Immunosuppressive Mechanisms in Pure Red Cell Aplasia—A Review*

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ABSTRACT

Pure red cell aplasia (PRCA) has been associated with a variety of clinical disorders, and various autoimmune mechanisms have been described to account for the red cell suppression. Primary PRCA occurs via both humoral and cell mediated mechanisms. Recent evidence using gene rearrangement studies indicates PRCA with T-lymphocytosis is a clonal chronic T cell lymphoproliferative disorder in which the T cells suppress erythropoiesis. Called T cell lymphocytosis and cytopenia (TCLC), this disorder has unique features, such as frequent rheumatoid arthritis (RA) and neutropenia. A subset of this disorder with natural killer (NK) like cells also exists, though direct NK cell suppression has not been proven. In secondary PRCA, both humoral and cellular suppression of erythropoiesis have also been described, except in chronic lymphocytic leukemia (CLL) where T cell suppression primarily accounts for the red cell aplasia. A role for the cell-adherent layer of the bone marrow, including macrophages, has also been demonstrated.

Introduction

Pure red cell aplasia (PRCA) is a disorder characterized by a normocytic anemia, reticulocytopenia, and severe erythroid hypoplasia of the bone marrow associated with relatively normal myeloid and megakaryocytic cell lines. This distinct clinicopathologic entity has been described in conjunction with numerous other conditions, including thymoma, infection (viral and bacterial), drugs, hemolytic anemia, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), pregnancy, nutritional deficiencies, T cell lymphoproliferative disorders, and hematologic malignancies. Various autoimmune mechanisms have been described which account for the suppression of red cell production in PRCA, though a small percentage of cases (primary or idiopathic PRCA) have failed to demonstrate any associated conditions or immune mediated suppression. In this report, the available literature is reviewed on autoimmune mechanisms identified in PRCA, concentrating on the T cell dependent
mechanisms. Some of the recent findings on the etiology of various chronic T cell lymphoproliferative disorders associated with PRCA are also presented.

**Review of Literature**

The following discussion separates PRCA into primary and secondary categories; however, in light of recent evidence it appears that the distinction is no longer clear.

**Primary PRCA**

A significant number of cases of PRCA are not associated with underlying disease conditions.\(^9,18,25\) Krantz first established an autoimmune mechanism for primary PRCA, demonstrating a complement dependent IgG inhibitor of red cell precursors.\(^19,20,47\) This serum inhibitor disappeared with immunosuppressive therapy and was not present upon recovery from the PRCA. Marmont and colleagues found two different IgG inhibitors, including one directed against erythropoietin.\(^25,37\) Romano et al described a patient who had normal T cell suppressor activity, no marrow erythropoietin suppression, but who did have IgG antibodies directed against marrow erythroblasts (including their nuclear membrane).\(^40\) A patient has also been reported with an antibody inhibitor blocking differentiation of erythroid burst forming units (BFU-E).\(^29\)

Primary PRCA also appears to be mediated in some patients via T cell suppression. A case of PRCA with an absolute increase in T cells bearing receptors for the Fc portion of IgG has been reported.\(^21\) In this case, as well as several others, both BFU-E and erythroid colony forming units (CFU-E) increased markedly following removal of these T cells in vitro and/or immunosuppressive therapy in vivo.\(^2\) Many investigators have described an absolute or relative T lymphocytosis in these patients in the blood and/or bone marrow.\(^21,26,27\) Phyliky et al described three patients and reviewed 22 similar cases where T lymphocytosis and an indolent lymphoproliferative disorder were seen in association with frequent anemia and neutropenia.\(^36\) The T cells in all of these cases were of the suppressor/cytotoxic phenotype. In a review of 21 cases of chronic T cell lymphoproliferative disorder, Newland et al found two with red cell aplasia.\(^34\) Most of their patients had distinct features differing from classic chronic lymphocytic leukemia (CLL), such as neutropenia, frequent rheumatoid arthritis (RA), moderate (as opposed to severe) lymphocytosis, no lymphadenopathy, wider age range, and an indolent clinical course. Thus, when PRCA is associated with absolute or relative T lymphocytosis is a diagnosis of T cell lymphocytosis and cytopenia (TCLC) should be considered.

In the past, it had often been unclear whether this was a leukemic process or a benign lymphocytosis.\(^26,27\) Several investigators have recently demonstrated the monoclonal nature of the T cells via gene rearrangement studies.\(^5,13\) In one series, five of six patients with TCLC showed unique rearrangements on the T\(_\beta\) gene.\(^13\) Similarly, Berliner et al found gene rearrangements in five of five patients with "classic" TCLC.\(^5\) By "classic" they meant both peripheral and marrow lymphocytosis associated with cytopenia. Two other patients with only marrow lymphocytosis did not demonstrate unique gene rearrangements. A majority of their patients survived greater than three years, and no treatment was given to the two atypical patients.

In the last decade much research has also focused on the role of the natural killer (NK) cell or large granular lymphocyte (natural killer-like cell) in the pathogenesis of PRCA. Mangan and colleagues demonstrated that normal NK
cells are capable of suppressing proliferation of BFU-E and CFU-E in blood and bone marrow. Phylly found a predominance of large granular lymphocytes (LGL's) in 19 of 25 cases reviewed of T-cell CLL of the cytotoxic/suppressor type. A case of PRCA where 50 percent of marrow lymphocytes were LGL's has been described, in which the non-T blood lymphocytes inhibited BFU-E and CFU-E in vitro (through no direct proof of NK cell suppression was obtained). One patient had 30 to 45 percent LGL's in circulation during PRCA, but only two to three percent during remission. This patient demonstrated a cellular inhibition at the level between BFU-E and CFU-E. More recently, a patient with PRCA demonstrated increased numbers of activated T8 cells and NK-like cells in blood and bone marrow. During remission following cyclosporin treatment these cells were significantly reduced, only to reappear in relapse. Many investigators now believe that these cases represent a further subset of TCLC.

Secondary PRCA

Since nearly half of all cases of PRCA have an associated thymoma, this entity has been described in considerable detail. It is interesting to note that thymoma has also been associated with several other autoimmune diseases, such as myasthenia gravis and hemolytic anemia. Evidence for humoral and T cell mediated suppression has been reported. Mondhiry et al discovered an IgG inhibitor of erythropoiesis which disappeared following thymectomy. Eridani et al showed evidence for combined T cell mediated suppression and humoral suppression of red cell production, but these defects were unaffected by thymectomy. More recently, a group from Japan demonstrated an IgG inhibitor in a patient's serum that suppressed CFU-E and BFU-E in the presence of complement. In addition, they found T lymphocytes in the bone marrow which acted similarly. Finally, Murphy and colleagues described a patient in which erythropoiesis began only after the adherent cell layer of the bone marrow, which contains mostly macrophages, was depleted. Erythropoiesis was not stimulated after removal of T-cells, and no suppression occurred when the patient's serum was cultured with normal bone marrow, thus implicating only the cell adherent layer in this patient.

Several autoimmune disorders have been associated with PRCA, including systemic lupus erythematosus (SLE) RA, primary immune hypothyroidism, hyperthyroidism, idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia, and multiple gland dysfunction. Again, there is evidence for both T cell and antibody mediated suppression. Konwalinka and colleagues described a patient with RA whose serum did not inhibit erythropoiesis, but when T lymphocytes were removed from the bone marrow reticulocytosis ensued. In another case of RA, however, as well as in two cases of SLE and one case of autoimmune hemolytic anemia (all with PRCA), a patient's serum suppressed both BFU-E and CFU-E in the bone marrow.

The mechanisms involved in the pathogenesis of PRCA in infection and in pregnancy are not clearly defined. In infectious mononucleosis, immune suppression can result in pancytopenia or PRCA, which may be related to increased T cell suppressor activity. Hepatitis has been associated with aplastic anemia as well as PRCA and evidence exists for humoral as well as cell mediated suppression. In one pregnant patient with PRCA a serum inhibitor was found which suppressed erythropoiesis in vitro.

Of the hematologic malignancies associated with PRCA, CLL has been most commonly cited. There is good evidence
that T lymphocytes play the central role in inhibiting erythropoiesis, both in B-cell CLL (B-CLL) and the less common T-cell CLL (T-CLL). In later stages of B-CLL, the increase in T cells in the marrow correlated well with the amount of erythroid suppression. After removing T-cells from the marrow, growth of CFU-E and BFU-E increased in vitro. In a patient with T-CLL and PRC A, the malignant T cells strongly suppressed CFU-E of normal bone marrow. This suppression was reversed when the cells were pre-treated with anti-lymphocyte serum and complement. More recently, the leukemic cells in a patient with T-CLL were found to suppress allogeneic BFU-E. Again, treatment with antithymocyte globulin reduced the number of leukemic cells and improved erythropoiesis.

Other hematologic malignancies associated with PRCA include Hodgkin’s disease, non-Hodgkin’s lymphoma, chronic myelogenous leukemia (CML), and acute lymphocytic leukemia. A young patient with Hodgkin’s disease and PRCA demonstrated a serum IgG inhibitor whose anemia and serum inhibitor disappeared after chemotherapy. Patients with malignant lymphoma, histiocytic type and poorly differentiated lymphocytic lymphoma have been described with PRCA, and although the pathogenesis is unproven, it was presumed to be autoimmune. In a patient with CML, a serum IgG inhibitor was identified which was cytotoxic to the patient’s marrow erythroblasts.

Thus, in secondary PRCA most associated conditions have demonstrated both humoral and cell mediated suppression of erythropoiesis, with the exception of CLL which acts primarily via T cell mediated suppression.

Discussion

The concept of autoimmune immunosuppression (especially T-cell suppression) is certainly not unique to PRCA. For example, in aplastic anemia, several studies have shown an inverse CD4+/CD8+ T-cell ratio which is at least partially corrected (as well as the anemia) by anti-lymphocyte globulin treatment. Suppressor T-cells have been identified which suppress both CFU-GM and BFU-E (granulopoiesis as well as erythropoiesis). In one patient with aplastic anemia, a role for the marrow-adherent cells was also demonstrated.

As stated, in two separate studies of patients with T cell lymphocytosis and cytopenia, five of six and five of seven patients demonstrated the monoclonal nature of the T cells. In the latter study the two of seven patients who did not reveal unique gene rearrangements showed only central (i.e., bone marrow) lymphocytosis. The prognostic significance of the gene rearrangement study remains unclear. The two “atypical” TCLC patients in the Berliner study did not require treatment. It may be that these patients (i.e., no unique gene rearrangements or lack of peripheral lymphocytosis) have a more benign prognosis. There is currently insufficient evidence to determine if Prednisone would be equally effective in the majority of patients where unique gene rearrangements are present.

References

5. BERLINER, N., DUBY, A. D., LINCH, D. C., et al.: T cell receptor gene rearrangements define a


34. NEWLAND, A. C., CATOVSKY, D., LINCH, D., et