Livedo reticularis associated with autoimmune hemolytic anemia: prolonged remission induced by peripheral blood stem cell transplantation relapse after 10 years and restoration of hemoglobin levels by rituximab

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ABSTRACT

Autoimmune hemolytic anemia (AIHA) is a disease where patients produce antibodies against erythrocytes directed towards membrane glycoproteins adsorbed onto the erythrocyte surface. Drugs and other associations have been implicated. It is described and discussed a case of livedo reticularis associated with AIHA treated with peripheral blood stem cell transplantation (PBSCT) that went into full remission for 10 years. After that period the patient relapsed and was treated with antibody anti-CD20, rituximab, and is now in full remission. The role of PBSCT and rituximab in the treatment of AIHA will be discussed.

Keywords: cell transplantation, autoimmune hemolytic anemia, livedo reticularis.

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is a disease where patients produce antibodies against erythrocytes directed towards membrane glycoproteins adsorbed onto the erythrocyte surface. The etiopathology is still not fully understood. Drugs, viral infections, and association with other autoimmune diseases have been implicated. Steroids are the first choice treatment, followed by intravenous immunoglobulin, in cases where there is no response and control can only be achieved by maintenance with high dose of corticosteroids. Danazol, cytotoxic drugs, and splenectomy also have been used as an alternative treatment.[1,2]

It is described and discussed a case of livedo reticularis associated with AIHA treated with peripheral blood stem cell transplantation (PBSCT) that went into full remission for 10 years. After that period the patient relapsed and was treated with the antibody anti-CD20 rituximab and is now in full remission. The role of PBSCT and rituximab in the treatment of AIHA will be discussed.

CASE REPORT

LKS, female, 67 years old, presented with bilateral livedo reticularis in lower limbs and chronic anemia. A diagnosis of cold immune hemolytic anemia was performed on May 1994 by conventional methods including biochemistry, immunological testing and bone marrow evaluation. She was treated with dexamethasone 8 mg/day for three consecutive months followed by prednisone 1 mg/kg/weight. The skin

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lesions disappeared and her hemoglobin levels stabilized around 10.0 g/dL. Due to the presence of severe side effects, the patient was switched to chlorambucil (dose 0.2 mg/kg/weight – 61 kg) on December 1994 till June 1995. At that time chlorambucil was increased to 12 mg/day. On September 1995 she was admitted to our hospital with marked pancytopenia (maybe chlorambucil related). Marrow was hypoplastic with spotted morphologic signs of dysplasia. She was treated with granulocyte factor and transfusions, with recovery of the leukocyte and platelet series. However, hemoglobin remained low with signs of active hemolysis and presence of cold agglutinins. Autologous stem cell transplantation was performed using mobilization with granulocyte colony stimulating factor (G-CSF) and conditioning with high dose of cyclophosphamide (750 mg/m^2 every 12 hours during four days – total dose 6 g/m^2). Simultaneous sessions of plasmapheresis were also performed. The patient was discharged two months after the procedure and between mid-1996 and August 2007 she received intermittent blood transfusions. These transfusions may reflect a late clinical remission scenario. The patient presented in August 2007 with signs and symptoms of relapse with anemia, presence of cold agglutinin, arthralgias and livedo reticularis. Direct Coombs was positive, with presence of immunoglobulin G monoclonal protein (IgG) in electrophoresis. Computed tomography (CT) scans of the chest and abdomen were normal, with no presence of peripheral lymphadenopathy detected. Bone marrow biopsy was negative for lymphocyte infiltration.

On August 2007 she was started on rituximab, four weekly injections (375 mg/m^2) and went into remission. On March 2008 the patient relapsed again and received a new course of rituximab, and subsequently three additional cycles using the same previous scheme.

After recurrence, it was decided to use rituximab instead of starting rotation prior to therapy of corticosteroids, intravenous immunoglobulin (IVIG), considering previous failure. Rituximab's eventual failure would bring the possibility of a second stem cell transplant, which was not described as required.

DISCUSSION

Since 1996, data have been reported suggesting that PBSCT is an option for treatment of severe autoimmune disease patients who failed conventional therapy. In 1999 Tyndall et al.[3] published the first results of a multicenter prospective trial which enrolled 74 consecutive adult patients with severe autoimmune disease treated with PBSCT. Of 60 patients who were available for evaluation after transplantation, 40 showed clear disease's improvement.[4] A subsequent publication by the same authors 10 years later reports on over 700 patients suffering from severe autoimmune disease. On that series, 11 patients had AIHA, but the outcomes were not reported. Subsequent studies by the National Institutes of Health and the registry of the European Group for Blood and Bone Marrow Transplantation reported data on refractory autoimmune cytopenias. The USA group had a 57% response rate and no early deaths. On the European group there were seven cases; two were not PBSCT but allogeneic. The latter went into remission, while on the PBSCT only one patient had a transient response. In summary, data reported so far shows that approximately half of the patients developed complete response, and the remainder split among partial responses, no response, or severe adverse events, including death.[5] Our case seems to present the longest follow up period reported so far, and from our reviews one patient's remission lasted over four years. The disappearance, remission and reappearance of livedo reticularis with cryoagglutinin indicate that instead of other causes of livedo reticularis (such as ischemic ulcers or acrocyanosis), they appear to be related with the presence of autoantibody.

The possibility of eliminating autoreactive B cell clones with the chimeric monoclonal antibody rituximab has made it an attractive treatment for antibody mediated autoimmune diseases. Its use in AIHA has generated growing interest and the incidence of response has been high in most series including as well other immunecytopenias.[6–11] At the time of diagnosis, this medication was not available; however, we believe that the observed response is the longest reported in the literature. Almost all patients with immune cytopenias relapse after periods of time. Our patient relapsed after six months and a new course of anti-CD20 was applied. When stem cell transplantation is successful in such cases, remission is in general considerably longer than after rituximab use. Advantages and disadvantages of both procedures and proper comparison could come from head-to-head studies, which currently are not available and perhaps never will, taking into consideration the high incidence of adverse events associated with transplantation.[12–14]

Where did B cell autoimmune clones hide for 12 years, like in our case, is subject of intense speculation. Very recent data show that using highly sensitive flow cytometric analysis, one can detect clonal B lymphocytes in the peripheral blood as long as six years before the appearance of chronic lymphocytic leukemia. It is possible that similar techniques in patients like ours may find similar results. In the meantime, where autoimmune B cells hide (as recently suggested by Vogt and Kyle) remain a secret.[15]

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