Autoimmune Hemolytic Anemia and Pure Red Cell Aplasia Associated with Immunotherapy

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Introduction

Autoimmune hemolytic anemia (AIHA) is an acquired premature destruction of red blood cells by antibodies that target red blood cell antigens without adequate compensation. Symptoms include weakness, dizziness, dyspnea, and pallor. Treatment includes stopping the offending agent, corticosteroids, and rituximab. Immunotherapy, especially immune checkpoint inhibitors (ICIs), has expanded in the treatment of cancer leading to an increase in immunotherapy associated adverse effects. Although AIHA and pure red cell aplasia (PRCA) are rare adverse effects, they can occur at any time after initiating immunotherapy and are life-threatening.

Case

A 48-year-old male with a past medical history of metastatic melanoma to liver, brain, and lung treated with Ipilimumab/ Nivolumab and radiation presented with fevers and fatigue. Initial hemoglobin was 4.5 g/dL (baseline 9 g/dL), and blood transfusion was given. The last dose of Ipilimumab/Nivolumab was nine days prior to admission. Laboratory studies demonstrated elevated LDH of 750 U/L, elevated bilirubin of 1.9 mg/dL, low red blood cell (RBC) count of 1.67 mill/cmm, low reticulocyte count of 0.0014 mill/cmm, and low haptoglobin of < 3. Direct antiglobulin test was positive for IgG. COVID-19, hepatitis, parvovirus, and HIV were negative. Findings were consistent with AIHA and pure red cell aplasia secondary to Ipilimumab/Nivolumab. The patient received one dose of pulse dose steroids, followed by IV solumedrol 100 mg twice daily, and was tapered to oral prednisone 100 mg daily. He also received IVIG and rituximab with resolution of symptoms. Repeat testing one week after hospitalization demonstrated hemoglobin of 6.2 g/dL, RBC count of 2.25 mill/cmm, reticulocyte count of 0.0032 mill/cmm, bilirubin 0.5 mg/dL, and LDH of 286 U/L. The patient was treated with rituximab instead of immunotherapy and remained on steroids for nine months.

Discussion

Over the last decade, immunotherapy has played a major role in the treatment of metastatic melanoma, which has a poor five-year prognosis. Tumor cells secrete cytokines that suppress the body's T-cell mediated cytotoxic destruction. Immune checkpoints keep T cells inactive to protect normal host tissue. In the presence of cancer cells, ICIs allow T cells to appropriately respond to invading tumor cells. Two of the most clinically studied ICIs are anti-PD-1 (i.e. Nivolumab) and anti-CTLA-4 (i.e. Ipilimumab). Combination immunotherapy with Ipilimumab/ Nivolumab was approved in 2015. There have been case reports demonstrating single agent immunotherapy associated with AIHA, but possibly only one other case report demonstrating double agent immunotherapy associated AIHA as seen in this case.[1] This case is unique because not only did the patient have AIHA associated with immunotherapy, but they also had PRCA. Despite not having bone marrow biopsy results, low reticulocyte count that improved with discontinuation of immunotherapy would support this diagnosis. AIHA and PRCA are rare, life-threatening complications of immunotherapy that need prompt treatment and take several months to resolve.

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