Pure Red Cell Aplasia as an Autoimmune-mediated Disorder

Key words: autoimmune, erythropoiesis, immunosuppressive therapy

Pure red cell aplasia (PRCA) is a clinical syndrome characterized as an anemia with almost complete absence of red-cell precursors in the bone marrow but essentially normal granulopoiesis and megakaryopoiesis (1). The patients generally have severe anemia with a low count of reticulocytes while the platelet count, leukocyte count and leukocyte differential are normal. The clinical course is either acute and self-limiting or chronic with rare spontaneous remissions, depending on the pathogenesis.

There are two forms of PRCA. One is the congenital type, described as Diamond-Blackfan syndrome, where most cases appear to be a result of severe genetic defects predominantly affecting the erythropoietic lineage (2). Anemia is usually noted at birth or in early childhood, and other physical anomalies such as short stature and congenital heart disease are present in about thirty percent of the cases. The other type is the acquired form; PRCA in adults is usually an acquired disease.

Acquired PRCA may be idiopathic or associated with other medical problems, such as autoimmune, viral, and neoplastic diseases including thymoma, rheumatoid arthritis, systemic lupus erythematosus, hepatitis, mononucleosis, lymphoma, B-cell chronic lymphocytic leukemia, large granular lymphocytic leukemia, and allogeneic bone marrow or stem cell transplantation (3). Among the viral infections, human parvovirus B19 (B19) infection may induce PRCA called 'transient aplastic crisis (TAC)' or result in a chronic PRCA (4). The main target of parvovirus B19 infection is the erythroid progenitor cell and the basis of this erythroid tropism is the parvovirus B19 cellular receptor globoside, known as the blood group P antigens (5). PRCA may also occur in association with pregnancy. Many of the drugs such as phenytoin, azathioprine, chloramphenicol, procainamide, and isoniazide that may cause aplastic anemia may also cause PRCA. In some cases PRCA is the initial manifestation of myelodysplastic syndrome (MDS).

Although the pathophysiology of acquired PRCA seems heterogeneous, several published data suggest that autoimmune mechanisms underlie in most PRCA cases. In some cases, immunoglobulin molecules directed at erythropoietin, at erythropoietin-responsive erythroid precursor cells, or at erythroblasts themselves may block the effect of erythropoietin or destroy erythroid cells (6–8). Even in cases in whom a plasma inhibitor of erythropoiesis can not be determined, cellular immunity may play a role in the pathogenesis of PRCA. T cells or natural killer cells have been proposed to secrete factors selectively inhibiting erythropoiesis (9, 10). Lysis of erythroblasts can be

induced by T-cells resulting from classic T-cell receptor (TCR)-mediated antigen recognition, or by natural killer cells mediated by major histocompatibility complex (MHC) unrestricted effector-target cell recognition because erythroid precursors progressively lose expression of MHC class I (11–13). Furthermore the beneficial effect of resection of thymoma, and immunosuppressive therapy using corticosteroids, cyclophosphamide, anti-thymocyte globulin (ATG), cyclosporine, or methotrexate may support an autoimmune mechanism as a cause of the anemia (3, 14, 15).

To determine the immunologically mediated pathogenesis of PRCA, *in vitro* studies have been carried out. Antibodies have been demonstrated to block specifically differentiation of erythroid colony-formation *in vitro* (16). Alternatively, erythroid colony-formation *in vitro* can be inhibited by T_H cells or mononuclear cells (17, 18).

In this issue of the Journal, Okoshi et al report an acquired PRCA patient who showed positivity for an antiglobulin test (19).

See also p 589.

Moreover the patient's serum inhibited the growth of an erythropoietin-dependent cell line AS-E2, suggesting that the serum contains the inhibitor against erythroid precursors. The patient responded well to prednisolone therapy. In remission, antiglobulin test became negative, and inhibitor against erythroid precursors could not be detected.

Based on the pathophysiology, autoimmune-mediated PRCA is usually treated with immunosuppressive therapy. Approximately two-thirds of the patients respond well to prednisolone alone or with ATG, cyclosporine, azathioprine, or cyclophosphamide. In case of the relapse, a second or subsequent course of the same or alternative immunosuppressive therapy may be effective. The optimal treatment of PRCA, however, still remain uncertain.

In some situation, inhibitory receptors for HLA class I are involved in the pathogenesis of PRCA associated with large granular lymphocyte expansions. If novel pharmacological agents could signal through these inhibitory HLA class I receptors, but without binding to the T-cell receptors, a new approach to PRCA is expected blocking the destructive function of large granular lymphocytes without broadly inhibiting T-cell responses (1). Further studies are necessary to elucidate the precise mechanism underlying an autoimmune PRCA will be required.

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