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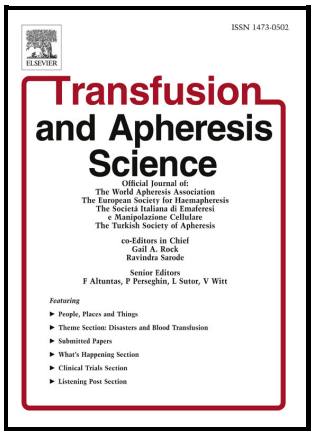

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PD-1 Blockader-associated Atypical Hemophagocytic Lymphohistiocytosis: A Cautionary Case Report

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a fatal immune hyperactivity syndrome with high mortality. It seriously endangers human health. HLH associated with immune checkpoint inhibitors is rare, and no particular diagnostic guidelines or treatment regimens exist. A 36-year-old patient with metastatic right atrial angiosarcoma was treated with programmed cell death-1 (PD-1) blockader toripalimab and pazopanib, a vascular endothelial growth factor receptor blockader. However, the patient presented to our center with HLH, and he accepted combination therapy of therapeutic plasma exchange (TPE) and immunotherapy. The patient improved quickly, after only one TPE procedure. Finaly, he was discharged after completing two TPE procedures. We summarize a case of PD-1 blocker associated

atypical HLH that was successfully treated with TPE. Further evidence is needed to elucidate whether TPE has therapeutic potential for immunotherapy associated HLH.

Keywords:

therapeutic plasma exchange; immune checkpoint blockade; PD-1 blockader; hemophagocytic lymphohistiocytosis; case report

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal clinical syndrome. Excessive stimulation of type 1 T helper cells (Th1 cells) and macrophages induces the production of Th1 cytokines, which can induce inflammation and immune-mediated organ damage.[1] It is currently believed that hyper cytokinemia and possibly hyperchemokinemia are generated by uncontrolled activation of histiocytes, and these cause multiple organ failure (MOF). [2] HLH occurs either as primary HLH or as acquired HLH. Primary HLH manifests mainly in childhood, with mutations in the genes encoding perforin of T lymphocytes and natural killer cells (NKs). Acquired HLH is subclassified as viral, autoimmune, neoplasia, or drug related.[3] The precise pathophysiology of HLH still awaits full elucidation.[4]

With the introduction of novel immunotherapies, unique syndromes of treatment-related adverse events have emerged.[5,6] Nonetheless, these therapies are seeing increasing use because of their effectiveness. Pembrolizumab and other FDA-approved PD-1 and PDL-1 immune checkpoint inhibitors such as nivolumab, ipilimumab, and atezolizumab have been repeatedly shown to trigger immune-related adverse events.[7] Toripalimab is a recombinant humanized monoclonal antibody against PD-1, which can bind to PD-1, prevent PD-1 from binding to programmed death ligand 1 (PD-L1) and 2 (PD-L2), activate the immune system, and kill malignant cells.[8] However, cases of HLH caused by immunotherapy are rarely reported. To appropriately and expeditiously diagnose and manage this complication, physicians should be familiar with the HLH profiles of these novel therapies. In this report, we present a metastatic right atrial angiosarcoma patient diagnosed with HLH that had been triggered by toripalimab and pazopanib during immunotherapy. He was treated successfully with TPE and infiliximab after appropriate diagnosis.

Case presentation

A 36-year-old man diagnosed as primary right atrial angiosarcoma with pulmonary metastasis. Considering the unresectable nature of primary cardiac angiosarcoma, the patient had to receive immunotherapy (toripalimab plus pazopanib). However, after the last round of pazopanib, the patient was admitted to the hospital on June 19, 2019 with high fever, nausea, and delirium. In addition, his platelet count decreased significantly to 35×10^9/L (normal range: 100–300×10^9/L), and there were no split cells in the peripheral blood smear. On the third day of hospitalization the biochemical profile showed hypertriglyceridemia (triglyceride level, 6.13 mmol/L [normal values: 0.4–1.7 mmol/L]), high ferritin (81,769 ng/mL [normal values: 30–400 ng/mL]), and high lactate dehydrogenase (1057.4 U/L [normal values: 40–250 U/L]). Coagulation studies showed D-dimer > 20 μg/ml (normal values: 0–0.5 μg/ml) and hypo fibrinogen 0.65 g/L (normal values: 2.0–4.0 g/L). Abdominal ultrasound showed splenomegaly. No evidence of infection was found in laboratory or radiology tests. The patient's nervous system, blood coagulation system, liver and kidney functions are impaired and he met 4 (fever, thrombocytopenia, hypertriglyceridemia and hypo fibrinogen, high ferritin, splenomegaly) out of 8 criteria for the diagnosis of atypical HLH. NK cell activity and sCD25 tests were not performed due to the unavailability of the necessary testing equipment in the hospital. On the first day of hospitalization based on these clinical and laboratory features, he began an HLH-directed therapeutic regimen with 3 days of high-dose methylprednisolone (500 mg/day) and 1 day of infliximab(300 mg). Considering that the patient had developed a cytokine storm, two continuous TPE on the third and the fourth day of hospitalization was started with 1.3 plasma volume and fresh frozen plasma as replacement fluid. After the patient had underwent 2 consecutive days of TPE treatment, his mental state improved considerably. Liver and kidney function improved significantly. Thus, methylprednisolone was tapered off to 80 mg/day within 2 days. On the 7th day of hospitalization the patient was then given a maintenance regimen of oral methylprednisolone (40 mg/day) for 10 days. The patient discharged on the 8th day of hospitalization and he is still in remission as of 4 months after treatment (Figure 1).

Discussion

Secondary HLH is associated with various diseases, including infections, tumors, rheumatic diseases, and others. Infection is the main factor inducing HLH. Infection is the most common cause of secondary HLH, and EBV is the main inducing factor.[3] However, in this case, the relative viral testing result was negative. This patient had primary right atrial angiosarcoma with pulmonary metastasis treated with PD-1 blockader (toripalimab) and VEGFR inhibitor (pazopanib) and developed HLH. We used the Naranjo Nomogram, a method for estimating the probability of adverse drug reactions, to assess the correlation between the adverse effect and Toripalimab; the correlation was 'probable,' a score of 5.[9]

Boosting the immune system is a double-edged sword, on the one hand, it can prolong the survival period of patients[10,11], on the other hand, activation of the immune system by immune checkpoint inhibitors can lead to a myriad of immune-related adverse events[12]. Shah et al.[13] reported a patient who developed HLH after 9 months of pembrolizumab treated with etoposide and dexamethasone. Laderian et al[14]. reported a case of thymic cancer that benefited from anti-PD-1 therapy but developed HLH one year later and eventually died. Sadaat[15] and Zachary Holmes[12] also highlights immunotherapy may be a potential cause for HLH. Although PD-1 blockader has received considerable attention for its role in tumor immunosuppression, toxicity and immune-related adverse events have been observed.[16] Thus, we speculated that this case of HLH was caused by PD-1 blockader drugs.

HLH is the result of over-secretion of a series of cytokines (including IFN - γ, sIL-2R, TNF-α, IL-2, IL-6, IL-12, and IL-18). [17,18]We speculated that PD-1 blockader not only serves as a key molecule killing tumor cells through negative immune regulation but also boosts immune responses, producing large numbers of cytokines and so promoting HLH. Although it is not completely clear which cytokines play the most important roles in HLH, it is speculated that tumor necrosis factor α (TNF-α) may play a key role. In addition, Henzan *etal.* suggested that HLH patients not responding to conventional therapy, anticytokine treatment with infliximab may represent one of promising options[19]. We speculated that TNF-α in this patient may be one of the causes of hemophagocytic syndrome. So we obtained the patient's consent for administration of infliximab, a chimeric monoclonal antibody against TNF-α. After the first dose of infliximab, the patient's laboratory results improved. Levels of creatinine, lactate

dehydrogenase, triglyceride, alanine aminotransferase, aspartate, and aminotransferase declined significantly; levels of fibrinogen rose visibly.

There are no treatment guidelines based on randomized trials for HLH induced by immune checkpoint blockaders.[3] High-dose glucocorticoids, etoposide, methotrexate, and cyclosporin are the main components of the treatment regimens cited in HLH-94 and 2004[20,21]. However, the efficacy and results of these regimens in immunotherapy-induced HLH are questionable. Patients with primary HLH can continue to receive maintenance therapy before allogeneic hematopoietic cell transplantation. For patients with secondary HLH, the root cause needs to be treated.

The initial treatments for primary and secondary HLH are similar. In addition to supportive treatment, specific treatment aims to control cytotoxicity and inhibit the increase of inflammatory response. Intravenous immunoglobulin therapy has a reported survival rate of 59%–75%, and TPE has a survival rate of approximately 80% (20/26; survival of patients with cancer 9/10, autoimmune disease 6/8, infection 5/7, idiopathic 0/1).[3] In addition, the recommended level of TPE for treating HLH in guidelines on the use of therapeutic apheresis in clinical practice is III/2C[22]. Pandy *etal*[23] and Bosnak *etal* [24]also emphasize that TPE can produce a rapid improvement in patients with hemophagocytic syndrome.. Biotherapy (such as rituximab, infliximab, and etanercept), anti-tumor necrosis factor drugs, anti-interleukin-1 (anakina), anti-interleukin-6 (tocilizumab), and B-cell depletion drugs (rituximab, belim mAb) showed different degrees of clinical efficacy against different HLH subtypes.[1,3,25] Our case was successfully treated with one dose of infliximab and 2 procedures TPE, suggesting that HLH produced by immune checkpoint blockaders may respond to infliximab and TPE, especially during the early stage of the disease.

Before and Post-TPE changes in blood test parameters

	Hb (g/L)	PLT (10^9/L)	ALT (U/L)	AST (U/L)	Cr (μmol/L)	LDH (U/L)	TG (mmol/L)	Fib (g/L)
Before TPE D1	136	136	136	136	136	136	136	136
Before TPE D2	120	120	120	120	120	120	120	120
1st TPE	117	117	117	117	117	117	117	117
2nd TPE	118	118	118	118	118	118	118	118

After 2nd TPE D1	114	114	114	114	114	114	114	114
After 2nd TPE D2	90	90	90	90	90	90	90	90
After 2nd TPE D3	79	79	79	79	79	79	79	79
After 2nd TPE D4	83	83	83	83	83	83	83	83

Conclusion

Our case and other reported cases suggest that HLH may be caused by immunotherapy, which may lead to progressive organ failure; therefore, early diagnosis and treatment are very important. There is still no consensus on treatments for HLH caused by immune checkpoint blockaders and other immunotherapeutic agents. As suggested by our case and other reported cases, early intervention with TPE may produce a rapid improvement during treatment of HLH caused by immune checkpoint blockaders. We believe that TPE can produce a rapid improvement by scavenging cytokines until physicians have a chance to select and begin other therapies.

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Conflicts of interest

We declare that we have no conflicts of interest relevant to the content of this paper.

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Figure legend

Figure 1. Clinical course of a case of HLH treated with drug therapy (Infliximab plus methylprednisolone) and 2 daily TPE procedures. Treatment and examination results during hospitalization. The patient attained remission with combination therapy.