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Pure Red Cell Aplasia; A Tripod of Cases

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Abstract

Pure red cell aplasia (PRCA) is a syndrome defined by a normocytic normochromic anemia with severe reticulocytopenia and marked reduction or absence of erythroid precursors from the bone marrow. PRCA is a rare disorder that can affect any age and both genders equally. PRCA may be congenital or acquired. Diamond-Blackfan anemia is a congenital form of PRCA. Herein, we present a series of three cases of pure red cell aplasia presenting with unusual clinical and other rare haematological findings. PRCA is a rare disorder with varied etiology, where no cause can be established, it is labelled as idiopathic PRCA, treatment is done with corticosteroids (first line of therapy), which show a response by 4 weeks. Any anaemia of prolonged duration, not responding to conventional therapy should be evaluated by bone marrow studies to rule out ineffective erythropoiesis, dysplastic syndromes, infiltrative diseases of the bone marrow or a selective erythroid suppression.

Keywords: *Anaemia; Idiopathic; PRCA*

Introduction

PRCA is a rare disorder. It is the result of isolated depression of erythroid series and is characterized by normocytic normochromic anaemia, reticulocyte count < 1%, marrow erythroblasts < 0.5% [1]. It is a rare disorder that affects any age and both male and females equally. PRCA may be congenital or acquired. Acquired PRCA may be primary or secondarily associated with thymoma, chronic lymphocytic leukemia, lymphoma, solid organ malignancy, parvovirus B19 infection, HIV, hepatitis, tuberculosis, autoimmune disorders, Systemic Lupus Erythematosus (SLE), rheumatoid arthritis, due to some nutritional deficiency, drug induced or may present as an idiopathic disorder [2]. We report 3 cases of PRCA (Table 1).

Case	Patient details	Presenting complaints	Clinical examination	CBC findings	Peripheral smear findings	BMA findings
1)	Female child (1 year)	Fever and cough (7 days)	Pallor + nt hepatosplenomegaly with liver and spleen 7cm and 4cm below costal margin	Hb- 6.3g%, TLC- 11000/cumm DLC- N-58%, L-39% E-01%, M-02% Platelets - 1.5 lac/cumm RBC count - 2.5 million/cumm Hematocrit - 17% Alkaline phosphatase - 234 U/L (raised) Serum ferritin levels > 1000 ng/m	RBC- normocytic normochromic (NCNC)	Hypercellular marrow with increased M:E ratio (10:1) and depression of erythroid series. Only < 5% giant proerythroblasts were seen. Consistent with diagnosis of PRCA

2)	Male (17 year)	Fever, dry cough, vomiting and loss of appetite (1 week) patient was on antimalarial drug	No organomegaly was noted	Hb -10.2 gm/dl TLC-12,000/cumm DLC- N-57%, L-37%, E-02%, M-4%, PCV-32.3% MCV-92.9 fL Platelet count-2.8lac/cumm RBC count-3.9 million/cumm Reticulocyte count < 0.2%.	RBC- mild anisocytosis and normocytic normochromic	Cellular marrow with a profound erythroid hypoplasia and a high myeloid/erythroid ratio, consistent with PRCA
3)	Male (5 year)	Fever, generalised body ache, arthralgia with burning micturition (1 month)	Pallor + nt No organomegaly was noted	Hb -6.8 gm/dl TLC-11,300/cumm DLC- N -44%, L-40%, E-07%, M-07%, PCV-20.3%, MCV-78.9 fL, Platelet count-7.5 lac/cumm RBC count-2.9 million/cumm, Reticulocyte count < 0.2%	RBC-mild anisocytosis and normocytic normochromic	Cellular marrow with paucity erythroid cells and a high myeloid/erythroid ratio. Few proerythroblasts which are large in size and with intranuclear inclusions were noted, consistent with PRCA

Table 1: *Clinical details, complete hemogram, along with peripheral blood smear findings and bone marrow aspiration findings of the three cases reported as PRCA.*

Case Reports

Case 1

A 1 year old female child, presented with complaints of fever and cough for past 7 days. There was no complaint of jaundice, weight loss, loss of appetite, body rash, joint pains. Patient was treated with antimalarial drugs. No significant family history was available. On examination pallor was present along with hepatosplenomegaly with liver and spleen 7 cm and 4 cm below costal margin. No remarkable finding was seen in any other system clinically. On investigation, her hemoglobin was 6.3 g/dL, total leucocyte count (TLC)- 11000/cumm, Differential leucocyte count (DLC): Neutrophils- 58%, Lymphocytes- 39%, Eosinophils- 01%, Monocytes- 02%, platelets- 1.5 lac/cumm, Red blood cell (RBC) count- 2.5 million/cumm, hematocrit- 17%. On peripheral blood film examination normocytic normochromic picture of RBCs was seen with no polychromasia, no nucleated RBC (nRBC). Her alkaline phosphatase was raised 234 U/L. serum ferritin levels were more than 1000 ng/ml. Stool for occult blood was negative. Sputum for acid fast bacilli (AFB) was negative. Test for scrub typhus was also negative. Patient was rheumatoid arthritis (RA) factor negative, anti-nuclear antibody (ANA) negative. Bone marrow aspiration (BMA) was performed and the smears revealed a moderately hypercellular marrow with increased myeloid to erythroid (M:E) ratio (10:1) and depression of erythroid series (Figure 1). Only < 5% giant proerythroblasts were seen which are large sized, round nuclei, opened

up chromatin with intranuclear inclusions and moderate amount of basophilic cytoplasm (Figure 2). Myeloid series showed normal differentiation and maturation. Megakaryocytes were adequate and functional. Keeping in view the clinical history and examination, laboratory findings and bone marrow aspiration findings, a diagnosis of PRCA was made. It was considered most probably secondary to chloroquine intake or viral infection. The patient was initially managed with hematinics and was given immunosuppressive therapy with glucocorticoids. Following the medication there was a steady rise in haemoglobin and it ultimately hematological parameters were with in normal limit.

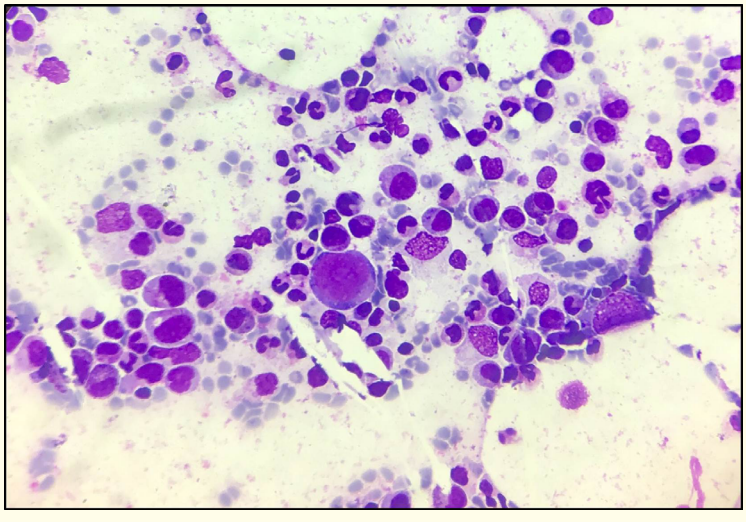

Figure 1: *Low power view of the bone marrow showing cellular marrow trails and paucity of erythroid series (Giemsa stain X 100).*

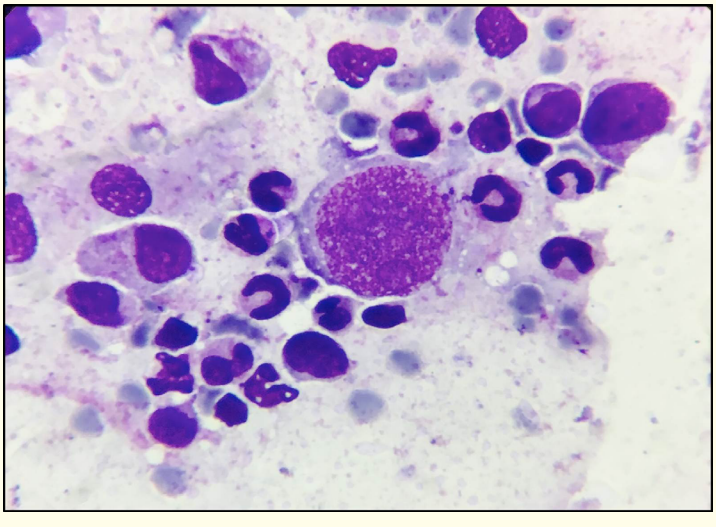

Figure 2: *High power view of the bone marrow, Erythroid series prominently show proerythroblasts with no erythroid maturation (Giemsa stain X 400).*

Case 2

A 17-year male came with complaints of fever, dry cough, vomiting and loss of appetite for 1 week. There was no history of breathlessness, chest pain, oliguria, jaundice or rashes. Patient had past history of cochlear implant surgery. Patient was on antimalarials drugs. His initial general physical examination revealed nothing abnormal. No organomegaly was noted. On investigation his Hb was 10.2 gm/dl, RBC count- 3.9 million/cumm, TLC- 12,000/cumm, DLC-polymorphs- 57%, lymphocytes- 37%, eosinophils- 02%, monocytes- 04%, Packed cell volume (PCV)- 32.3%, mean corpuscular volume (MCV)- 92.9 fL, Platelet count- 2.8 lac/cumm, reticulocyte count-less than 0.2%. Peripheral blood film smear showed mild anisocytosis and normocytic normochromic red blood cells. Bone marrow aspirate smears revealed cellular marrow with a profound erythroid hypoplasia and a high myeloid/erythroid ratio. The morphology and maturation sequence of the myeloid cells and megakaryocytes was normal. The plasma cells and mononuclear lymphoid cells were also normal. The marrow picture was consistent with acquired pure red cell aplasia. Anemia resolved by 14 days after cessation of antimalarial drug.

Case 3

A 5-year old male came with complaints of fever, generalised body ache, arthralgia for 1 month associated with burning micturition. There was no history of breathlessness, chest pain, oliguria, jaundice or rashes. On examination pallor was present along with tenderness over back and thigh due to which there was difficulty in walking. No organomegaly or other significant finding was noted. On investigation his Hb was 6.8 gm/dl, RBC count- 2.9 million/cumm, TLC- 11,300/cumm, DLC-polymorphs- 44%, lymphocytes- 40%, eosinophils- 07%, monocytes- 07%, PCV- 20.3%, MCV- 78.9fL, Platelet count- 7.5 lac/cumm, reticulocyte count-less than 0.2%. Peripheral blood film smear showed mild anisocytosis and normocytic normochromic red blood cells. Bone marrow aspirate smears revealed cellular marrow with paucity erythroid cells and a high myeloid/erythroid ratio. Few proerythroblasts which are large in size and with intranuclear inclusions were noted. The morphology and maturation sequence of the myeloid cells and megakaryocytes was normal. Mild prominence of plasma cells, mononuclear lymphoid cells, and eosinophil's were observed. The marrow picture was consistent with idiopathic pure red aplasia. Patient was lost to follow up.

Discussion

PRCA is characterized by decreased RBC precursors with normal granulopoiesis and megakaryopoiesis in the bone marrow presenting clinically as anaemia [3]. The blood reticulocyte count usually is very low (10,000/l) and hemoglobin levels decrease at a rate of approximately 0.1 g/dl per day (1 g/L per d), corresponding to the red blood cell lifespan; thus, patients rapidly become transfusion dependent. All other lineages are present and seem morphologically. This pattern distinguishes PRCA from aplastic anemia, which usually involves all three cell lineages. Even after extensive study of literature, exact incidence of PRCA could not be ascertained.

The hallmark of PRCA is the absence of erythroblasts from an otherwise normal bone marrow. In classic cases, the bone marrow aspirate and/or trephine biopsy shows a virtual absence of red cell precursors (in many cases 5% erythroblasts), whereas the cellularity of the bone marrow is normal, with normal myeloid cells and megakaryocytes. Because iron use is largely abolished in PRCA as a result of the absence of marrow erythropoietic activity, serum ferritin increases to very high levels, as does the transferrin saturation. Thus, serum ferritin levels of 1000 g/L and transferrin saturation levels of 70% are characteristic of this condition [4]. In adults, PRCA may be associated with systemic autoimmune disease, drugs, toxins, solid organ transplantation, malignancy, systemic infections like tuberculosis [4] parvovirus B19 infection out of these, is of particular interest is, infection with Parvovirus B19. BMA in parvovirus B19 infection showed large proerythroblasts with large vesicular nuclei with loosely distributed chromatin and prominent, inclusion body-like nucleoli, surrounded by a basophilic cytoplasm which is a characteristic finding [5-7].

PRCA presenting in conditions such as collagen vascular disease, autoimmune disease, tuberculosis, post transplantation, associated with thymoma seem to have an immunologically mediated suppression of erythropoiesis which may be antibody mediated [8,10], T cell

mediated, or Natural killer (NK) cell mediated. Patients of autoimmune disease show IgG antibody directed against erythroblasts leading to a complement mediated lysis of RBC progenitors.

It has been seen that T cells in patients with B-CLL suppress erythroid colony formation *in vitro* probably by secretion of inhibitory lymphokines [6]. In addition to more than 30 drugs have been implicated in the etiology of PRCA with only phenytoin, isoniazid and azathioprine having a proven causative role [8]. Pathogenesis include direct effect on RBC precursors as well as induction of autoimmunity [9].

Understanding the pathophysiology of PRCA has provided us with novel therapeutic options including cyclosporine, cyclophosphamide, rituximab, anti-thymocyte globulin. Following treatment response to therapy is assessed by serial evaluation of reticulocyte count and hematocrit [10].

These cases discussed above highlight a rare cause of anaemia. The diagnosis was possible due to meticulous investigation especially of the bone marrow. Pure red cell aplasia was confirmed by the finding of a maturation block in the erythroid series. The patients were managed with symptomatic therapy.

Conclusion

Any anaemia of prolonged duration, not responding to conventional therapy should be evaluated by bone marrow studies to rule out ineffective erythropoiesis, dysplastic syndromes, infiltrative diseases of the bone marrow or a selective erythroid suppression. PRCA is a rare disorder with varied etiology.

Whenever a causative agent can be established, rapid response follows with the treatment of underlying cause or withdrawal of incriminating drug. In cases where no cause can be established, labelled as idiopathic PRCA, treatment is done with corticosteroids (first line of therapy), which show a response by 4 weeks. Other agents that can also be used are cyclosporine, cyclophosphamide, azathioprine, rituximab.

Source of Support

Nil.

Conflict of Interest

None.

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