Acquired Pure Red Cell Aplasia in a Patient of Rheumatoid Arthritis

Prasant Kumar Parida · Shilin N. Shukla ·
Shailesh S. Talati · Sonia K. Parikh

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Abstract Pure red cell aplasia (PRCA) is characterized as a normocytic anemia associated with reticulocytopenia and the absence of erythroblasts in the bone marrow. PRCA can be induced by various causes such as thymoma, connective tissue disease, viral infection, lymphoma, and adverse drug reactions. There have been only a few reports of PRCA associated with rheumatoid arthritis (RA). We report a 45 year old female presented with symptomatic anemia of several months duration on a background of long standing seropositive deforming RA. Bone marrow examination revealed marked suppression of erythroid precursors with normal myeloid and megakaryocytic series, thereby confirming PRCA. Anemia improved following therapy with prednisolone 1 mg/kg/day. This article also reviews the current status of therapy in acquired PRCA.

Keywords Pure red cell aplasia (PRCA) · Rheumatoid arthritis (RA) · Normocytic anemia · Thymoma · Corticosteroids (CS)

Introduction

Acquired pure red cell aplasia is a rare, generally chronic condition of profound anemia characterized by a severe reduction in the number of reticulocytes in the peripheral blood and the virtual absence of erythroid precursors in the bone marrow. Acquired PRCA in the adult is most often idiopathic, although a number of underlying causes can exist.

PRCA can be induced by diseases such as thymoma, connective tissue disease, viral infection, lymphoma, and adverse drug reactions. There have been only a few reports of pure red cell aplasia associated with rheumatoid arthritis.

Here we describe a case of long standing rheumatoid arthritis with severe refractory anemia, which was proven to be due to PRCA and it responded to steroid therapy.

Case Report

A 45 year old female presented with history of weakness, fatigue and breathlessness on exertion since 6 months. There was no history of orthopnea, paroxysmal nocturnal dyspnea, dependent edema, syncope, tingling of the extremities and cutaneous bleeding in any form. She had history of chronic arthritis for last 10 years, and she was taking NSAIDs, as and when necessary for joint pain, and there was no history of immunosuppressant therapy. She was transfused with ten units of whole blood over the last 6 months. There was no other extra-articular manifestation.

On examination, apart from pallor, general physical examination revealed no abnormality. On systemic examination there was boutonniere and swan neck deformity in small joints of hand and foot. All other systems were within normal limits, except a functional systolic murmur.

Investigations

Hb = 4.2 gm%, PCV = 12 %; RBC count = 1.5 million/cumm, Retic = 0.4 % (corrected reticulocyte count = 0.042 %). However, red cell indices were within normal limits. Peripheral smear shows anisopoikilocytosis, normocytic normochromic red cells with occasional microcytic and hypochromic cells. The total count was 4,200/ μ L,

P. K. Parida (✉) · S. N. Shukla · S. S. Talati · S. K. Parikh
Department of Medical and Pediatric Oncology, Gujarat Cancer
and Research Institute (GCRI), Asarwa, Ahmedabad 380016,
India
e-mail: drprasantdm@gmail.com

and her platelet count was 265,000/ μ L. Tests for hemolysis including osmotic fragility, G6PD, coombs test, sickling test were negative and LDH was normal. Renal and liver function tests were within normal limits, Stool for occult blood and ova—negative. Serology for HIV, HCV and HBV were negative. Serum antinuclear and anti-dsDNA antibodies were negative. The results of a chest X-ray, abdominal ultrasonography, and CT scan of chest (to rule out thymoma) were normal. Her X-ray of hand showed joint deformity and bone erosion.

Serum rheumatoid factor was significantly raised (RF = 124.23 IU/ml, Ref range <30 IU/ml). Her ESR was 135 (after 1 h) and CRP was positive. So in view of chronic symmetrical arthritis, joint deformity, significantly raised RF and evidence of bone erosion, she was diagnosed to be a case of Rheumatoid arthritis.

Bone marrow aspiration (Fig 1) and trephine biopsy revealed marked suppression of erythroid precursors, but myeloid precursors and megakaryocytes were well preserved. Marrow was normocellular with staining for iron and reticulin were negative and there was no evidence of dyshemopoiesis. As a result of severe anaemia with the reticulocyte count being <1 % and mature erythroblasts in a normocellular marrow being <0.5 %, she was diagnosed as a case of PRCA associated with Rheumatoid arthritis. Then she was started treatment with prednisolone 1 mg/kg/day. Our patient responded to prednisolone with improvement of symptoms and rising Hb level. Her Hb was completely normalized after 2 months of starting treatment. Then prednisolone gradually tapered. But she relapsed after 8 months with progressive anemia, for which she was started on CsA and prednisolone.

Discussion

Pure red cell aplasia is a disorder that was first described in 1922 by *Kaznelson* and is characterized as a normocytic

Fig. 1 Bone marrow aspirate showing markedly decreased erythroid series with normal myeloid and megakaryocytes

anemia associated with the absence of erythroblasts in the bone marrow. It is a progressive normochromic anemia with no signs of regeneration in the peripheral blood, no polychromasia, no reticulocytes, with normal leukopoiesis and thrombopoiesis and no enlargement of the spleen or lymph nodes [1]. It may be congenital or acquired. In the Congenital PRCA there is injury to the stem cells in utero [2].

The acquired form of PRCA presents either as an acute self-limited disease, predominantly seen in children, or as a chronic illness that is more frequently seen in adults. It may present as a primary hematological disorder in the absence of any other disease, or secondary to causes such as thymoma, autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, malignancies (leukemia, lymphoma, multiple myeloma, and carcinomas of several organs), drugs (alpha interferons, lamivudine, INH, diphenylhydantoin, sodium valproate, carbamazepine etc.) and infections like infectious mononucleosis, viral hepatitis, parvovirus B19 and tuberculosis [2]. Acquired primary PRCA commonly occurs at a mean age of 60 years. The male to female ratio is 2:1.

Pathogenesis involves immune dysfunction with antibodies directed against erythroid precursor cells or erythropoietin, or due to T cell mediated suppression of erythropoiesis [2]. This is based on a number of studies implicating a pathological role of serum auto-antibodies, natural killer (NK) cell-mediated or T lymphocyte-mediated effects impairing various stages and mechanisms of erythropoiesis as extensively reviewed by Fisch et al. [3].

The major objective in the treatment of PRCA is to induce a remission with the recovery of erythropoiesis, thus providing relief from transfusions and avoiding transfusion-associated problems. The therapeutic plan usually focuses on the sequential use of various immunosuppressive therapies until a remission is obtained. Remissions have been achieved by treatment with corticosteroids (CS), cyclophosphamide (CY), cyclosporine A (CsA), anti-thymocyte globulin (ATG), splenectomy, and plasmapheresis. In general, remission can be easily achieved in the majority of patients. To date, the efficacy of CS, CY and CsA for patients with primary or secondary PRCA has been reported to be between 30 and 62, 7 and 20, 65 and 87 %, respectively [4] (Table 1). More recently, the efficacies of the anti-CD20 monoclonal antibody, rituximab, and anti-CD52 monoclonal antibody, alemtuzumab to induce remissions of therapy-resistant PRCA have also been reported [5, 6].

Other therapeutic options like thymectomy has been recommended as the initial treatment of thymoma-associated PRCA, with an expected haematological response rate of 25–30 % [7]. Intravenous immunoglobulin (IVIG) contains neutralizing antibody against parvovirus B19 and has been reported to be effective for PRCA due to parvovirus B19 infection [2, 8]. PRCA due to autoantibodies

Table 1 Treatment of pure red cell aplasia (PRCA)

Agent	Response rate	Mean time to response	Need for maintenance therapy
Corticosteroids; CS (methyl-prednisolone/prednisolone)	30–62 %	2–5 weeks	Required (most patients relapsed during the taper of CS)
Cyclosporine A; CsA	65–87 %	12 weeks in patients with primary idiopathic PRCA (65 % of responders achieved remission within 2 weeks)	Required in patients with primary idiopathic PRCA (86 % relapsed after discontinuation of CsA while 11 % relapsed during the maintenance of CsA)
Cyclophosphamide; CY (CY + CS)	7–20 % (40–60 %)	11 weeks	Unknown: required in some patients

against endogenous EPO are rare, usually seen in recombinant human EPO (rhEPO) treated patients. Recently, a novel peptide based EPO receptor agonist called Hematide has been developed, which could be a treatment option for rhEPO-related PRCA.

Although vigorous immunosuppressive treatments induce and maintain remissions in a majority of patients of PRCA, they carry an increased risk of serious complications. CS has been considered the treatment of first choice although relapse is not uncommon. CsA has become established as one of the leading drugs for treatment of PRCA. Recently, the efficacies of the anti-CD20 monoclonal antibody, rituximab and anti-CD52 monoclonal

antibody, alemtuzumab, to induce remissions of therapy-resistant PRCA have also been reported.

Conclusion

Here we reported a rare case of PRCA associated with long standing rheumatoid arthritis. The case was treated with CS and transfusion, reflecting the previous literature. The patient showed an early response to corticosteroids and successfully achieved remission after 2 months of treatment. So we conclude that PRCA is a rare but treatable cause of anemia in RA and should be considered when there is severe normochromic anemia in the absence of obvious blood loss or hemolysis.

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