Case Reports in Oncology

Case Rep Oncol 2020;13:508–514
DOI: 10.1159/000507281
Published online: May 12, 2020

Case Report

Hemophagocytic Lymphohistiocytosis Secondary to PD-1 and IDO Inhibition in a Patient with Refractory Glioblastoma

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Keywords

Hemophagocytic lymphohistiocytosis · Programmed cell death receptor-1 · Indoleamine-pyrrole 2,3-dioxygenase · Immune checkpoint inhibition · Immune-related adverse events · Glioblastoma

Abstract

Immune checkpoint inhibition (ICI)-based approaches have transformed the treatment landscape of numerous solid tumors. Glioblastoma (GBM) is an aggressive and almost universally fatal disease which is in need of novel treatment options, and combinations of immune checkpoint inhibitors, including dual agent therapy, are starting to be explored in refractory GBM. Growing adoption of ICI-based approaches in solid tumors has been met with improved understanding of immune-related adverse events (IRAEs), including primary hematologic adverse events. Although management guidelines for multiple hematologic IRAEs have been established, the emergence of hemophagocytic lymphohistiocytosis (HLH) secondary to ICI therapy has only rarely been described, and its pathogenesis and optimal management are incompletely understood. We present the case of a 74-year-old male with a history of refractory GBM treated with PD-1 and indoleamine-pyrrole 2,3-dioxygenase (IDO) inhibition who experienced acute liver injury, followed by progressive fevers, altered mental status, and cytopenias. Serum studies and examination of spleen and bone marrow pathology were consistent with HLH, which was refractory to steroids and ultimately resulted in his rapid clinical decline. Here, we review prior cases of HLH secondary to ICI therapy across solid tumors, and explore potential mechanisms contributing to the rapid onset and refractory nature of our

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patient's HLH syndrome. We hope to further highlight HLH as an emerging hematologic IRAE secondary to ICI therapy, and suggest that new practice guidelines begin to recognize HLH as a characteristic hematologic IRAE in patients treated with PD-1 and other immune checkpoint inhibitors.

Background

Immune checkpoint inhibition (ICI) can produce durable responses in subsets of solid tumor patients, and is therefore starting to be widely explored across cancers. Glioblastomas are the most common primary brain cancers in adults, and despite aggressive multimodal management, virtually all patients eventually face recurrence and die of their disease. In this setting, there has been a strong interest in exploring immunotherapeutic treatments for patients with glioblastomas. ICI therapy is classically associated with characteristic immune-related adverse events (IRAEs), including colitis, hepatitis, pneumonitis, and endocrinopathies [1]. However, the emergence of new and less common IRAEs, including hematologic toxicities, continues to be explored, particularly in the setting of dual ICI therapy and clinical trials of novel ICI agents. Management of hematologic IRAEs including autoimmune hemolytic anemia, acquired TTP/hemolytic uremic syndrome, aplastic anemia, immune thrombocytopenia, and acquired hemophilias have been described in recent practice guidelines [2]; however, the presentation and management of hemophagocytic lymphohistiocytosis (HLH) secondary to ICI therapy has yet to be rigorously explored or described in practice guidelines. Recently, several reports have described HLH in solid tumor patients treated with ICI [3–11]; these HLH syndromes varied in terms of method of diagnosis, onset, severity, and response to immunosuppressive modalities. In this case report, we describe a patient with recurrent glioblastoma who developed HLH while on a clinical trial with the PD-1 inhibitor nivolumab and a novel indoleamine-pyrrole 2,3-dioxygenase (IDO) inhibitor.

Case Presentation

A 74-year-old male with a history of glioblastoma, coronary artery disease, atrial fibrillation, hypertension, hyperlipidemia, and type 2 diabetes mellitus presented to our service with abnormal liver enzymes found at an outpatient clinic visit. Thirteen months prior to admission, he had developed aphasia resulting from a left temporal lobe enhancing mass found on imaging. Subsequent surgical resection revealed a BRAF V600E mutated, IDH1 wild type, MGMT promoter unmethylated glioblastoma. His disease progressed following 6 weeks of fractionated radiation with concurrent temozolomide and four cycles of monthly adjuvant temozolomide. He was then enrolled in a phase I trial of nivolumab and anti-IDO immunotherapy for patients with first glioblastoma recurrence (NCT03707457). He received a single infusion of nivolumab, and then was started on monthly nivolumab and once daily BMS-986205, an oral IDO1 inhibitor. On cycle 2, day 17 of nivolumab and BMS-986205, he was found to have an elevated AST of 832, ALT of 1,378, alkaline phosphatase of 152, and total bilirubin of 4.1, and was admitted to the inpatient service. Duplex liver ultrasound, CT imaging, and markers for autoimmune, infiltrative, and viral etiologies of liver injury proved unremarkable. As a result of this negative workup, he was treated for immune-mediated hepatitis, secondary to his anti-PD-1 and/or anti-IDO therapy, and was initiated on IV methylprednisolone. His liver enzymes continued to uptrend to a peak of AST 1,064, ALT 1,675 on day four of admission leading to an increase in steroid dosing followed by a liver biopsy. Pathology was significant

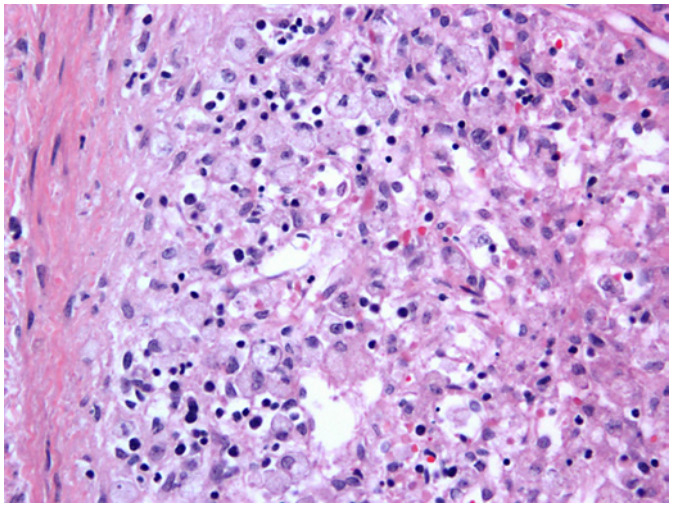

Fig. 1. Histologic examination of the spleen, showing infiltration of foamy histocytes containing occasional hematolymphoid cells.

for focal bile duct injury, mild portal inflammation, and minimal lymphocytic lobular infiltration. Overall, these findings were non-specific but possibly supportive of a resolving hepatitis. His transaminases began to downtrend and he was weaned to oral prednisone.

On day 8 of admission, he started to experience new fevers, progressively worsening mental status, new leukopenia to a total WBC of 460 per mm^3, and new neutropenia to an absolute neutrophil count of 350 per mm^3. His worsening mental status was not thought to be reflective of worsening liver dysfunction or steroid-related delirium, and was concerning for an infectious or inflammatory cause. He underwent a lumbar puncture which showed 18 WBCs per mm^3 (95% lymphocytes), a normal glucose of 61 mg/dL, and a slightly elevated total protein of 74.4 mg/dL, which raised some concern for an autoimmune encephalitis that had been unresponsive to steroids. CSF was positive for malignant cells. A broad serum, urine, and CSF infectious workup was sent but was only significant for low level serum and urine BK virus, low level serum JC viremia, and negative JC virus in CSF; his clinical syndrome was not thought to be consistent with BKV meningoencephalitis. CT chest, abdomen, and pelvis showed mild duodenal and perinephric fat stranding, an irregular posterior bladder wall with a hyperattenuating nodule, and splenomegaly to 15.6 cm. Given the progressive neutropenia and fevers, he was broadly covered with IV vancomycin, ceftazidime, metronidazole, amphotericin B, acyclovir, and atovaquone.

Given the progressive cytopenias, fevers, altered mental status, splenomegaly, and continued bilirubin elevation without a clear alternate cause, the diagnosis of HLH was considered. Ferritin was elevated at 33,738 ng/mL (normal <400), IL-6 ELISA was elevated at 37.3 pg/mL (normal <5), and triglycerides were elevated at 843 mg/dL (normal <150). Whether this represented a true HLH process or simply reflected profound inflammation in the setting of severe hepatitis, undiagnosed infection, or other IRAE was unclear. Accounting for the patient's rapid clinical decline and lack of further safe treatment options, his family declined a bone marrow biopsy. He was ultimately transitioned to comfort measures, became progressively somnolent, and expired on day 15 of admission.

Postmortem soluble IL-2 receptor was found to be significantly elevated at 28,985 pg/mL (normal 532–1,891). Postmortem autopsy was completed. Gross pathology was significant for generalized jaundice, hepatomegaly (2,350 g; reference range: 1,500–1,800 g), and splenomegaly (350 g; reference range: 150–200 g). Histologic examination of the spleen (Fig. 1) and bone marrow (Fig. 2) was supportive of HLH, showing scattered infiltration by foamy histiocytes which occasionally contained hematolymphoid cells and/or cell debris,

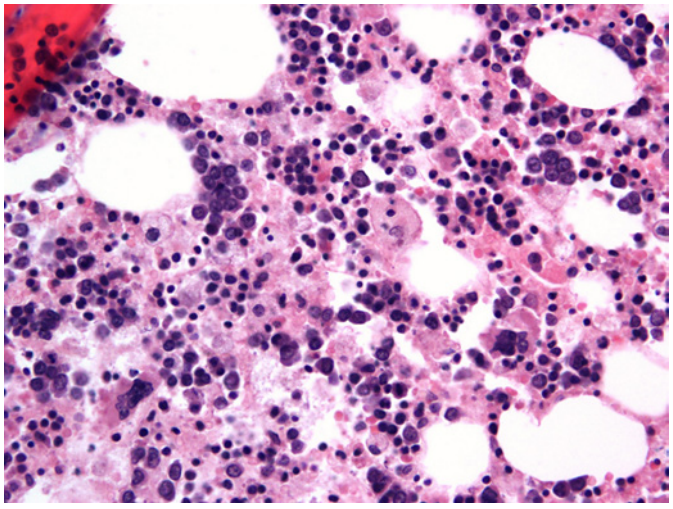

Fig. 2. Histologic examination of the bone marrow, showing infiltration of foamy histocytes containing occasional hematolymphoid cells.

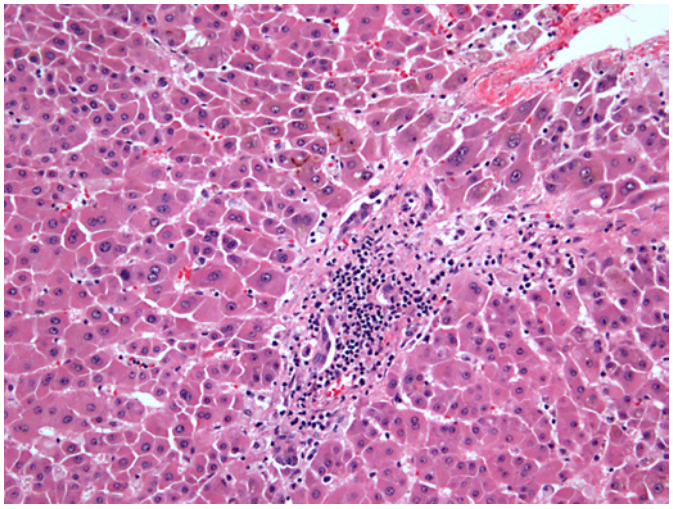

Fig. 3. Histologic examination of the liver, showing canalicular and intrahepatic cholestasis, centrilobular hepatocellular dropout, scarring of central veins, and mild mixed portal inflammation and foci of lobular inflammation.

consistent with hemophagocytosis. His final HScore was 239, reflecting a 98–99% probability of HLH. Histologic examination of the liver showed canalicular and intrahepatic cholestasis (Fig. 3). There was also centrilobular hepatocellular dropout, which was seen in coordination with scarring and/or distortion of the central veins. It was difficult to characterize the etiology of the central vein injury, but it may have represented the effects of a prior vasculitis. There was only mild mixed portal inflammation and rare foci of lobular inflammation, which was unconvincing for an antecedent ICI-induced autoimmune hepatitis, and there was no evidence of HLH in the liver (Fig. 3). Hence, the liver pathology was not consistent with either HLH or ICI-induced autoimmune hepatitis, and perhaps could have been secondary to sinusoidal congestion from drug-induced liver injury, or an incompletely characterized vasculitis.

Discussion/Conclusions

HLH represents a rare, severe inflammatory reaction characterized by overstimulation of lymphocytes and macrophages, and is characterized by high levels of serum cytokines, the presence of hemophagocytosis in the reticuloendothelial and lymphoid systems, and often

Table 1. List of prior cases of HLH secondary to ICI therapy

Reference	Type of ICI	Timing/cycles of therapy	Primary malignancy	Method of diagnosis	BM biopsy/ pathology	Treatment	Clinical outcome
Takeshita et al., 2017 [3]	Nivolumab	2 doses	NSCLC	BM biopsy	BM biopsy + for HLH	Steroids	Improvement
Malissen et al., 2017 (case 1) [4]	Nivolumab	17 months	Melanoma	BM biopsy	BM biopsy + for HLH	Steroids	Death
Honjo et al., 2019 [10]	Nivolumab	4 doses	NSCLC	Ferritin, soluble IL-2R, triglyceride elevation	N/A	Steroids, mycophenolate mofetil	Improvement
Sadaat and Jang, 2018 [9]	Pembrolizumab	6 doses	Melanoma	NK cell functional assay, soluble CD163 elevation	N/A	Steroids	Improvement
Shah et al., 2017 [5]	Pembrolizumab	9 months	Bladder cancer	BM biopsy, NK cell functional assay, soluble IL-2R elevation	BM biopsy + for HLH	Steroids and etoposide (HLH 2004)	?
Okawa et al., 2019 [6]	Pembrolizumab	1 dose	NSCLC	BM biopsy, soluble IL-2R, ferritin elevation	BM biopsy + for HLH	Steroids	Improvement
Laderian et al., 2019 [7]	Pembrolizumab	12 months	Thymic cancer	BM biopsy, liver biopsy, soluble IL-2R, ferritin elevation, cytopenias	BM biopsy + for HLH	Steroids, IVIG, anakinra	Death
Malissen et al., 2017 (case 2) [4]	Ipilimumab	1 dose of ipilimumab; prior history of 9 months of nivolumab	Melanoma	Ferritin, triglyceride elevation, cytopenias	BM biopsy negative for HLH	Steroids	Improvement
Malissen et al., 2017 (case 3) [4]	Avelumab	1 dose	Merkel cell carcinoma	Ferritin, triglyceride elevation, cytopenias	N/A	Steroids	Death
Hantel et al., 2018 [8]	Ipilimumab and nivolumab	4 doses of ipilimumab, 1 dose of ipilimumab and nivolumab (3 weeks prior)	Melanoma	BM biopsy, soluble IL-2R elevation	BM biopsy + for HLH	Steroids	Improvement
Satzger et al., 2018 [11]	Ipilimumab and nivolumab	4 doses	Melanoma	Liver biopsy, ferritin, triglyceride, soluble IL-2 elevation, cytopenias	N/A	Steroids, mycophenolate mofetil	Improvement

results in multi-organ failure, particularly of the liver and bone marrow [12]. HLH can be primary (genetic cause, usually presenting in childhood) or secondary to a number of causes including infections (particularly viral including EBV, as well as bacterial, and fungal), hematologic malignancies (particularly of T and NK lineages), autoimmune conditions (including SLE and adult-onset Still's disease), immunodeficient states (including chemotherapy or modes of immune suppression) [12], and is starting to be described in patients receiving ICI therapy.

We found a total of six pathology-proven cases of HLH in the setting of ICI for solid tumors, including nivolumab [3, 4], pembrolizumab [5–7], and combined ipilimumab and nivolumab [8] (Table 1). We also found an additional five cases [4, 9–11] which were diagnosed based on serum findings, including elevated ferritin, soluble IL-2 receptor, triglycerides, NK cell functional assays, and cytopenias (Table 1). The majority of patients were receiving ICI for melanoma or NSCLC (eight of 11 cases); no prior cases were described in patients with glioblastoma. All 11 patients received steroids. Three received additional immunosuppression, including two with mycophenolate mofetil [10, 11], and one with IVIG and anakinra [7]. One received etoposide according to HLH-2004 protocol [5]. In contrast to our patient, five of seven showed clinical improvement with steroids alone [3, 4, 6, 8, 9]; in addition, our patient experienced HLH earlier than all cases except two, with one case occurring after one dose of pembrolizumab [6] and another after one dose of avelumab [4]. Overall, this suggested that our patient may have had a particularly aggressive manifestation

of the syndrome, and we wondered whether concurrent IDO1 inhibition could have contributed. Upregulation of the IDO pathway has been implicated as an escape mechanism to PD-1 blockade, and acts by metabolizing tryptophan to kynurenine, which can promote differentiation of T regulatory cells and induction of T cell tolerance [13]. However, patients with HLH have been shown to have high plasma kynurenine to tryptophan ratios [14], and IDO1 knockout murine models have not been shown to affect clinical outcome in secondary HLH models [15]. This suggested that PD-1 blockade was likely the main driver of our patient's immunotoxicity.

Conclusions

Taken together, this case represents a particularly early and aggressive form of HLH secondary to combination ICI therapy, and the first described in a patient receiving combined PD-1 and IDO inhibition. As new ICI agents continue to be explored in the management of solid tumors, the increasing incidence of HLH as a possible severe IRAE should be considered, and practice guidelines should begin to recognize HLH is a more commonly observed hematologic IRAE.

Acknowledgement

We thank the patient's family for agreeing to the report of his case.

Statement of Ethics

The study (ClinicalTrials.gov ID: NCT03707457) was approved by the Institutional Review Board (IRB) of the Johns Hopkins Medical Institutions. Informed consent for participation in the clinical trial (ClinicalTrials.gov ID: NCT03707457) had been obtained by the patient. Consent for publication was obtained from the family.

Disclosure Statement

M.H. has consulted or served on an advisory board for Celgene, Abbvie, BTG International, and NewLink Genetics. M.L. has research support from Arbor, BMS, Accuray, DNAtrix, Tocagen, Biohaven, and Kyrin-Kyowa, and has consulted for Tocagen, SQZ Technologies, VBI, and Stryker. The authors declare that there are no competing interests.

Funding Sources

This study was supported by the Sidney Kimmel Comprehensive Cancer Center Core Grant No. P30CA006973.

Author Contributions

R.T., T.H., S.K., R.C., J.L., R.C., M.L., and M.H. took clinical care of the patient. J.S., D.S.P., and A.S.D. provided pathology figures and interpreted pathology specimens. R.T. wrote the manuscript with input from all authors. All authors read and approved the final manuscript. M.H. reviewed and interpreted the data presented in this case report, coordinated this project, contributed to writing the manuscript, and has approved the final manuscript.

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