CLINICAL VIGNETTE

Suspected Pure Red Cell Aplasia in a 73-Year-Old Woman

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Case Presentation

A 73-year-old female with hypertension, hyperlipidemia, diabetes mellitus type 2, chronic diastolic heart failure, chronic respiratory failure with hypoxia, chronic pleural effusions, end-stage renal disease on hemodialysis, cirrhosis with recurrent ascites, paroxysmal atrial fibrillation, coronary artery disease, history of myocardial infarction and percutaneous coronary intervention, mitral regurgitation, chronic transfusion-dependent normocytic anemia, presented with dyspnea due to recurrent ascites. She had previous hospitalizations for weakness, ascites and acute on chronic anemia, requiring intermittent transfusions and paracenteses. During this hospitalization, an ultrasound-guided paracentesis was ordered and completed with 3.8 liters removed. Thereafter, the patient was noted to have decreased hemoglobin of 6.0g/dL requiring transfusion of 1 unit of packed red blood cells. The patient initially had improvement of her hemoglobin to 7.2g/dL, however the following day it decreased to 6.6g/dL, requiring transfusion of 2 additional units of packed red blood cells. No overt bleeding including melena, hematochezia or hematemesis was noted and CT abdomen and pelvis did not demonstrate any intra-abdominal bleed. Hematology was thus consulted during hospitalization given ongoing workup of her anemia of unclear etiology.

A bone marrow biopsy had been performed prior to admission. It demonstrated normocellular marrow with tri-lineage hematopoiesis with relative erythroid hypoplasia and granulocytic hyperplasia. Other evaluations included immunohistochemistry for parvovirus and MDS FISH panel and were negative. The patient's bone marrow noted increased iron storage before admission. She had complete output the patient had also received a thorough gastroenterology workup. The bone marrow biopsy also showed significant erythroid hypoplasia suggestive of pure red cell aplasia. This may have been due to the epoetin alfa treatment. She was started on oral Cyclosporine 150mg twice a day and erythropoietin was held. Her hemoglobin level improved to 8.8g/dL and increased to 10.0g/dL at discharge. After discharge she continued to have intermittent episodes of acute on chronic anemia requiring transfusions. This was thought to be multifactorial from pure red cell aplasia as noted above, as well as end-stage renal disease and cirrhosis.

Discussion

Pure red cell aplasia (PRCA) is characterized by normochromic, normocytic anemia, low reticulocyte count, and a lack of erythroid precursors in the bone marrow. Normal white blood cell and platelet counts are observed unless there is an underlying hematologic disorder. It is rare and can be due to various causes. PRCA is categorized as primary (including a primary autoimmune cause such as IgG-mediated inhibition of erythropoiesis, clonal myeloid or lymphoid disorder), versus secondary (from autoimmune disorders such as systemic lupus erythematosus, lymphoproliferative disorders, ABO-incompatible stem cell transplantation, non-hematologic neoplasms, infection such as B19 parvovirus, drugs).[1] In secondary causes of PRCA, the underlying mechanism may be due to T-cell mediated processes.[1,2] One type of acquired PRCA is anti-erythropoietin (EPO) antibody-mediated PRCA associated with patients on dialysis. The incidence of cases of EPO-associated PRCA increased in 1998. This was associated with use of recombinant human erythropoietin, initially marketed outside of the United States. This was linked to the method of packaging and preparation, with incidence peaking in 2001-2002. It has since returned to baseline after changes in formulation and administration.[1,3]

The diagnosis of PRCA is generally confirmed with bone marrow biopsy, with absent or near-absent erythroblasts (<1% to 5% of total cellularity and increased myeloid:erythroid ratio).[2] Other bone marrow diagnoses are suggested if there is erythroid dysplasia, ringed sideroblasts, or ineffective erythropoiesis. Initial evaluation for PRCA includes peripheral smear, complete blood count, reticulocyte count, Coombs test, rheumatologic studies, serum electrophoresis, serum immunofixation, immunoglobulin levels, and virological studies. Bone marrow studies include: standard aspirate and biopsy stains, cellular immunology, as well as standard cytogenetics.[1,2] T-cell receptor gene arrangement studies may be ordered to rule out clonal T-cell disorders and large granular lymphocyte (LGL) leukemia. STAT3 mutations may be seen in LGL leukemia.

Treatment varies by the cause and includes supportive care, treatment of underlying disorders, and immunosuppressive therapy with agents such as glucocorticoids and Cyclosporine. This patient had possible PRCA related to EPO administration, and EPO was discontinued.[4] Another patient with thymoma-associated PRCA was recommended to have thymectomy followed by immunosuppressive therapy. Cyclosporine is considered the first-line immunosuppressive agent. It is most effective, with a response rate of 70-75%, and requires monitoring of renal function. If effective, a response can be seen in

6-8 weeks up to 3 months after initiation[2]. Corticosteroids can also be used as a first-line agent or in conjunction with Cyclosporine. Treatment with immunotherapy is considered if patients do not have a concurrent self-limiting illness and have severe anemia for 3-4 weeks. With refractory disease, treatment with a cytotoxic agent such as Cyclophosphamide, Azathioprine, or Sirolimus is pursued. Alemtuzumab can be considered in refractory cases, but increased risk of infection must be weighed given more profound immunosuppression. Prognosis for PRCA is good with appropriate therapy. While there are various effective options for treatment of PRCA, many patients require ongoing treatment to maintain remission. Treatment options are often limited by side effects.[5] Studies that analyze and recommend the best treatment strategy are challenging given the rarity of disease, differences in treatment approaches and duration of follow-up which affects interpretation of treatment efficacy.[6]

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