Anemia in Lymphoproliferative Disorders

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The onset of anemia in patients with lymphoproliferative disorders can be attributed to various causes, including autoimmune hemolytic anemia, pure red cell aplasia, and anemia of chronic disease. A variety of interventions can provide benefit.

Introduction

The etiologies of anemia in patients with lymphoproliferative disorder (LPD) are diverse. Causes such as acute blood loss or deficiencies in iron or vitamins (folate/B12) are considered in the initial evaluation. In many instances, the anemia can be attributed to marrow infiltration by the LPD. Treatment with chemotherapy can suppress erythropoiesis. Other causes that occur more often with LPD are autoimmune phenomena such as autoimmune hemolytic anemia (AIHA) or pure red cell aplasia (PRCA). Finally, after excluding these conditions, anemia of chronic disease (ACD) is considered as the basis for the anemia.

In this review, the clinicopathologic features of AIHA, PRCA, and ACD associated with LPD are featured, and treatment options are discussed.

Autoimmune Hemolytic Anemia

AIHA is a common manifestation associated with LPD, particularly chronic lymphocytic leukemia (CLL). It is estimated that 10% to 20% of patients with CLL may develop AIHA sometime during the course of their illness.1-3 The development of AIHA does not have implications for the staging of CLL; instead, it is usually reported as a complication of progressing CLL.3

Classification

AIHA can be classified based on the characteristics of the autoantibody. Warm autoantibodies have optimum affinity for red blood cells at 37°C. In contrast, cold autoantibodies have optimum affinity for red blood cells at lower temperatures. AIHA associated with CLL is usually of the warm type. Waldenström’s macroglobulinemia is the most common LPD associated with cold AIHA.

Clinical Features

Clinical features of AIHA include symptomatic anemia, jaundice, and often splenomegaly. In addition, characteristic findings of the associated LPD are present. The diagnosis of AIHA can be suspected by a review of the peripheral blood smear that reveals characteristic findings of polychromasia, indicative of reticulocytosis, and spherocytes. Laboratory evidence of hemolysis includes indirect hyperbilirubinemia, a low haptoglobin, and a high serum LDH.

The definitive diagnosis of AIHA rests on demonstration of immunoglobulin or complement bound to red blood cells. The direct antiglobulin test can determine whether red blood cells are coated with IgG alone, complement alone, or IgG and complement. Further testing can determine the specificity of the autoantibody.

Pathogenesis

The pathogenesis of AIHA in CLL is not clear. CLL is characterized by a clonal expansion of CD5+ B cells. A normal CD5+ B-cell population has been identified, with a preponderance of these cells observed in fetal liver. It is of interest that these normal CD5+ B cells make autoantibodies, an observation that raises the question of whether the malignant CD5+ clone is responsible for the production of the autoantibodies seen in this condition. Most evidence would suggest that these autoantibodies are not products of the malignant clone.4 Recently, however, two studies have suggested otherwise. In these studies, eluted autoantibodies from red blood cells of two patients with AIHA expressed the same monoclonal light chain as the CLL clone.5 Efremov et al5 showed restricted V\textsubscript{H} gene utilization in leukemic cells from CLL patients with AIHA. Moreover, a similar CDR3 region observed in leukemic cells from four patients suggested that autoantibodies produced by CLL cells were directly involved in the pathogenesis of AIHA.

Treatment

The mainstay of treatment of AIHA associated with CLL is prednisone, at a dose of 1 mg/kg per day. Cytotoxic agents such as cyclophosphamide can be prescribed in cases of prednisone failure. Splenectomy is considered in patients refractory to these treatments.1

Pure Red Cell Aplasia

PRCA is characterized by a severe normochromic, normocytic anemia, reticulocytopenia, and erythroid hypoplasia. Megakaryocytic and myeloid development is normal. Autoimmune diseases, thymoma, and LPD diseases are known to be associated with PRCA. The largest single institutional experience regarding PRCA was recently published from the Mayo Clinic (Table 1).5 More than half of the cases remained idiopathic. However, approximately one third were associated with LPD, and large granular lymphocyte (LGL) leukemia is the disorder most commonly associated with PRCA, being observed in almost 20% of these cases. LGL leukemia is caused by a clonal proliferation of LGL.7 Phenotypically, these cells are CD3+, CD8+, CD57+, and clonality can be demonstrated using T-cell receptor gene rearrangement studies. It is likely that the association between LGL leukemia and PRCA is stronger than reported since T-cell receptor gene rearrangement studies were not performed in the majority of patients in the Mayo Clinic series.6

Table 1. -- Pure Red Cell Aplasia: Mayo Clinic Experience in 47 Adult Patients With Pure Red Cell Anemia
Pathogenesis and Treatment

Several pathogenetic mechanisms of PRCA have been elucidated, including IgG- or lymphocyte-mediated suppression of erythropoiesis. T-cell-mediated suppression appears to be the usual explanation for PRCA in patients with LPD, particularly in patients with LGL leukemia. A variety of treatments have been reported in PRCA associated with LPD. The best responses seem to be attained with oral cyclophosphamide or cyclosporine.

Anemia of Chronic Disease

ACD is characterized as a moderate normo-chromic, normocytic anemia (Table 2). Several mechanisms have been implicated in the pathogenesis of ACD, including shortened red cell survival, impaired iron utilization, and decreased responsiveness to erythropoietin (EPO). Current thinking hypothesizes that ACD is a cytokine-mediated disorder.

Treatment of Lymphoproliferative Diseases With Erythropoiesis

Because LPD patients often have inappropriately low EPO levels for their degree of anemia, a few studies have examined whether they might respond to administration of EPO (Table 3). Osterborg and colleagues gave EPO to 37 patients with low-grade non-Hodgkin’s lymphoma (NHL) and to 19 patients with CLL. Although a trend showed an increased response rate (rise in hemoglobin above 2 g/dL) in patients treated with EPO compared with the control group not receiving EPO, this difference was not statistically significant. In contrast to this result, Cazzola et al reported a favorable response in EPO-treated patients with LPD compared with similar patients not receiving EPO. This study reported an approximate 60% response rate to EPO in patients with either multiple myeloma or LPD. Sixty-two patients with NHL/CLL were included in this analysis. The best predictor of EPO responsiveness was an inappropriately low EPO level.

References

DR SPIVAK

Recently I noticed a report from France about erythropoietin antibodies in a patient with red cell aplasia. To my way of thinking, erythropoietin is such a highly conserved protein on an evolutionary basis that, in all the patients who have received recombinant erythropoietin, it is almost impossible to find a one who has an antibody. I then found two more reports on erythropoietin antibody. All three of these reports involved patients with red cell aplasia, so I have adjusted my thinking. For example, I saw a patient last week who has had an intractable thymoma for 10 years and now has red cell aplasia. I drew an erythropoietin level, just to see where we were, because if it is high, the question of antibody involvement arises. In the differential diagnosis of red cell aplasia, I think we must start thinking about the possibility of antierythropoietin antibodies.

DR ZUCKERMAN

Along a similar line, there are patients with CLL who have monoclonal immunoglobulin who happen to have anti-red cell function. Did these people present with anemia, and then CLL was discovered? You would think this to be the case if they have that antibody all the time.

DR LOUGHRAN

I think that these patients were found to have CLL first.

DR ZUCKERMAN

Why do CLL patients get it? Is their defect that they cannot make antibodies appropriately? If so, then why make inappropriate ones? Why are they so readily able to immunize against their red cells when they cannot immunize against nasties from outside?

DR LOUGHRAN

I am not sure we know the answer. It may be related to abnormal regulation of B cells by T cells. A similar observation is found in aging with declining T-cell function. So, presumably, it is a similar situation in CLL, where there are also known defects in T-cell function.

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