Successful Treatment of Pure Red Cell Aplasia Secondary to Chronic Lymphocytic Leukemia Using Cyclosporine A

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Pure red cell aplasia is a rare disease in which the erythroid precursors in the bone marrow are selectively destroyed, resulting in severe anemia. The classical presentation is normochromic normocytic anemia, with reticulocytopenia but no other evidence of bone marrow dysfunction (e.g., dysplasia, leukopenia). In cases where no apparent trigger can be identified PRCA is defined as primary or idiopathic. In many cases this severe phenomenon is caused by another underlying condition such as thymoma, various hematologic malignancies or collagen vascular diseases, or it might be caused by drugs (phenytoin, azathioprine, isoniazide), infections (parvovirus B_{19}, human immunodeficiency virus) and even pregnancy. In these instances PRCA is defined as secondary, with a presumed immunologic pathogenesis [1]

Chronic lymphocytic leukemia is a common hematologic neoplasm where malignant B lymphocytes circulate in the peripheral blood and invade lymphoid organs. This leukemia is also known for its propensity to cause immune cytopenias, the most common being autoimmune hemolytic anemia which affects up to 15% of patients. Pure red cell aplasia is uncommon in this population, occurring in 1%–6% of CLL patients [2,3]. The occurrence of anemia in a CLL patient is usually attributed to marrow occupation by the tumor or to autoimmune hemolytic anemia. The diagnosis of PRCA in this setting requires a high index of suspicion and, when suggested, a bone marrow aspiration or biopsy is required. The purpose of these inspections is to examine the marrow's erythroid precursors and to rule out other causes of anemia in CLL. We present the rare case of a patient with known CLL who suddenly developed pure red cell aplasia.

PRCA = pure red cell aplasia
CLL = chronic lymphocytic leukemia

PATIENT DESCRIPTION

The patient, a 68 year old man who was diagnosed with CLL at the age of 62, was hospitalized in March 2012 due to symptomatic anemia. His disease was notable only for a +4 positive immunoglobulin G antiglobulin test (DAT, direct Coomb's test) with no evidence of hemolysis. His CLL remained stable at Rai stage I for 6 years and he therefore did not need any treatment. He was medically treated for hypertension and had mild chronic renal failure with creatinine levels of 1.1–1.5 mg/dl. At the age of 66 he underwent a coronary balloon angioplasty with stent insertion in the right coronary artery.

On admission he presented with a sudden onset of severe anemia with hemoglobin 4.3 g/dl, manifesting as angina pectoris and 2 mm anterolateral ST depression on electrocardiogram. Initial workup also revealed 99,140 white blood cells/μl with 83% lymphocytes, 3% neutrophils and 53,000 platelets/μl. DAT was again strongly positive with detection of immunoglobulin-G on red blood cells, but with no evidence of hemolysis (bilirubin, lactate dehydrogenase and haptoglobin levels were all within normal range). Reticulocyte count was 7000 cells/μl (less than 0.5% of red blood cells). Peripheral blood smear revealed abundant small lymphocytes, with dense nuclear chromatin, as expected in CLL. We also noticed thrombocytopenia, and no reticulocytes, spherocytes or fragmented cells. A thorough anemia workup including parvovirus B_{19} serology yielded no findings, and there was no bleeding.

The patient was promptly treated with packed red blood cell transfusions until resolution of the ischemic complaints. We also reassessed his CLL status. Physical exam revealed mild axillary and cervical lymphadenopathy and an enlarged spleen was palpated 4 cm below the costal margin. Bone marrow aspiration and biopsy showed extensive and diffuse marrow infiltration by small lymphocytes, consistent with CLL. Normal hematopoiesis was hardly detected and erythroid precursors were lacking. Fluorescent in situ hybridization demonstrated deletion of chromosome 13q in 95% of tumor cells.

We now faced the dilemma of whether this patient had advanced (i.e., stage IV) CLL or stage II CLL with concomitant immune cytopenia. This differentiation is not merely academic: stage IV CLL warrants anti-neoplastic therapy while early-stage CLL with immune complications usually requires immunosuppressive treatment, targeting the immune dysregulation rather than the malignant clone. While hospitalized the patient was started on prednisone 1 mg/kg/day for a possible immune cytopenia; however, the complete lack of response after 2 weeks along with the massive infiltration of marrow led us to the conclusion that active and advanced CLL was the main reason for the cytopenia.

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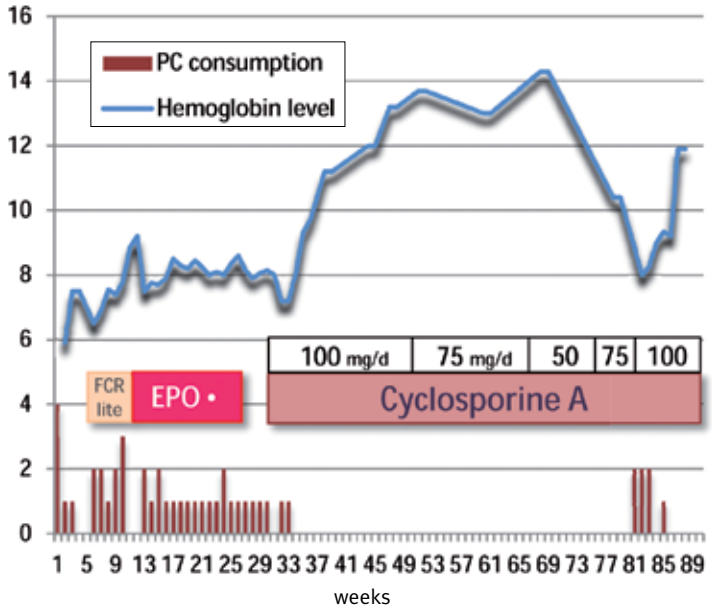
Figure 1. Treatments and their effect on the patient's anemia. Note the drop in hemoglobin and renewal of blood consumption while tapering the cyclosporine A dose, and prompt response upon dose return to 100 mg/day.



EPO = erythropoietin-alpha, FCR lite = reduced dose of fludarabine, cyclophposphamide and rituximab

We initiated combination therapy with rituximab and an attenuated dose of fludarabine and cyclophosphamide according to the Israeli clinical trial protocol (FCR-lite) to which the patient was recruited. Treatment was begun 6 weeks after his presentation [Figure], and the second cycle was administered 4 weeks later. His WBC and lymphocyte counts promptly dropped, normalizing 10 days since the first day of therapy. However, treatment had to be stopped after two cycles (out of six planned) due to persistent neutropenia, and the patient was excluded from the trial. Although the platelet count gradually improved over time, his neutrophils did not recover and his hemoglobin was hardly affected by the treatment. On week 10 we initiated subcutaneous administration of recombinant erythropoietin-alpha at the standard dose of 40,000 units/week. This treatment lasted for 16 weeks but had no effect. The patient continued to be transfusion dependent, requiring on average 1 unit of packed red blood cells per week to prevent angina [Figure]. On week 18 we performed a second bone marrow aspiration and biopsy in view of the persisting anemia and leukopenia. Again, bone marrow was heavily infiltrated by CLL cells, albeit to a lesser extent than at diagnosis. Although some foci of hematopoiesis could be seen, still no erythroid precursors were evident.

On reassessing the patient's data we reached the conclusion that his anemia was caused by secondary PRCA. Since prednisone had failed to ameliorate his anemia in the past, we decided to switch to cyclosporine A. Because of borderline baseline renal function and already decreased immune function, we began therapy with a low dose of approximately 1 mg/kg/day in two daily doses. Treatment started in week 32, and by week 34 a steep rise in hemoglobin level obviated the need for transfusion. We started tapering down the dose gradually at week 51, but after several weeks while on a dose of 50 mg/day he again developed severe anemia requiring hospitalization and blood transfusions. The patient was put back on cyclosporine A dose of 100 mg/day in week 81 resulting in a rapid response [Figure]. He is now in the 90th week of follow-up, free of transfusions with no documented infection or worsening renal function.

COMMENT

Anemia in CLL can be attributed to several causes. The obvious explanation, especially in advanced cases, is marrow infiltration by the malignant clone. Another common etiology is autoimmune hemolytic anemia, reported to occur in 10–15% of CLL patients [2]. Other less frequent causes include chemotherapy-induced anemia, evolution of a myelodysplastic syndrome, and PRCA. The latter complication is infrequent with several possible mechanisms; however, the most plausible explanation is immunologic attack. Although CLL is a disease of malignant B cells, the immune complications accompanying it, including PRCA, are probably T or NK cell derived. Activated T/NK cells, referred to as large granular lymphocytes, from CLL patients have been shown to inhibit erythroid growth in vitro. Patients with CLL and pure red cell aplasia have increased numbers of LGL in marrow, and remission of PRCA in many cases correlates with clearance of these cells. Of note, the two diseases most frequently associated with PRCA are thymoma and LGL leukemia, both of which are T/NK cell neoplasms [4].

As a general rule, treatment of the underlying disorder, if feasible, is always preferred to treating the complication itself. However, as demonstrated by our patient, this is not always the case in CLL. In these instances second-line drugs, usually agents with immune-modulating properties, are chosen. The drawback with these drugs is the increased risk of infections and/or secondary malignancies resulting from prolonged immune suppression. It is important to remember that

WBC = white blood cell

LGL = large granular lymphocytes

CLL patients are already at increased risk for developing such late complications, rendering the decision to start immune modulators even more complicated.

Several treatment options are available for patients with pure red cell aplasia in general; all are relevant for CLL patients as well [1,3]. In many cases prednisone is the first agent used, initiated at a dose of 1 mg/kg/day. Response occurs in 30–60% of patients and is usually evident by 2–3 weeks of treatment. On tapering the dosage, up to 80% might relapse and of those, 80% respond to retreatment with steroids. Still, the side effects accompanying this regimen – such as hyperglycemia, myopathy, edema, infections and compression fractures – result in a high rate of discontinuation. Another well-described agent is cyclosporine A, probably modulating its effect through inhibition of interleukin-2 necessary for cytotoxic T cell activation. The usual dose ranges from 5 to 12 mg/kg/day, yielding a response rate of 65–87%. Sawada et al. [5] found that within 1 month of cyclosporine A treatment 74% of their patients no longer needed transfusion. Again, stopping the drug might cause relapse, and many advocate using cyclosporine A also as a maintenance regimen in PRCA, albeit at increased risk of renal failure, infections or malignancy [2,3]. Other treatments, such as cycolphosphamide, anti-thymocyte globulin, rituximab, alemtuzumab and intravenous immunoglobulin, or various combinations, have been described. The evidence level supporting these agents is lower, although they have been used successfully in various settings. Of note, in vitro immunoglobulins are considered effective especially when pure red cell aplasia is caused by parvovirus B_{19} infection. Rituximab and alemtuzumab are two monoclonal antibodies targeting CD_{20} and CD_{52}, respectively, with proven efficacy in CLL. Each has been reported, separately, to have activity in pure red cell aplasia and is therefore a valid option in patients with CLL-related PRCA, especially in refractory cases. Again, data are still too sparse to generate definite recommendations.

In conclusion, we have described an infrequent occurrence of pure red cell aplasia in a previously known CLL patient, whose anemia clearly responds to cyclosporine A treatment. A bone marrow examination is necessary whenever anemia and reticulocytopenia occur in the presence of a normal anemia workup. Absence of erythroid precursors is the hallmark of this rare diagnosis and a mandatory key to providing adequate treatment.

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“The luck of having talent is not enough; one must also have a talent for luck”

Hector Berlioz (1803-1869), French composer

“Manners are a sensitive awareness of the feelings of others. If you have that awareness, you have good manners, no matter what fork you use”

Emily Post (1872-1960), American author and columnist famous for writing on etiquette