Pembrolizumab associated hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal disease, resulting from uninhibited T-cells causing a cytokine storm, and histiocytes engulfing other blood or marrow cells. The resulting syndrome, if left untreated, can cause a rapid demise of a patient. We describe a patient who was on immunotherapy with pembrolizumab and developed HLH.

A 76-year-old Caucasian male with a history of metastatic bladder cancer on pembrolizumab for 9 months presented with a 4-day history of worsening fatigue and fever of 101°F. Findings on physical examination were pertinent for sinus tachycardia, pallor, maculopapular rash, and splenomegaly. Laboratory investigation revealed new-onset pancytopenia with a hemoglobin of 9.4 gm/dl, white blood cell count of 1.9 K/µl, platelets of 28 K/µl and absolute neutrophil count of 800/µl. He also had an acute renal failure with a creatinine of 3.8 mg/dl. Peripheral blood smear did not show evidence of schistocytes. Further work up revealed high ferritin of more than the assay limit of 100 000 ng/ml, fibrinogen 122 mg/dl, normal prothrombin time, increased soluble IL-2R level of 10 353 lg/ml, and decreased Natural Killer cell function. Ultrasound of the abdomen showed splenomegaly of 17 cm in craniocaudal dimension. Imaging showed no active malignancy. Bone marrow aspiration and biopsy demonstrated normocellular bone marrow with histiocytic hyperplasia and hemophagocytosis. (Picture 1) The patient met eight out of eight criteria for the diagnosis of HLH. Extensive work up for autoimmune diseases and infections were negative except for Epstein–Barr virus (EBV) PCR of 6707 copies/ml. EBV IgG and antibody to EBV nuclear antigen were positive whereas EBV IgM was negative. Given the diagnosis of HLH, he was started on etoposide and dexamethasone per the HLH 2004 treatment protocol.

HLH is a hyperinflammatory syndrome defined by a number of clinical and laboratory features that can develop due to hyperactivation of T-cells and histiocytes. Treatment involves prompt diagnosis and initiation of corticosteroids and chemotherapy such as etoposide and cyclosporine [1]. T-cells, mainly CD8+ cytotoxic T-cells are highly activated in HLH [2]. Secondary HLH, in the absence of underlying genetic predisposition, usually develops in adulthood and is associated with autoinflammatory/ autoimmune conditions, viral infections or malignancy [3]. Secondary HLH has been reported after treatment with chimeric antigen receptor T-cells due to its immunomodulatory effects [4]. Pembrolizumab, and other FDA approved immune checkpoint inhibitors like nivolumab, ipilimumab and atezolizumab have been repeatedly shown to trigger immune-related adverse events [5]. Since HLH is believed to be immune related, we speculate that in this case, pembrolizumab may have facilitated exaggerated immune response perpetuating HLH in the setting of EBV infection. Heightened awareness is required to identify this condition when patients are on immunotherapy.

D. Shah*, R. Shrestha, R. Ramlal, J. Hatton & H. Saeed
Hematology and Bone and Marrow Transplantation, University of Kentucky, Lexington, USA
(*E-mail: darshil@gmail.com)

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References

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Figure 1. Bone marrow aspirate of our patient showing a histiocyte phagocytosing red blood cells, lymphocyte and platelets.