case report

Rituximab therapy in a patient with autoimmune hemolytic anemia and immune thrombocytopenia associated with chronic lymphocytic leukemia

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Autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia are relatively common in chronic lymphocytic leukemia (CLL), but the presence of both in the same patient is rare. The combination of AIHA and immune thrombocytopenia is known as Evans syndrome which is an idiopathic disorder without an underlying cause.[1] Evans syndrome may also develop as a secondary syndrome in association with a variety of conditions like CLL, systemic lupus erythematosus (SLE) and following autologous or allogeneic stem cell transplantation.[2-5] This syndrome can be resistant to a variety of therapeutic measures and associated with significant morbidity and mortality. Rituximab is a monoclonal antibody against CD20 antigen present on B-lymphocytes. It has shown promise in the treatment of many hematologic and non-hematologic immunologic disorders. We present the case of a 68-year-old patient with AIHA and immune thrombocytopenic purpura (ITP) associated with CLL and discuss the role of rituximab in its management.

CASE

A 68-year-old Saudi male presented to the emergency department with dizziness, fatigability, anorexia and undocumented weight loss associated with intermittent fever and sweating of 3 months duration. He also complained of dark colored urine of a few days duration. The severity of symptoms increased 2 weeks prior to presentation. He was known to suffer from bronchial asthma and hypertension, which were well controlled on regular treatment. Physical examination revealed jaundice, pallor and generalized lymphadenopathy. The largest lymph nodes measured 2×2 cm in the axilla. He was apyrexial with normal vital signs. Examination of the chest, heart and nervous system was normal. Abdominal examination revealed an enlarged liver 6 cm below the costal margin and a palpable spleen 5 cm below the costal margin. Full blood count revealed a high white blood cell (WBC) count at 33×10^9/L (normal range, 4-11×10^9/L), low hemoglobin at 4.3 g/dL (normal range, 13-17 g/dL) and low platelets at 97×10^9/L (normal range, 150-400×10^9/L). The white cell differential was 16% neutrophils and 82% lymphocytes. A peripheral smear showed lymphocytosis with small mature lymphocytes, many smear cells and polychromasia. Total and indirect bilirubin were raised (38 and 25.3 μmol/L, respectively) with normal liver enzymes. The direct Coombs test was strongly positive. Hematinic assays (serum iron, vitamin B12 and folate level) were within the normal range. Bone marrow aspiration and biopsy showed hypercellular bone marrow heavily infiltrated with small mature lymphocytes. Erythropoiesis was increased but megakaryocytes were normal in number. Normal or increased megakaryocytes are very much consistent with ITP, particularly in a patient with bone marrow infiltrated with CLL, like our patient. Cell markers on the peripheral blood and bone marrow were positive for CD5, CD23, CD19/CD20, weakly positive for surface membrane immunoglobulins and negative for CD10, CD79b, CD103 and FMC-7, consistent with B-cell CLL. The patient was diagnosed as having CLL associated with AIHA and immune thrombocytopenia (secondary Evans syndrome) on the basis of these findings.

He received blood transfusions and was started on methylprednisolone 100 mg daily. Chlorambucil pulse therapy was started at a dose of 20 mg daily for 7 days. He continued to hemolyze and the platelet count dropped to 18×10^9/L after 4 weeks despite administration of steroids and the one pulse of chlorambucil therapy. There was no change in the lymph node and

spleen size. Therapy with a fludarabine-based regimen was considered but withheld because of the fear of exacerbating the immune phenomena. He was started on rituximab 375 mg/m^2 weekly for 4 doses. His platelet count improved to 47×10^9/L three weeks after starting rituximab and his hemoglobin started to improve. The platelet count reached 122×10^9/L and remained stable above 100×10^9/L. The hemoglobin normalized 3 weeks after the last dose of rituximab. The peripheral lymph nodes disappeared completely and the spleen became impalpable. He continued to do well for 7 months when his platelet count dropped again to 15×10^9/L. The WBC count and hemoglobin remained normal. A repeat bone marrow biopsy showed continued infiltration with CLL, but with increased megakaryocytes (Figure 1). He received a course of steroids along with intravenous immunoglobulins without any improvement in platelet count. In view of this, a second course of rituximab was started. His platelet count started to improve after the second weekly dose and normalized after the third dose (173×10^9/L). He continued to do well, maintaining a platelet count above 100×10^9/L after 6 months of follow-up. Treatment modalities in relation to the response of hemoglobin and the platelet count are shown in Figure 2.

DISCUSSION

CLL is a common lymphoproliferative disorder and may be associated with immunological disorders like AIHA and ITP. Both of these disorders, particularly AIHA, are common in CLL at presentation or during the course of the disease, but the presence of both at the same time or sequentially is rare. The combination of Coombs-positive hemolytic anemia (AIHA) and ITP is known as Evans syndrome. This is a rare immunological disorder with an absence of an underlying etiology that was first described by Robert Evans in 1951.[1] Evans syndrome may also develop as a secondary syndrome in association with different diseases like collagen vascular diseases, lymphoproliferative disorders like CLL and multicentric Castleman disease, following autologous or allogeneic stem cell transplantation, or in response to certain chemotherapeutic or biological agents like interleukin-2 therapy.[2-8] The combination of AIHA and ITP in association with other disorders including CLL has been labeled as "secondary Evans syndrome" by various authors and investigators and is well documented in the literature.[2-4]

Evans syndrome appears to be rarer in adults as most of the studies published are from the pediatric age group.[9,10] There are a few reports in adults, mostly in the form of case reports.[2,11] Various therapeutic regimens, including corticosteroids, intravenous immunoglobulins, splenectomy and immunosuppressants have been used in primary and secondary Evans syndrome. It appears that most of these measures are unsuccessful in refractory cases[4,9-11] and even bone marrow transplantation has been carried out in some of these patients.[12] A survey in North America showed that Evans syndrome is a chronic disorder with significant morbidity and mortality.[10] It has also been shown that one component (AIHA or ITP) of Evans syndrome may respond to treatment while the other component remains refractory to therapeutic measures.[10,11] Because of the resistant nature of this disease and refractoriness to different modalities of treatment, there is a need to develop new forms of therapy with minimal toxicity.[4]

Rituximab (Mabthera, F. Hoffman-La Roche Ltd, Basel, Switzerland) is a chimeric monoclonal antibody that targets CD20 antigen on B lymphocytes.

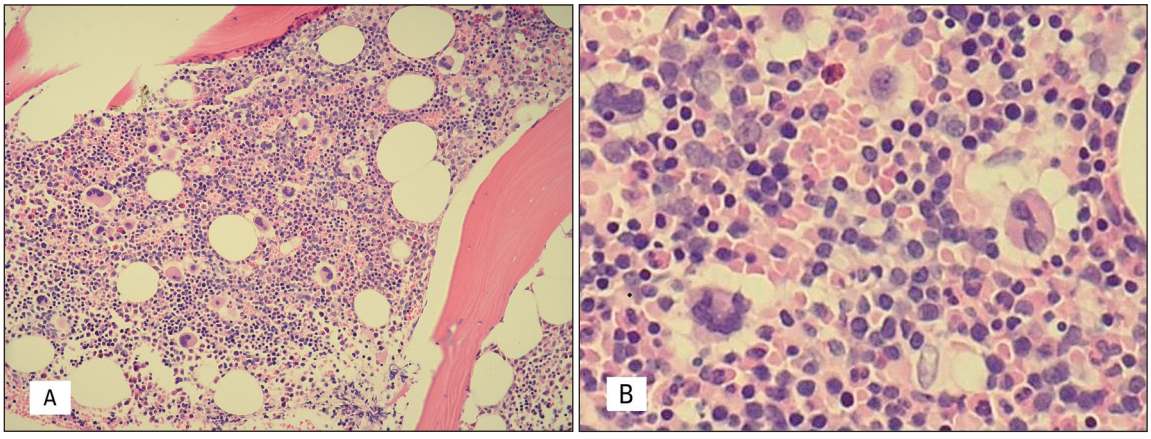

Figure 1. Bone marrow trephine biopsy of the patient showing diffuse infiltration with small lymphocytes and plentiful megakaryocytes in (a) low power (hematoxylin and eosin stain ×20) and (b) high power (hematoxylin and eosin stain ×40).

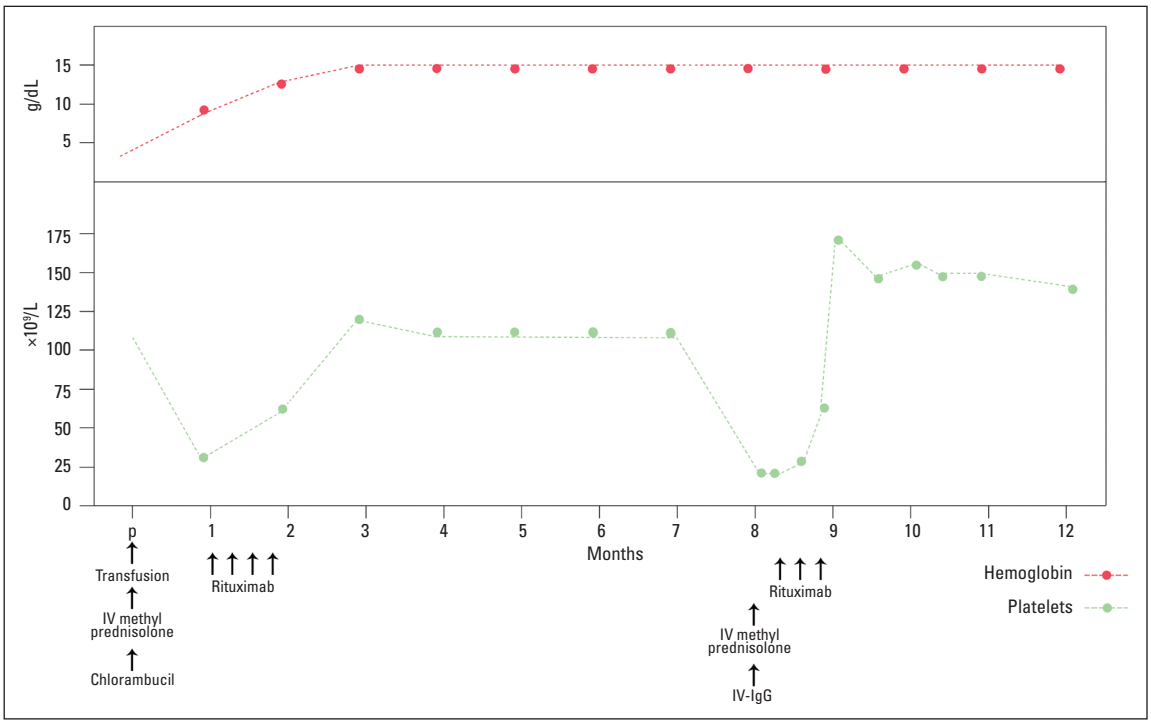

Figure 2. Hemoglobin and platelet count in relation to treatment.

Mechanisms of action of rituximab are believed to be induction of apoptosis, complement-mediated cell toxicity and antibody-dependent cell toxicity.[13] It has efficacy against various B-cell lymphoid malignancies and has become a part of the therapeutic regimens in different types of non-Hodgkin's lymphomas and CLL.[14]

Because of the action of rituximab on B-lymphocytes and its ability to reduce antibody production, it seems to have effectiveness in many immune hematological disorders.[15] During the last few years, reports have appeared showing the effectiveness of rituximab in many resistant immune hematological disorders, particularly isolated ITP and AIHA as well as in these disorders when associated with CLL.[16-22] Evans syndrome associated with CLL is very rare. Our literature search identified only one such case treated with rituximab. Seipelt et al reported a case of prolymphocytoid transformed B-CLL with Evans syndrome refractory to alkylating agents and purine analogues. The patient was successfully treated with rituximab leading to an improvement in platelet count and a drop in lymphocyte count.[3] Our case highlights the use of rituximab in a patient with AIHA and ITP associated with CLL at the time of initial diagnosis. Some patients with CLL who receive fludarabine may develop ITP or AIHA,[23,24] hence our hesitation to use this treatment in our patient. Interestingly, CLL patients who develop ITP or AIHA due to fludarabine, may respond to rituximab.[25,26]

In summary, our case and other previously reported cases suggest that rituximab may be an effective therapy in patients with AIHA and ITP (Evan syndrome). It may have the additional benefit of reducing the leukemia burden and should be considered in patients resistant to conventional treatment.

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