Efficacy of Rituximab in Refractory Cold Agglutinin Hemolytic Anemia in a Patient with Ataxia-Telangiectasia

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Ataxia-telangiectasia (A-T) is a rare autosomal recessive multisystem disorder caused by mutations in the ATM gene and characterized by progressive neurodegeneration, cerebellar ataxia, oculocutaneous telangiectasia, and chromosomal instability, with an increased risk of malignancy and immunodeficiency [1]. Cold agglutinin disease (CAD) is a poorly understood disorder that comprises about 15% of chronic autoimmune hemolytic anemia. It usually presents in the seventh decade of life and predominantly affects women. It is caused by high titers of cold antibodies, usually immunoglobulin M (IgM) against red blood cell antigens, triggering the activation of complement and resulting mainly in C3b antigen sequestration followed by extravascular hemolysis in the reticuloendothelial system, and to a lesser extent intravascular hemolysis associated with C5 activation [2]. Cold agglutinin hemolytic syndromes comprise idiopathic CAD, and CAD secondary to other conditions, including lymphoproliferative disease, infections such as Mycoplasma pneumonia and Epstein-Barr virus, and paroxysmal cold hemoglobinuria. Although CAD associated with infection may be mild and self-limited, treatment of other forms of cold agglutinin hemolytic anemia may be challenging.

Because lymphoma is common in patients with A-T, it is particularly important to exclude underlying malignancy when chronic hemolysis is observed in these patients. We describe here a young male patient with A-T who presented with severe CAD resistant to corticosteroid and intravenous immunoglobulin (IVIG) treatment. An excellent response to the monoclonal anti-CD20 antibody rituximab was observed.

PATIENT DESCRIPTION

An 18 year old male presented with severe weakness. He had been diagnosed with A-T at the age of 4 years after presenting with motor delay, ataxia and oculocutaneous telangiectasias. The diagnosis was confirmed by elevated alpha-fetoprotein levels, increased chromosomal sensitivity to ionizing radiation, and deficient ATM protein expression demonstrated by Western blotting. At age 13 years, following recurrent viral and pulmonary infections and appearance of hypogammaglobulinemia, monthly IVIG replacement therapy was initiated.

On admission he looked extremely pale and was tachycardic, with good peripheral perfusion. Laboratory evaluation revealed a hemoglobin concentration of 4.1 g/dl, normal white blood cell and platelet counts, and findings consistent with hemolysis (undetectable serum haptoglobin, indirect hyperbilirubinemia, elevated lactate dehydrogenase, reticulocytosis). Numerous nucleated red blood cells (RBC), normochromic normocytic red cells and spherocytes, but no lymphoblasts were observed on a smear of peripheral blood. Direct Coombs' test was strongly positive for C3d and IgM. RBC agglutination was observed at 4°C and room temperature, but not at 37°C. Cold agglutinin titer was high. No monoclonal bands were detected by serum electrophoresis. Cryoglobulins were absent.

To further evaluate the etiology of the anemia and to exclude malignancy, a bone marrow examination was performed, revealing erythroid hyperplasia, increased number of megakaryocytes, and absence of malignant cells. The rest of the hematological workup, including coagulation tests, serum levels of folic acid, iron, transferrin, and total iron binding capacity, was unremarkable.

Infection workup was negative for cytomegalovirus, Epstein-Barr virus and human immunodeficiency virus blood DNA examined by polymerase chain reaction. No IgM antibodies to parvovirus B 19, human herpes virus or Mycoplasma pneumonia were found. Hepatitis B surface antigen, hepatitis B and C serology were negative. Immunology workup was normal, including antinuclear antibody, circulating lupus anticoagulants, anticardiolipin and anti β2 glycoprotein IgM and IgG antibodies, and levels of complement C3 and C4. Magnetic resonance imaging of the head, spine and chest, chosen because of radiosensitivity in A-T patients, did not reveal findings consistent with malignancy. An abdominal ultrasound showed splenomegaly.

The patient was treated with pre-warmed packed red blood cells (PRBC), intravenous methylprednisolone (1000 mg/day for 3 days), IVIG in immunomodulatory dose (2 g/kg) and additional high dose intravenous corticosteroids, but hemolysis persisted, requiring 19 PRBC transfusions.

Treatment with rituximab, an anti-CD20 monoclonal antibody, at a dose of 500 mg

was added once weekly. After four doses, corticosteroids were discontinued, and the patient's hemoglobin level returned to normal with no signs of hemolysis; Coombs' test was negative. During 23 months of follow-up, the patient's hemolytic anemia remained in complete remission, with a hemoglobin level of 16 mg/dl.

COMMENT

Autoimmune phenomena, once considered paradoxical, are frequently observed in patients with various primary and secondary immunodeficiencies. Several molecular and cellular mechanisms that interconnect these conditions have been described.

A-T patients have combined humoral and cellular immunodeficiency. The humoral abnormalities are caused by disturbed naive B and T cell homeostasis, which leads to reduced immune repertoire and reduced memory B cell formation. The most common humoral findings include decreased serum concentrations of IgA, IgG2 and IgG4, abnormal IgM levels, and impaired functional antibody responses, particularly to polysaccharide antigens. The cell-mediated immune abnormalities include decreased numbers of naive CD4 T cells and T cell receptor excision circles in peripheral blood, as well as a restricted alpha-beta T cell receptor repertoire [3].

CAD, classically seen in older adults, is caused mainly by monoclonal IgM and is associated with lymphoproliferative disorders. In younger patients, post-infectious polyclonal cold agglutinins may appear following certain viral and bacterial infections. Our patient had neither a history nor signs of recent infection. In addition, various conditions associated with an acute-phase reaction, such as febrile illness or trauma, may cause exacerbation of the CAD hemolysis, possibly by enhanced production of complement [2]. Hemolysis may be due to immune dysregulation.

In a large series of CAD patients, underlying hematologic diseases (monoclonal gammopathy and lymphoproliferative disorders) were identified in 76% of patients [2]. Although the risk of developing cancer in A-T patients is 1000 times higher than in the general population, with hematologic malignancies leukemia and lymphoma being the most common, an extensive evaluation for possible malignancy was negative in our patient.

Treatment of chronic CAD includes corticosteroids, steroid-sparing immunosuppressive drugs and alkylating agents. However, response is often unsatisfactory. Splenectomy, considered the most effective second-line therapy for chronic autoimmune hemolytic anemia, is not effective in CAD. Significantly better response to rituximab therapy has been reported recently in elderly adults [4].

Rituximab is a humanized monoclonal antibody directed against CD20, an antigen expressed on normal B cells and tumor B cells. Symptomatic hypogammaglobulinemia has been observed in some patients who received multiple courses of this form of therapy [5]. However, this is of less concern regarding A-T patients receiving immunoglobulin replacement therapy for hypogammaglobulinemia. Rituximab mechanisms of action include B cell depletion and suppression of B cell pathologic activities, such as autoantibody production, complement and antibody-dependent cytotoxicity and antigen presentation.

To the best of our knowledge this is the first reported case of cold agglutinin hemolytic anemia in a patient with A-T. This entity should be considered as a differential diagnosis of anemia in A-T patients, and treatment with rituximab may achieve good results in these patients.

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References

1. Savitsky K, Bar-Shira A, Gilad S, et al. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. *Science* 1995; 268: 1749-53.
2. Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. *Blood* 2013; 122 (7): 1114-21.
3. Kraus M, Lev A, Simon AJ, et al. Disturbed B and T cell hemostasis and neogenesis in patients with ataxia telangiectasia. *J Clin Immunol* 2014; 34 (5): 561-72.
4. Petz LD. Cold antibody autoimmune hemolytic anemias. *Blood Rev* 2008; 22 (1): 1-15.
5. Casulo C, Maragulia J, Zelenetz AD. Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. *Clin Lymphoma Myeloma Leuk* 2013; 13 (2): 106-11.