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Hemophagocytic lymphohistiocytosis due to pembrolizumab therapy for adenocarcinoma of the lung

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder of dysregulated inflammation. It is most commonly seen in children who have a predisposing genetic mutation. However, adults can contract an acquired version of the disorder secondary to an infectious, neoplastic, or other inflammatory insult. There have been several documented cases of HLH being induced by treatment with immunotherapy. Here, we present the case of a 71-year-old man who was receiving pembrolizumab for lung adenocarcinoma when he developed HLH following his 14th cycle of therapy. Although bone marrow biopsy was negative, he nevertheless fulfilled the diagnostic criteria of the HLH 2004 report and was treated with high-dose steroids followed by a prolonged taper, with resolution of his symptoms and normalization of his blood counts.

KEYWORDS Hemophagocytic lymphohistiocytosis; immune checkpoint inhibitors; immunotherapy; pembrolizumab

Immunotherapy has introduced a new frontier in cancer treatment, leading to increased survival with less treatment-associated toxicity. However, new treatment modalities designed to stimulate a patient's immune system will inevitably lead to a rise in cases of autoimmune and other hyperinflammatory conditions.[1] Here, we present the case of a man who developed hemophagocytic lymphohistiocytosis (HLH) due to pembrolizumab therapy.

CASE PRESENTATION

A 71-year-old man with a past medical history of type 2 diabetes mellitus, hyperlipidemia, and atrial fibrillation was diagnosed with lung adenocarcinoma, and further workup revealed a stage IIA (pT3pN0M0) tumor. The patient underwent two cycles of neoadjuvant chemotherapy with cisplatin and pemetrexed followed by right lower and middle lobectomies. After disease recurrence 1 year later, the patient was started on pembrolizumab, resulting in a complete response. However, 3 weeks after his 14th cycle, he presented to the hospital for progressive fatigue, dyspnea, recurrent fevers, and unintentional weight loss of 10 pounds in the previous week. Initial assessment was notable for new onset normocytic anemia and hepatosplenomegaly without clinical evidence of bleeding.

The patient became pancytopenic, with platelets reaching a nadir just under 100,000/μL. Vitamin B12 was near low, and he was started on supplementation but remained transfusion dependent. Peripheral smear was unremarkable for hemolysis, though low-density lipoprotein was elevated and haptoglobin was low. His reticulocyte count was depressed, and human immunodeficiency virus, hepatitis panel, parvovirus, cytomegalovirus, and Epstein-Barr virus serologies were negative for an acute infection. Direct antiglobulin testing was negative for an autoimmune source, ferritin peaked at 1303 ng/mL, and triglycerides were 288 mg/dL. He was on chronic warfarin therapy for an atrial arrhythmia, but this was held due to the ongoing anemia. Bone marrow biopsy had variable cellularity without hemophagocytosis. Levels of soluble IL-2 receptor (CD25) and hemoglobin-haptoglobin receptor (CD163) were elevated at 2721 pg/mL and 2425 pg/mL, respectively. Natural killer cell function was normal.

The patient continued to be transfusion dependent. Although results for the CD25, CD163, and natural killer

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cell activity levels were still pending at the time, the patient fulfilled five of the eight HLH 2004 diagnostic criteria given his fever, cytopenias, elevated ferritin, elevated triglycerides, and splenomegaly. He was given prednisone 1 mg/kg for 2 weeks with improvement in his blood counts, and after a 3-month prednisone taper, he remained asymptomatic with stable counts. Pembrolizumab was discontinued, and the patient was switched to another regimen to complete his treatment.

DISCUSSION

Immunotherapy is designed to train the immune system to target tumor cells, but autoimmunity and other hyperinflammatory side effects need to be monitored.[2] Its increasing use means these effects will become more prevalent.[1] The immune checkpoint inhibitors that disrupt PD-1 to PD-L1 binding can cause HLH by their effects on leukocytes, both cytotoxic T cells as well as macrophages.[3] The resulting cytokine storm that can occur as a side effect of these novel immunotherapies, as well as those targeting CTLA4 and chimeric antigen receptor T cells, can cause tissue injury or destruction, progressive organ failure, and even death.[4,5] Histologically, this is seen as macrophages phagocytosing other hematologic components, though this is neither required for nor pathognomonic of a diagnosis of HLH.[4,6]

A 2018 review of data from the World Health Organization revealed 49,833 immune checkpoint inhibitor–related adverse reactions. Of these, HLH occurred (or was suspected of occurring) in 38 patients, with a male-to-female predominance of >2:1. In 34 of the cases (90%), the immune checkpoint inhibitor was the sole suspected inciting factor. The review found that HLH tended to occur a median of 6.7 weeks after initiation of treatment (interquartile range, 2.9–15.4 weeks).[7] Thus, this patient's presentation after 50 weeks was late compared with others.

HLH can have a variable course. Many patients develop a life-threatening condition with a high mortality, while some present with a more indolent syndrome.[4,8] In this case, the patient remained transfusion dependent until he was started on steroids but was otherwise clinically stable and did not require critical care monitoring. HLH treatment prognosis can be related to the underlying cause. In a 2019 update on the treatment of HLH, La Rosee et al identified HLH secondary to novel immunotherapies as a distinct category of disease, recognizing that discontinuation of the offending agent or a period of corticosteroids alone is often curative.[5]

In conclusion, with the growing use of immunotherapies, providers need to be increasingly aware of potential side effects related to overstimulation of the immune system, including autoimmune disorders as well as HLH.

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