

Missing Erythroid Series (Pure Red Cell Aplasia)

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Abstract

Background: Pure red cell aplasia (PRCA) is a rare disorder, characterized by reticulocytopenia (<1%) associated with a marked reduction of the bone marrow erythroid precursors (<5%) which is often clinically missed. **Aim:** To investigate the demographic profile and different causes of PRCA in the institution. **Material and Methods:** During a 5 year period, all cases which were reported as erythroid hypoplasia were reviewed. Based on the accepted criteria, 19 cases were included in the study. The cases were classified based on causes as primary and secondary. The clinical and laboratory profile of the cases were reviewed and followed up. **Results:** Among the 19 patients, two children were considered as primary PRCA as there was no other cause. The rest were secondary - 1 patient developing PRCA secondary to thymoma and 11 patients developed drug induced PRCA. 4 of them were on ART. The patient who had developed PRCA secondary to Thymoma was a 53 year old male presented with dyspnoea for more than a month. CT scan showed a mass in the anterior mediastinum which was diagnosed as thymoma and confirmed histopathologically. The four patients on ART had Zidovudine in the regimen which is known to cause PRCA. **Comments and Conclusions:** The present study showed 19 patients with PRCA with diverse causes. Since PRCA is a rare disorder, haematologists should be alert to include PRCA in the differential diagnosis in cases of severe normochromic and normocytic anaemia combined with reticulocytopenia and normal production of the white blood cell and megakaryocytic lineages. The major goal in treating PRCA is to induce a remission with the recovery of erythropoiesis, thereby providing relief from transfusions and avoiding transfusion-related complications.

Keywords: Pure red cell aplasia; Thymoma; Teticulocytopenia.

Introduction

Pure red cell aplasia (PRCA) was initially described by Kaznelson in 1922, is a rare disorder, characterized by the presence of a severe normochromic, normocytic anaemia

and reticulocytopenia (<1%) associated with a marked reduction of the bone marrow erythroid precursors (<5%) while the production of the white blood cell and megakaryocytic lineages are maintained¹. The classification of PRCA involves - the congenital disorders of PRCA, which usually manifest early in life, primary PRCA, which occurs in the absence of any underlying disorder and (iii) the acquired or secondary PRCA syndrome. Secondary PRCA can be associated with various haematological disorders ranging from neoplastic to non neoplastic conditions. The

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aim of the present study is to investigate the demographic profile and different causes of PRCA in the institution.

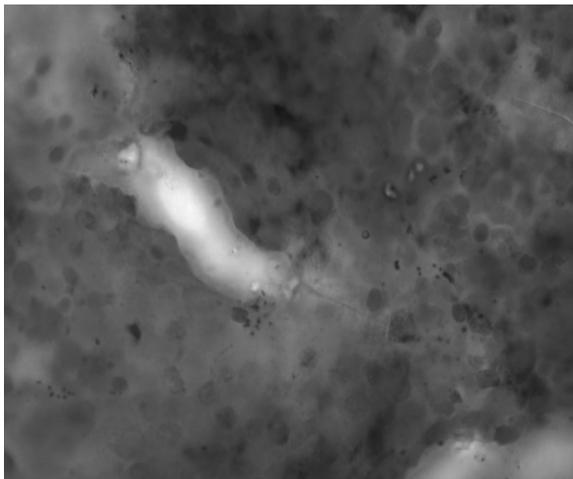
Material and Methods

During a 5 year period, all cases which were reported as erythroid hypoplasia were reviewed. Demographic and hemogram details including haemoglobin, WBC total and differential count, platelet count and Reticulocyte count done by manual method after staining with brilliant cresyl blue were retrieved from the archives. The peripheral smear and bone marrow were stained by leishman's stain. All bone marrow slides were assessed for cellularity and a minimum of 200 cells were counted to determine myeloid: erythroid ratio. Perl's stain was done for assessment of iron stores and were graded from 1-6 where grade 1-3 was considered normal and grade 4-6 were considered as increased. The trephine biopsy was stained by hemotoxylin and eosin stain. The following criteria were followed to include the case as PRCA:

- the reticulocyte count was less than 1%
- the erythroid series in the bone marrow aspirate was less than 5% and
- the Perl's stain of bone marrow showed increased iron stores.

Based on the criteria, 19 cases were included in the study.

Figure 1: Bone Marrow Aspirate shows Increased Iron Stores Perls Stain x 1000



The cases were classified based on causes as primary and secondary. The clinical and laboratory profile of the secondary cases were reviewed and followed up.

Results

Based on the criteria 19 patients were included for the study. Among the 19 patients, two children were considered as primary PRCA as there were no other cause was found. The rest were secondary - 1 patient developing PRCA secondary to thymoma and 11 patients developed drug induced PRCA. 4 of them were on ART. Among the other 5 patients two of them had collagen vascular disorders and two had haemolytic anemia. One of them was suspected of parvovirus infection but could not be proved.

The age ranged from 8 years to 55 years, the maximum incidence was between 20 and 40 years. The male: female ratio was almost equal (1.1:1)

The haemoglobin level dropped to as low as 2 gms in primary PRCA, while in the others it ranged from 4 to 9 gms. The patients on ART had mild anemia, the haemoglobin ranging from 7 to 9 gm%. The total WBC count and platelet counts were normal in all the patients. This was reflected in the bone marrow aspirate and the trephine biopsy with adequate myeloid series and megakaryocytes. 7 patients showed

Figure 2: Haemotoxylin and Eosin Stain x 100

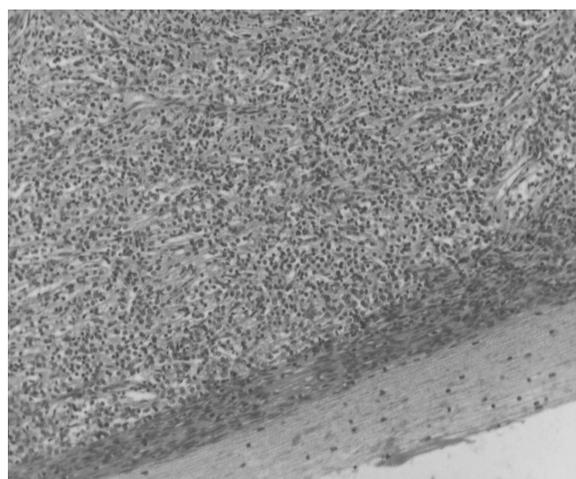
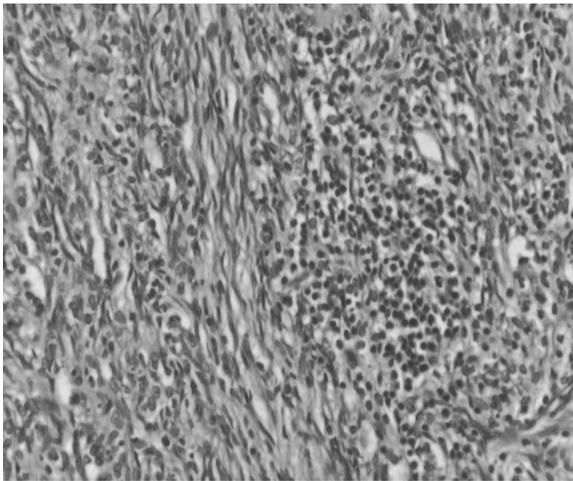


Figure 3: Hemotoxylin and Eosin stain x 400



Figures 2 and 3 show section from thymoma. Figure 3 shows admixture of epithelial cells with lymphocytes

increase in eosinophils. All patients also showed increased iron stores indicating ineffective erythropoietin (Figure 1).

Two children who were diagnosed as primary PRCA were 8 and 9 years old presented with progressive pallor, tiredness and dyspnoea for 4 months. One of them was admitted to hospital for vomiting for one week. Both of them were diagnosed on the aspirate as PRCA and were treated with steroids.

The patient who had developed PRCA secondary to Thymoma was a 53 year old male presented with fatigue and pain in the lower limb and dyspnoea for more than a month. CT scan showed a mass in the anterior mediastinum which was diagnosed as thymoma and confirmed histopathologically. The patient condition improved after the resection of thymoma (Figure 2 and 3).

Among the four patients on ART, three of them were switched to Lamivudine from Zidovudine. One patient expired during follow up.

Discussion

The present study showed 19 patients with PRCA with diverse causes. Pure red cell aplasia appears to be more common than the literature has revealed and has stimulated much

investigation into an immune pathogenesis for marrow failure. PRCA is a rare bone marrow failure disorder without geographic or racial predilection. All ages can be affected. Former nosology included various terms like chronic hypoplastic anaemia, pure red-cell agenesis, primary red-cell anaemia, and erythrophthisis. Clinicians often fail to diagnose PRCA. Since PRCA is a rare disorder, haematologists should be alert to include PRCA in the differential diagnosis in cases of severe normochromic and normocytic anaemia combined with reticulocytopenia and normal production of the white blood cell and megakaryocytic lineages.

Acquired PRCA occurring in childhood (transient erythroblastopenia of childhood) may be difficult to distinguish from Diamond-Blackfan anaemia.[2,3] Short stature with frequently associated somatic malformations like craniofacial anomalies, upper limb and genitourinary anomalies are more common in Diamond Blackfan anemia. A history of normal blood counts, late onset of manifestation, and transient disease course are characteristic of transient erythroblastopenia of childhood. Response to corticosteroids is observed. A distinction between myelodysplastic syndrome (MDS) with erythroid hypoplasia and idiopathic PRCA might be more difficult.

Thymic neoplasms are the first to be associated with PRCA.[4] The incidence varies from 15% to 4%. PRCA may precede the development of thymoma, co-exist with thymoma or develop years after the surgical removal of the neoplasm. Studies have shown that the plasma of the patients with thymoma have an inhibitor of erythroid cell development.

Drug induced PRCA is relatively uncommon and usually presents as an acute form of erythroblastopenia and remits after withdrawing the drug.[5] It may appear after the first exposure of the drug or after significant time. In ART patients, Zidovudine which is used in the first line regimen causes PRCA secondary to IgG mediated destruction or directly affecting the DNA synthesis.[6] The 3 patients who were switched over to

Lamivudine responded well probably because of the above factor.

The antigenic targets for autoantibodies have not been well characterized, but various stages of erythroid differentiation can be affected, as seen in the reduction of erythroid burst-forming units or erythroid colony-forming units. In certain cases of antibody-mediated PRCA, the involvement of the complement system is prerequisite to disease causation. Some other cases of adult autoimmune PRCA might be induced by antibodies produced following a viral or bacterial infection that might cross-react with erythroid precursor cells or erythropoietin.[7]

The major goal in treating PRCA is to induce a remission with the recovery of erythropoiesis, thereby providing relief from transfusions and avoiding transfusion-related complications. The therapeutic strategy usually focuses on immunosuppressive treatments, until a remission is obtained. Remissions have been achieved by treatment with corticosteroids, cyclophosphamide, cyclosporine A (one of the leading drugs for PRCA treatment, a T-cell targeted therapy), antithymocyte globulin, splenectomy, and plasmapheresis. Recently, the efficacies of the anti-CD20 monoclonal antibody, rituximab, and anti-CD52 monoclonal antibody, alemtuzumab, have been reported to induce remission in resistant cases of PRCA⁸. Other therapeutic options include intravenous immunoglobulin, thymectomy, or peptide-based agonists for the erythropoietin receptor.

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