Pure Red Cell Aplasia, a Disease of a Great Diversity

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Abstract:
Pure red cell aplasia (PRCA) is a type of normocytic or sometimes macrocytic anemia characterized by reticulocytopenia. The cause of hypo erythropoiesis is varied. It could be of a congenital or an acquired type. A congenital PRCA is different than anemia caused by congenital dyserythropoiesis. The classification of acquired PRCA can be primary when no cause is identified or secondary due to underlying or associated pathology. The primary PRCA is a disease of exclusion. There are many disorders such as autoimmune disorders, hematological and nonhematological malignancies, some infections, and medications that cause secondary PRCA. Immune-mediated mechanism plays an important role in both primary and secondary types. Therefore, immunomodulating agents are important in the treatment of primary type and many secondary types. Other therapy modalities include surgery, plasmapheresis, and hemopoietic stem cell transplantation. The assessment of hemoglobin level and absolute reticulocyte count with the frequency of blood transfusion are important to monitor therapy response achievement. Achievement of complete response is important to eliminate demands for blood transfusion and to avoid blood-transfusion risks. Herein, we review this disorder which has broad diversity, its causes, approach to its cause, therapy modalities.

Keywords: Dyserythropoiesis, pure red cells aplasia, reticulocytopenia

Introduction

Pure red cell aplasia (PRCA) is a type of malproductive disorder characterized by isolated normocytic, or sometimes macrocytic, normochromic anemia with marked reticulocytopenia as absolute reticulocyte count is <10,000/μL (or <1%) due to marked hypoproliferative erythropoiesis.[1,2] The other blood cell lineages are usually normal in PRCA unless another concurrent disorder is co-existing.[1,2] PRCA could be a congenital disorder or acquired one.[2] The therapeutic options of PRCA depend on its associated or underlying pathogenesis.[1] This article has a brief review of PRCA classification, underlying or associated disorder, diagnosis, and treatment.

Classification of pure red cell aplasia
PRCA is broadly classified into a congenital type and an acquired type [Table 1]. The most common well-known congenital PRCA is Diamond-Blackfan anemia (DBA) or Diamond-Blackfan syndrome.[1,3] DBA is a type of congenital PRCA that is presented in early infancy and associated with dysmorphic features due to mutational defects involve ribosomal proteins genes.[1] Strabismus, webbed neck, thumb and finger abnormalities, inverted nipples, renal anomalies, and hypogonadism are possible findings in those patients with DBA.[3] There is no clear identified cause of DBA, but it is believed that it is linked to a defect in purine metabolism.[3] The anemia of Diamond-Blackfan syndrome is commonly normocytic, but macrocytic anemia can be seen.[1] Increased serum erythropoietin (Epo), normal or slightly low leukocyte count with normal or slightly high platelet count are also features of DBA.[3] The presence of
(i) red blood cells antigen and elevated hemoglobin F are evident in DBA. Pearson syndrome, which is a congenital mitochondrial disorder characterized by exocrine pancreatic insufficiency, dyserythropoiesis and congenital sideroblastic anemia, can be also associated with hypo erythropoiesis. Acquired PRCA can be primary with no identified underlying cause or secondary in association with a variable number of disorders. The primary PRCA is a disorder of an autoimmune-mediated mechanism that involves erythroid precursors most likely due to selective T-cell or natural killer NK-cell. This cell-mediated mechanism affects early erythroid progenitors at the stages of the erythroid colony (colony-forming unit-erythroid) and burst (burst-forming unit-erythroid) forming units. In the pediatric population, the transient erythroblastopenia of childhood is a self-limited type of primary acquired PRCA, particularly in the age between 3 months and 4 years. There are many causes of secondary acquired PRCA. The acquired PRCA can be of an acute self-limited course particularly in children or of chronic course as in adults. Autoimmune or collagen vascular disorders as systemic lupus erythematosus, rheumatoid arthritis, as well as viral infection, especially B19 parvovirus and human immunodeficiency virus, pregnancy, and malignancy, can contribute to secondary acquired PRCA. Epstein–Barr virus, cytomegalovirus, and viral hepatitis are also other contributable viral infections that can cause secondary acquired PRCA. Other infections that can lead to PRCA include tuberculosis.

Human B19 parvovirus is the most commonly known viral cause of transient or reversible PRCA presented as aplastic crises in patients with sickle cell anemia and other chronic hemolytic anemia like hereditary pyropoikilocytosis. Figure 1 shows bone marrow aspirate of a young patient with sickle cell anemia and transient PRCA (transient aplastic crises) due to B19 parvovirus infection. B19 parvovirus causes PRCA because of its cytotoxic effect on the early erythroid progenitor cells after binding to the P antigen on the red cell surface. In immunocompromised patients, B19 parvovirus can lead to chronic PRCA and also pancytopenia due to suppression of hematopoiesis of early marrow progenitor cells.

From hematological malignancy, lymphoproliferative disorder is known to have an association with PRCA. PRCA can proceed with lymphoproliferative disorder or diagnosed simultaneously or during the treatment course of the neoplasm. It can be seen with large granular lymphocytic leukemia and chronic lymphocytic leukemia. Lymphoma, unapparent clonal T-cell disorders, plasma cell disorders as Waldenstrom macroglobulinemia and myelomatous disorder can also lead to PRCA. In rare cases, PRCA can be the first or the only manifestation of myelodysplastic syndrome. Although PRCA is rarely seen in myelodysplastic syndrome, hypo erythropoiesis in bone marrow is frequently seen in 5q-syndrome and there are several myelodysplastic syndromes with PRCA has been reported. PRCA associated with myelodysplastic syndrome has poor prognostic value. Herein, it is very crucial to emphasize on the dysplastic feature of other hematopoiesis lineages and exclude secondary causes of myelodysplasia.

Thymoma is the best known nonhematologic neoplasm associated with PRCA. It is believed that the frequency of thymoma and PRCA can reach 50%, and recently, it is found that 7%–10% of thymoma presenting as PRCA. Breast cancer, gastric cancer, thyroid cancer, and renal cell carcinoma are shown to have an association with PRCA, too.

Recombinant human Epo (rhEpo) is an important cause of PRCA and erythropoiesis-stimulating agents were recognized as a cause of secondary PRCA in 2002. The first reported case of erythropoiesis-stimulating agents associated with PRCA was in a patient with anemia due to chronic renal disease in 1998. The mechanism of PRCA with those patients treated with Epo-stimulating agents is still not confirmed, but the production of neutralizing antibody against Epo is a suggested theory, and it is believed that rhEpo-induced PRCA is a unique form of autoimmune PRCA. There are also cases of primary autoimmune PRCA caused by de novo antibodies against endogenous nonrecombinant Epo but rarely found. The incidence of rhEpo-induced PRCA varied according to the pharmaceutical form used. When the storage and handling of Eprex, subcutaneous epoetin, was improved in 2002, the incidence of rhEpo-induced?
PRCA has dropped by 83% worldwide in patients with chronic kidney disease.\(^\text{[7]}\)

Major mismatch of ABO-blood groups in not contraindication in stem cell transplantation, but it is found as a cause of PRCA in 7.5% of ABO-incompatible transplant.\(^\text{[1,2,8]}\) The type of used conditioning regimen in allogeneic stem cell transplantation may affect the incidence of this type of PRCA.\(^\text{[6]}\) Conventional myeloablative regimens using cyclophosphamide with busulfan or total body irradiation may have a higher incidence than modern reduced-intensity conditioning or reduced-toxicity regimens.\(^\text{[8]}\)

Pregnancy-associated PRCA is a rare finding but exists and it was reported.\(^\text{[2,9]}\) It is more to be presented in early pregnancy.\(^\text{[8,10]}\) It has not yet exactly found the real pathogenesis of pregnancy-associated PRCA, but it is proposed that progestins play an important role in it as the hormonal changes provoke autoimmunity response that leads to the inhibition of erythroid colonies.\(^\text{[10]}\)

Riboflavin deficiency has been seen in experimental human studies to be a causative factor of PRCA in patients with malignancies treated with riboflavin antagonist or maintained on the riboflavin-poor diet.\(^\text{[11]}\)

Drugs-associated PRCA has been identified with some medications such as allopurinol, azathioprine, diphenylhydantoin, anticonvulsant, (e.g., valproic acid), antituberculotic (e.g., rifampicin).\(^\text{[12]}\)

**Clinical features, initial evaluation, and diagnosis of pure red cell aplasia**

Clinical presentation of primary acquired PRCA is not specific.\(^\text{[1]}\) It is a disorder of no geographical or racial predilection. It can affect both adults and pediatric age groups. In a case of secondary PRCA, the presentation might be of any features of the underlying or associated syndromes. The general features of both types are the symptoms and signs of anemia such as fatigue, dizziness, palpitation, shortness of breath, failure to thrive in infants, pallor, and tachypnea.\(^\text{[1]}\)

In laboratory evaluation, it is not difficult to diagnose PRCA as it is characterized by normocytic normochromic anemia with reticulocytopenia (reticulocyte percentage 1%) with normal platelets and normal white blood cells count. This peripheral blood picture is confirmed by marked hypo erythropoiesis in the bone marrow examination.\(^\text{[1,2]}\)

Macrocytic anemia also can be seen in PRCA as in the case of DBA.\(^\text{[3]}\) The diagnosis of PRCA requires complete clinical and laboratory work up to find the underlying cause.\(^\text{[1]}\) Therefore, primary PRCA is a diagnosis of exclusion. The previous history of drugs, infection, the associated disease is important.\(^\text{[1]}\) The assessment of liver functions, renal functions, and bone marrow examination are an important part of investigations to rule out hepatitis or underlying renal and hematological disorders, respectively.\(^\text{[1,2]}\) Complete blood count with differential leukocyte count and peripheral blood morphology are important not only to confirm anemia but also to demonstrate any other cytopenia and any other associated abnormality like granular lymphocytosis which is seen in large granulocytic leukemia large granular lymphocyte (LGL).\(^\text{[10]}\) Peripheral blood flow cytometry is helpful when characteristic findings of LGL as LGLs that have abundant pale cytoplasm and azurophilic granules are seen in the peripheral blood smear.\(^\text{[1,2]}\) Inverted CD4/CD8 ratio to be <1% and or an increase of CD3+/CD56-cells or CD3-/CD56+ are suggestive of LGL leukemia.\(^\text{[1]}\) Iron profile with the assessment of red cells folate and B12 levels are also important as iron deficiency anemia and or megaloblastic anemia can give hypo proliferative type of anemia, especially when both types of these anemias are co-existing as the red blood cells indices here might be not of characteristic microcytosis and hypochromia or macrocytosis, respectively. In primary acquired PRCA, the bone marrow cellularity is normal with normal megakaryocytic and myeloid maturation and almost absence of erythroblasts.\(^\text{[1,2]}\) A few early erythroid precursors as proerythroblasts might be seen in some cases, but it does not exceed 5% of the differential count.\(^\text{[2]}\) Bone marrow examination might show other findings that might be helpful in the diagnosis of secondary PRCA as the finding of large vacuolated proerythroblasts with cytoplasmic pseudopodia that are suggestive of B19 parvovirus infection as shown in Figure 1.\(^\text{[2]}\) Bone marrow examination is also helpful in both pediatric and adult age groups. In pediatric cases, especially in early childhood, it can differentiate between congenital PRCA with another cause of reticulocytopenia anemia such as congenital dyserythropoietic anemia or thiamine-responsive megaloblastic anemia.\(^\text{[13]}\) Table 2. Bone marrow in thiamine-megaloblastic anemia characterized by megaloblastic changes with the presence of ring sideroblasts. In adults, bone marrow examination is helpful to exclude erythroid dysplasia and ring sideroblasts if meylodysplasia is suspected.\(^\text{[2]}\) Figure 2 shows ring sideroblasts in a bone marrow aspirate specimen of an elderly patient with refractory anemia and ring sideroblast. In 5q-syndrome, erythroid hypoplasia can be seen but marked hypoplasia with maturation arrest that are seen in PRCA is unusual in this syndrome.\(^\text{[9]}\) However, there is a case report of 5q-meylodysplastic syndrome combined with PRCA in an old female confirmed with chromosomal study that demonstrated 46XX, del (5) (q15 q33)[18]/46, XX[2] with the presence of dysplastic, nonlobulated and hypo lobulated megakaryocytes.\(^\text{[9]}\) Chromosomal study of bone marrow, including T-cell receptor rearrangement, might
be helpful to rule out underlying lymphoproliferative disorder like large granular lymphocytic leukemia LGL leukemia.\(^1\) Other important investigations include the serological study of autoantibodies and rheumatoid factor to exclude underlying autoimmune pathogenesis. Virology screening as B19 parvovirus DNA using polymerase chain reaction, radiological study as magnetic resonance imaging and/or computed tomography to exclude underlying or associated neoplasm like thymoma are also important investigative tools.\(^1,2\) Table 3 summarizes the investigations needed to discover the cause and type of PRCA.

**Treatment**

The identification of underlying cause of PRCA is key to find the most appropriate therapeutic modality and initiate treatment of such disease.\(^1\)

The aim of therapy in PRCA is to achieve a complete response that shows sustained active erythropoiesis by rising of both hemoglobin and reticulocyte count to appropriate levels with the elimination of blood transfusion requirement after 8 weeks of treatment, [Table 4].\(^{12,14}\) When the frequency of blood transfusion by the end of 8 weeks of therapy initiation is declined but with the inappropriate rising of hemoglobin and/or reticulocyte count, the patient is expressing a partial response to therapy.\(^{12}\) Patients that failed to achieve appropriate hemoglobin and appropriate reticulocyte count with no decline of their blood transfusion requirements 8 weeks posttherapy are defined to have no response.\(^{12}\) High transfusion demands expose the patients to transfusion-associated risks such as viral infections, alloimmunization, febrile hemolytic and nonhemolytic transfusion reactions and hemosiderosis.\(^{14}\)

Since primary PRCA is an immune-mediated disorder, immunosuppressive therapy is used.\(^{1,2,14}\) Furthermore, PRCA associated with autoimmune/connective tissue disorders is treated with immunosuppression as the

**Table 1: Summary of classification of pure red cell aplasia**

| Congenital PRCA | Acquired PRCA |
|-----------------|---------------|
| DBA             | Primary acquired PRCA: Is a disease of exclusion |
| Pearson’s syndrome | Secondary acquired PRCA: Autoimmune/collagen vascular disorders |
|                 | Viral infection: HBV, HCV, HIV, B19 parvovirus, EBV, CMV |
|                 | Tuberculosis, leishmaniosis |
|                 | Hematological neoplasm, for example, MDS, Lymphoproliferative disorder, for example, LGL, plasma cell disorders, lymphoma |
|                 | Solid tumor, for example, renal cell carcinoma, gastric cancer, breast cancer |
|                 | Drugs, for example, anticonvulsant, rhEPO |
|                 | Nutritional cause, for example, riboflavin deficiency |

MDS=Myelodysplastic syndrome; LGL=Large granulocytic leukemia; PRCA=Pure red cell aplasia; HBV=Hepatitis B virus; HCV=Hepatitis C virus; HIV=Human immunodeficiency virus; EBV=Epstein-Barr virus; CMV=Cytomegalovirus; rhEPO=Recombinant human erythropoietin; DBA=Diamond-Blackfan anemia

**Table 2: Comparison between congenital pure red cell aplasia and congenital dyserythropoietic anemia**

| Congenital PRCA                  | CDA                                      |
|----------------------------------|------------------------------------------|
| Age of presentation              | Childhood or early adulthood             |
| Clinical features                | Variable upon its type. Splenomegaly, organomegaly, and jaundice are common |
| MCV                              | Variable on type of CDA as normocytic, microcytic, and macrocytic types of anemia all can exist |
| Reticulocyte count               | Decreased                                |
| Bone marrow                      | Erythroid hyperplasia with marked dyserythropoiesis (red blood cells binucleation, trinucleation, intranuclear chromatin bridging) depends on the type of CDA |
| Pathogenesis                     | Ineffective erythropoiesis, likely due to genes encode to cytokines, for example, CDAN1, SEC23B. Many other genes are also identified, depending on its type |

PRCA=Pure red cell aplasia; CDA=Congenital dyserythropoietic anemia; DBA=Diamond-Blackfan anemia; MCV=Mean corpuscular Volume
Cyclophosphamide is cytotoxic therefore, adjuvant immunosuppressive therapy can be used in case of inadequate response to prednisone. It has been reported to give a successful response in two-thirds of PRCA patients. Other agents such as cyclosporine, alemtuzumab, azathioprine, and sirolimus may also be used depending on the specific patient situation.

The secondary PRCA is treated with the treatment of underlying or associated disease. PRCA due to infections should be treated with the initiation of specific treatment for that disorder. B19 parvovirus associated PRCA treatment includes therapeutic dose of intravenous immunoglobulin. There is a reported case of PRCA due to B19 parvovirus with non-Hodgkin lymphoma diagnosed to have chronic PRCA due to parvovirus infection and his PRCA treated with rituximab. Rituximab is a monoclonal antibody to CD20+ B-cells receptor and used mainly with PRCA associated with lymphoproliferative neoplasm. The rationale behind using of rituximab is the elimination of antibody produced by neoplastic cells but the cure of PRCA in some cases with persistent residual neoplasm suggests other mechanism.

Alemtuzumab, anti-CD52 monoclonal antibody is one of the proposed targeted therapy in lymphoproliferative disorder-associated PRCA. Surgical resection is needed in a case of thymoma associated PRCA, but relapses are frequent here. Therefore, adjuvant immunosuppressive therapy is needed. Prolonged transfusion support might be needed in a case of post ABO-incompatible stem cell transplantation PRCA, but the prolongation of persistence isohemagglutination for >2 months may require immunosuppression, rituximab, donor leukocyte infusion, or plasma exchange. In a case of rhEpo-induced antibody-mediated PRCA as seen in renal disorder patients, immunosuppressive therapy is used. There is little experience of pregnancy-associated PRCA, but prednisolone is used in such cases. Prednisone is also used in a case of DBA. In DBA, 80% of patients have good therapy response and 20%
of the patients require frequent blood transfusion sessions.\[^{[18]}\] About 9%–10% of patients with DBA require stem cell transplantation.\[^{[18]}\] The dose of corticosteroids in pediatric age is 2 mg/kg/day for maximum of 4 weeks.\[^{[18]}\] Growth monitoring using an accurate growth chart is important in such age group to avoid steroid side effects.\[^{[18]}\] Those patients that are transfusion-dependent need iron-chelating agent after approximately 15 transfusion or after the age of 2 years.\[^{[18]}\] For those PRCA associated with myelodysplastic syndrome, lymphoproliferative disorders, the treatment of PRCA is with the treatment of those hematological malignancy.\[^{[1,2]}\] Intravenous antithymocytes globulin used as second- or third-line therapy.\[^{[14]}\] Plasma exchange or plasmapheresis to eliminate IgG autoantibodies with fresh frozen plasma, splenectomy, bone marrow transplantation, and immunoglobulin all are modalities that can be used in low response cases refractory to treatment.\[^{[2,14]}\] Table 5 Summarize the therapeutic modalities of pure red cell aplasia.

**Conclusion**

PRCA should be suspected in a case of anemia with reticulocytopenia are found. It is of diverse etiologies and could be primary PRCA or secondary as seen in most cases. The diagnosis of PRCA requires complete patient evaluation including a complete history and clinical examination with long list of laboratory investigations to determine its cause. Immunosuppressive agents are widely used in the treatment of primary PRCA while treatment of secondary PRCA is with the treatment of underlying or associated causes.

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**Conflicts of interest**

There are no conflicts of interest.

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**References**

1. Means RT Jr. Pure red cell aplasia. Blood 2016;128:2504-9.
2. Sawada K, Fujishima N, Hirokawa M. Acquired pure red cell aplasia: Updated review of treatment. Br J Haematol 2008;142:505-14.
3. Wilson NL. Understanding congenital pure red cell aplasia. Lab Med 1996;27:2.
4. Kim HD, Kim KW, Park SY, Ko HJ, An YY, Shin SY, et al. Myelodysplastic syndrome with erythroid aplasia following pure red cell aplasia. Korean J Intern Med 2004;19:193-5.
5. Park J. Del (5q) myelodysplastic syndrome combined with pure red cell aplasia. Blood Res 2018;53:104.
6. Pollock C, Johnson DW, Hörl WH, Rossert J, Casadevall N, Schellekens H, et al. Pure red cell aplasia induced by erythropoiesis-stimulating agents. Clin J Am Soc Nephrol 2008:3:193-9.
7. Bennett CL, Luminari S, Nissenson AR, Tallman MS, Klinge SA, McWilliams N, et al. Pure red-cell aplasia and epoetin therapy. N Engl J Med 2004;351:1403-8.
8. Aung FM, Lichtiger B, Bassett R, Liu P, Alousi A, Bashier Q, et al. Incidence and natural history of pure red cell aplasia in major ABO-mismatched haematopoietic cell transplantation. Br J Haematol 2013;160:798-805.
9. Aggarwal S. Reversible pure red cell aplasia of pregnancy: A therapeutic challenge. J Obstet Gynaecol India 2013;63:138-9.
10. Kashyap R, Pradhan M. Obstetric case report. [DOI: 10.3109/01443615.2010.501919].
11. Butensky E, Harmatz P, Lubin B. Nutritional anemias. Nutrition in Pediatrics, Hamilton. 4th ed. Ontario, Canada: BC Decker Inc.; 2008.
12. Balasubramanian SK, Sadaps M, Thota S, Aly M, Przychodzen BP, Hirsch CM, et al. Rational management approach to pure red cell aplasia. Haematologica 2018;103:221-30.
13. Iolascon A, Heimpel H, Wahlin A, Tamary H. Congenital dyserythropoietic anemias: Molecular insights and diagnostic approach. Blood 2013;122:2162-6.
14. Raghavachar A. Pure red cell aplasia: Review of treatment and proposal for a treatment strategy. Blut 1990;61:47-51.
15. Sharma VR, Fleming DR, Slone SP. Pure red cell aplasia due to parvovirus B19 in a patient treated with rituximab. Blood 2000;96:1184-6.
16. Long Z, Yu F, Du Y, Li H, Chen M, Zhuang J, et al. Successful treatment of refractory/relapsed acquired pure red cell aplasia with sirolimus. Ann Hematol 2018;97:2047-54.
17. Vlachaki E, Diamantis MA, Klonizakis P, Haralambidou-Vranitsa S, Ioannidou-Papagiannaki E, Klonizakis I. Pure red cell aplasia and lymphoproliferative disorders: An infrequent association. ScientificWorldJournal 2012;2012:473313.
18. Vlachos A, Muir E. How I treat diamond-blackfan anemia. Blood 2010;116:3715-23.