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CASE REPORT

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Recurrent autoimmune hemolytic anemia in splenic marginal zone lymphoma

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ABSTRACT

Autoimmune hemolytic anemia (AIHA) is a condition associated with an extensive differential diagnosis that includes lymphoid malignancies. Although AIHA occurs in about 10–25% of patients with chronic lymphocytic leukemia, it is also reported to occur in all of the other lymphoid subtypes. In this article, we report a case of recurrent AIHA in a 67-year-old woman with two acute episodes of hemolysis separated by 3 years of hematologic remission. Both episodes were severe enough to require blood transfusion, oral steroids, and rituximab. Bone marrow biopsy and immunophenotyping using flow cytometry done during both admissions confirmed the presence of splenic marginal zone lymphoma.

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Rituximab; autoimmune hemolytic anemia; splenic marginal zone lymphoma; prednisone; splenectomy

1. Case report

A 67-year-old woman presented to the emergency room with a 2-month history of generalized weakness, fatigue, night sweats, intermittent fever, and unintentional 9-kg weight loss. Three years prior to presentation, she reported similar symptoms and was diagnosed with autoimmune hemolytic anemia (AIHA) secondary to splenic marginal zone lymphoma (SMZL), managed with oral steroids and seven doses of rituximab leading to clinical remission.

Vital signs on this presentation were within normal limits, including normal oxygen saturation of 96% on ambient air. Physical examination revealed conjunctival pallor, scleral icterus, and bilateral axillary lymphadenopathy. Abdominal examination was notable for mild splenomegaly.

Laboratory tests showed hemoglobin count of 6.3 g/dL (12–16 g/dL) with mean corpuscular volume 107.7 fL (80–99 fL), reticulocyte count 18.8% (0.5–2.0%), lactate dehydrogenase level 270 U/L (100–225 U/L), haptoglobin level <30 mg/dL (44–215 mg/dL), and total bilirubin level 3.8 mg/dL (0.2–1.3 mg/dL) with Coombs test positive for antibodies detected on her red blood cells. Peripheral blood smear showed reticulocytosis and minimal spherocytosis with hypochromic cells. Platelet count, basic metabolic panel, iron studies, folate level, and vitamin B12 level were all within normal limits. Hepatitis C serology was negative. CT scan of the abdomen identified splenomegaly along with a partially calcified mass within the anterior spleen. Repeat bone marrow biopsy was performed, and histology revealed the presence of low-grade B-cell lymphoma. Peripheral blood immunohistochemistry analysis identified cells with CD19, CD20, and FMC7 but negative for CD3, CD5, and CD103.

She was initially transfused with packed red cells, and 80 mg oral prednisone daily was commenced with folic acid supplementation. Her hemoglobin count improved from 6.2 g/dL on admission to 8.4 g/dL on day 3. She responded promptly and was discharged on tapered steroid dose. She completed her course of oral steroid on the tenth day post-discharge and was followed up in the hematology clinic with regular monitoring of her hemoglobin. After about 3 months, a routine complete blood count (CBC) showed hemoglobin count of 7 g/dL, down from 11 g/dL the preceding month. This time, she was placed on oral prednisone 60 mg to taper and weekly rituximab for 4 weeks and thereafter maintained on rituximab every two months planned for the next 2 years, with close monitoring of CBC for early detection of recurrence.

2. Discussion

Autoimmune hemolytic anemia (AIHA) is a disorder that affects 0.017% of the general population [1]. It is caused by antibody production against red blood cell antigens, resulting in shortened red cell survival. AIHA can be idiopathic or secondary and characterized as warm, cold, or mixed types based on the thermal range of the antibody activity. Warm AIHA comprises 80–90% of all AIHA cases. It is mediated mostly by immunoglobulin G and is associated with connective tissue diseases, viral exposures, and malignancies including lymphomas [2].

Splenic marginal zone lymphoma (SMZL) is a rare type of non-Hodgkin lymphoma (NHL),

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accounting for approximately 1% of total B-cell NHL [3], and was believed to be the cause of recurrent AIHA in this case. In case series of SMZL patients, approximately 25% were documented to have some autoimmune disorders, most commonly autoimmune cytopenias, which are sometimes the presenting feature of the disease [4,5]. As described in our case, symptoms of AIHA may be nonspecific, including fatigue, intermittent fever, and weight loss. Splenomegaly is usually present due to chronic extravascular hemolysis. Markers of red cell hemolysis are usually present including decreased serum haptoglobin, elevated lactate dehydrogenase, and increased serum bilirubin. In cases of antibody-driven extravascular hemolysis, spherocytosis is present, as was in our patient.

Based on evidence of acute antibody-mediated hemolytic anemia and given the patient's history of SMZL, our top suspicion was a recurrence of her low-grade B-cell lymphoma. We also considered the possibility of other lymphoid malignancies. Chronic lymphocytic leukemia was excluded based on absence of lymphocytosis and negative CD38 on flow cytometry. Other T-cell markers were also absent on immunohistochemistry, essentially ruling out other T-cell lymphomas. Hodgkin lymphoma was excluded by the absence of Reed–Sternberg cells on bone marrow histology and by flow cytometry. Although genetic testing for NOTCH2 and TP53 was not done in our patient, studies have shown that these gene mutations are independent markers of poor prognosis [6]

Most patients respond to oral steroids, but only about 15–20% will undergo complete remission without requiring maintenance doses [7]. Steroid-resistant patients are treated with anti-CD20 therapies such as rituximab. Rituximab monotherapy is effective in SMZL with results similar to splenectomy and without the resultant post-splenectomy complications [8,9]. Studies comparing the overall survival of patients with SMZL treated with splenectomy and rituximab did not show any advantage of splenectomy over rituximab. Currently, no guidelines exist for splenectomy in SMZL patients, however, it can be considered in patients with bulky splenomegaly and cytopenias without extensive bone marrow infiltration or in patients with repeated failed rituximab treatments [10]. Management approach should be based on the extent of the disease and individual patient characteristics.

Studies have also shown that the presence of AIHA in patients with SMZL confers poor prognosis and serves as a marker of disease activity [11] hence the need to consider this during risk stratification of patients.

Learning points

- Although uncommon, recurrent autoimmune hemolytic anemia from SMZL does occur, sometimes being the harbinger of relapse.
- Rituximab remains the preferred treatment option in steroid-resistant patients with SMZL except in certain circumstances.

Disclosure statement

No potential conflict of interest was reported by the authors.

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