did not show any evidence of thymoma or lymphoma. Steroids and cyclosporine were administered, Epoetin Alfa was discontinued, two weeks later the patient came for follow up to nephrology clinic asymptomatic with stable and normal vital signs, his PCV surprisingly was 33.2%. At present, the patient is treated by cyclosporine and steroids with no response. The patient became blood transfusion dependant as needed. This case represents the importance of considering red cell aplasia in chronic kidney disease patients treated for anemia with erythropoietin. Special factors to consider in these patients are erythrocyte stimulating agent's formulation, route of administration, and the patient co morbid risk factors.

Discussion

Antibody mediated pure red aplasia has a great attention after 1998, and reached significant peak in 2002 after administration of subcutaneous epoietin Alfa formulation. By 2004 antibody-mediated pure red cell aplasia has been significantly reduced after removal of this formulation from the market, outside this historical episode antibody associated pure red cell aplasia with subcutaneous use has been estimated to be 0.5/10.000 cases patient-years.⁽⁴⁾

The remarkable features of antibody mediated pure red cell aplasia are rapid decline in Hb concentration at rate of 4g/dl per month, and reticulocytopenia less than 10.000/ml.⁽³⁾

An Increase in skin reactivity at the site of injection of erythropoietin stimulating agents [intravenous or subcutaneous] has been reported as early indicator prior to development of antibody mediated pure red cell aplasia.

Bone marrow biopsy of patients with this disorder showed reduction or absence of erythroblasts, granulocytic precursors are quantitatively normal with normal maturation and differentiation, and with adequate megakaryocytes.⁽⁵⁾

Definitive diagnosis of antibody mediated pure red cell aplasia is by detecting the presence of neutralizing antibody against erythropoietin, by using immunological assays like enzyme-linked immunosorbent assays (ELISA) and radioimmunoprecipitation (RIP) assays.⁽⁶⁾

It was found that using erythropoietin (epoietin) deficient human serum albumin (HAS) administered subcutaneously was associated with

significant risk of antibody mediated pure red cell aplasia, while erythropoietin containing human serum albumin administered subcutaneously carries lower risk of development of antibody mediated pure red cell aplasia.⁽⁷⁾

After establishing the diagnosis of antibody-mediated pure red cell aplasia, the offending erythropoietin stimulating agents should be stopped and not to resume another epoetin derived ESAs. Immunosuppressive drugs has been used to remove circulating antibodies and hasten endogenous erythropoiesis, a number of immunosuppressive agents have been used in the treatment of red cell aplasia. Recovery from red cell aplasia is considered when reticulocyte count increases more than 20.000 per micro liter in patients who are no longer blood transfusion dependant. Steroids alone or combined with cyclophosphamide or cyclosporine were used with success between 50% up to 80% without relapse after stopping the immunosuppressive drugs. Peginesatide, a peptide - based erythropoietin. Receptor agonist was used in the treatment of red cell aplasia, which avoids using immunosuppressive drugs.⁽⁸⁾

Conclusion

Treatment of pure red aplasia still investigative in its nature, careful follow up of dialysis patients with sudden and rapid decrease in hemoglobin level and reticulocyte count coincide with absence of erythroid precursors in bone marrow biopsy can identify those with pure red cell aplasia.

Following diagnosis of pure red cell aplasia, the offending ESA should be stopped, trial of

steroids and immunosuppressive drugs can bring significant benefit. Uses of (peginesatide) a peptide-based erythropoietin receptor agonist brought excellent results and avoid the use of immunosuppressive drugs.

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