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Review

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Hemophagocytic Lymphohistiocytosis Secondary to Immune Checkpoint Inhibitor Therapy

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a fatal systemic inflammatory syndrome. HLH has been reported as a rare immune-related adverse event (irAE) in patients receiving immunotherapy with nivolumab, ipilimumab, and/or pembrolizumab. The data are limited to case reports and case series. The objective of this research is to compile data on this rare but potentially life-threatening adverse event of immune checkpoint inhibitors (ICIs) and identify the common agents that cause this irAE, clinical spectrum, and successful management strategies to assist the treating oncologists. A review was done using PubMed database. Eligible articles included case reports and case series published from January 1, 2015, through February 1, 2021. Reports published in languages other than English were excluded. Data were compiled into a detailed supplementary table and simple descriptive analysis was used to interpret data. A total of 22 cases were included, which constituted 14 individual case reports and two case series. The immunotherapy prescribed consisted of antibodies against and programmed cell death 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1) in all 22 patients. Out of them, immunotherapy consisting of anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4) antibodies was prescribed in nine patients. Fever was the most common symptom at the presentation (90.9%). The most common laboratory findings were anemia (90.9%), thrombocytopenia (90.9%), and elevated ferritin (90.9%). All the patients received steroids (100%). HLH responded to treatment in 19 patients. Three patients died. Three patients were rechallenged with immunotherapy, with no recurrence of HLH. HLH in the setting of ICI therapy is life-threatening, but potentially treatable with early detection. However, diagnosis is often delayed due to difficulty in differentiating the presenting symptoms and laboratory findings from complications of cancer and other therapies. Majority have shown an adequate response to standard HLH treatment; however, some required a longer course of corticosteroids. HLH is not always associated with other irAE. Rechallenging with immunotherapy was successful in some patients after completing treatment for HLH.

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Introduction

The first association between Immunology and Oncology goes back to the late 19th century when a surgeon named William Coley reported that sarcomas shrink upon injection of killed bacteria into tissue [1]. Immunotherapy has shown a significant effect on long-term remission of different malignancies: melanoma, lung cancer, and renal cancer [2], etc.

Tumor cells evade immune surveillance via different mechanisms, including activation of immune checkpoint pathways that suppress antitumor activity [3]. Immune checkpoint inhibitors (ICIs) break the co-inhibitory signaling pathways and recondition the anti-tumor activity of immune cells. Immune checkpoint blockade promotes antitumor immunity by blocking intrinsic down-regulators of immunity, such as anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4) and programmed cell death 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1) [4]. Since the mechanism of action of ICI depends on the inhibition of the physiological barrier of immune activation, they could potentially cause immune-mediated inflammation of various organ systems [5]. These are recognized as immune-mediated or immune-related adverse events (irAEs). These irAEs usually have a delayed onset, prolonged duration and are unique compared to traditional cytotoxic chemotherapy [6].

Hemophagocytic lymphohistiocytosis (HLH) has been reported with few ICIs over the last 2 years and is a rare irAE [7]. HLH is an aggressive and hyperinflammatory syndrome induced by aberrantly activated macrophages and cytotoxic T cells comprising genetic/familial HLH and secondary HLH in the setting of infection, inflammation, and malignancy. This is a rare but potentially fatal syndrome resulting in cytopenia, bleeding and multi-organ failure [8]. HLH has clinical and laboratory features that are similar to cytokine release syndrome (CRS). CRS has become a topic of interest, especially in association with coronavirus disease 2019 (COVID-19) [9]. Both CRS and HLH have activation of macrophages and the reticuloendothelial system. Therefore, some patients who develop similar manifestations after immunotherapy may be diagnosed

with CRS rather than HLH [10]. The aim of this research is to compile data on the reported cases of HLH in the setting of ICI and identify the common agents, clinical spectrum, and successful management strategies.

Materials and Methods

Database and the keywords

A systematic review of the literature was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using the PubMed database for case reports and series of HLH associated with ICI from the date of database inception to February 2021. The following keywords were used: "hemophagocytic lymphohistiocytosis AND immune checkpoint inhibitors," "HLH AND immune related adverse events AND checkpoint blockade".

Definitions

HLH was defined based on fulfilling the published diagnostic criteria used in the HLH-2004 trial. In adults, heterozygosity of verified HLH-associated mutations or gene defects of other immune regulatory genes together with clinical findings associated with HLH or five of the following eight findings (fever ≥ 38.5 °C; splenomegaly; peripheral blood cytopenia; hypertriglyceridemia (fasting triglycerides > 265 mg/dL); hypofibrinogenemia (fibrinogen < 150 mg/dL); hemophagocytosis in bone marrow, spleen, lymph node, or liver; low or absent natural killer cell activity; ferritin > 500 ng/mL; and elevated soluble CD25 (soluble interleukin (IL)-2 receptor alpha)) are used to diagnose HLH [9]. Each case was carefully reviewed to confirm that the timing and the clinical presentation was highly suggestive that the symptoms were directly related to the ICI received by the patient.

Selection criteria

We selected only the cases of HLH that fulfilled the diagnostic criteria. We excluded duplicate articles, and cases with other potential precipitants of HLH.

Data collection

Two researchers independently identified and selected the titles, abstracts, and full texts obtained in the database search. After completing the PubMed PRISMA search, we completed a manual search by subsequently screening the reference lists of all selected articles. A total of 25 relevant cases were identified. Three cases of macrophage activation syndrome (MAS) were excluded as they did not contain sufficient data to fulfill diagnostic criteria for HLH [9]. Fourteen individual case reports and two case series each containing three and five cases were included in our review. For each case, we collected patient demographics, indication for ICI, clinical presentation, medical comorbidities, timing from the first dose to onset of symptoms, diagnostic criteria fulfilled for HLH, treatment, and clinical outcome on follow-up (Supplementary Material 1, www.wjon.org).

Results

A total of 22 cases constituted the final sample. The reported cases in this review were from the USA (n = 12), UK (n = 5), Japan (n = 3), Australia (n = 1) and Germany (n = 1). The main characteristics of these cases are summarized here (Supplementary Material 1, www.wjon.org). Majority of the 22 cases were men (n = 14), and the mean age of the patients was 55 years (range 26 to 78 years). Immunotherapy was prescribed for metastatic melanoma (n =12), lung cancer (n = 3) or other cancers (n =7). Other cancers were metastatic head and neck squamous cell carcinoma, glioblastoma, metastatic thymic carcinoma, metastatic prostate carcinoma, metastatic breast carcinoma, metastatic bladder cancer and pulmonary sarcomatoid carcinoma. The immunotherapy prescribed consisted of antibodies against PD-1/PD-L1 in all 22 patients. Out of them, immunotherapy consisting of anti-CTLA-4 antibodies were prescribed in nine. The time between the first infusion and the onset of HLH ranged from a few days to 1 year. A few patients developed other immune-related toxicities, such as immune-mediated hepatitis (n = 5), hypophysitis (n = 2), lymphocytic meningitis (n = 2), hepatic cytolysis (n = 2), colitis (n = 1), pneumonitis (n = 1), autoimmune hemolytic anemia (n = 1), thyroiditis (n = 1), autoimmune hemolytic anemia (n = 1) and autoimmune thyroiditis (n = 1).

The characteristics of the 22 patients are shown here (Supplementary Material 1, www.wjon.org). All patients fulfilled the HLH-2004 criteria for HLH and required in-patient level of care. Fever was the most common symptom at the presentation (90.9%). The most common laboratory findings were anemia (90.9%), thrombocytopenia (90.9%), elevated ferritin (90.9%). Only nine patients had an elevated soluble CD25 (40.9%). A bone marrow/liver biopsy was performed in 19 (86.36%) cases, revealing features of hemophagocytosis. One patient had a negative bone marrow biopsy initially and on repeat found to have hemophagocytosis. Although other potential causes of HLH such as infection and progression of the cancer were considered in all cases, there was no sufficient evidence to confirm the association. Thus, it was concluded that HLH was secondary to ICI except for one patient who developed HLH during treatment with dabrafenib and trametinib following pembrolizumab, and therefore was unable to confirm which agent caused HLH. All the patients received steroids (100%). Five patients were treated with etoposide (22.7%), one with intravenous immunoglobulin (4.6%), five with cytokine blockade (tocilizumab in four cases and anakinra in the other), and three patients received immunosuppressive therapy (mycophenolate mofetil, tacrolimus and cyclosporine). HLH was resolved by the treatment in 19 and three patients died. Three patients were rechallenged with immunotherapy, with no recurrence of HLH.

Discussion

As immunotherapy becomes more widely available, new irAEs are being reported [11]. Early identification is critical to prevent complications. As evidenced by our review, the most common presentations include fever, anemia, thrombocytopenia, and elevated ferritin. It is potentially treatable if identified early although mortality remains high [12-16].

HLH is characterized by excessive immune activation resulting in multi-organ failure, cytopenia and bleeding [9]. It has been reported in patients receiving immunotherapy with nivolumab, ipilimumab, and/or pembrolizumab [12-14, 17]. However, this is one of the rare irAEs; only one case was identified among the 745 patients included in one of the three pharmacovigilance databases [18]. HLH should be suspected when a patient on ICIs develops unexplained fever, cytopenia, and elevated transaminases. The diagnosis is challenging because it may mimic other common conditions in oncology patients such as sepsis, disseminated intravascular coagulation, and acute liver failure [19]. Other irAE such as autoimmune hepatitis may also present with similar clinical features and laboratory findings [20]. Extremely high ferritin, usually more than 3,000 µg/L is a helpful but a nonspecific marker for HLH. The diagnosis of HLH is based on fulfilling the published diagnostic criteria used in the HLH-2004 trial [9]. However, it is important to note that oncology patients have many other causes for elevated ferritin such as transfusion, sepsis, and liver inflammation [21, 22], etc. Soluble CD25/soluble interleukin-2 receptor (sIL-2R) alpha is a more specific biomarker, although it needs to be specifically studied in the ICI-HLH setting [23]. Further, hemophagocytosis in bone marrow can be seen in sepsis, after blood transfusions [24], etc. Overall, it is important to recognize the clinical and laboratory features of HLH and perform a comprehensive evaluation to find the underlying etiology [25].

In 1994 the Histiocyte Society initiated a prospective international collaborative therapeutic study (HLH-94) hoping to improve survival of patients with HLH. It combined chemotherapy and immunotherapy (etoposide, corticosteroids, cyclosporin A, and, in selected patients, intrathecal methotrexate), followed by bone marrow transplantation (BMT) in persistent, recurring, and/or familial disease. Initial treatment is given based on the HLH-94 protocol in addition to treatment of the causative disease. HLH-94-based therapy includes etoposide and dexamethasone given at tapering doses over 8 weeks. Upon review of three melanoma patients who developed ICI-related HLH, it was clear that anti-IL-6 therapy seems a very promising strategy for this entity allowing rapid resolution of symptoms and normalization of the abnormal laboratory results. Interesting trials testing alternative therapeutic approaches have been initiated, including those incorporating ruxolitinib, anakinra, alemtuzumab and emapalumab and currently are being explored [25]. It is important to note that therapy should not be delayed while awaiting specialized immunologic testing or genetic analysis [26].

ICI use in clinical practice has uncovered a spectrum of irAEs due to immune system hyper-activation. ICI-related HLH has been recently outlined in single case reports. The prognosis of ICI associated with HLH appears to be variable, ranging from complete resolution of symptoms to death. Further data are needed to confirm the association of either the PD-1 pathway or CTLA-4 inhibition with the development of HLH [7]. Interestingly, nivolumab has provided a potential cure for patients with HLH induced by Epstein-Barr virus (EBV) infection on review of seven patients.

Future Work

As scientists and physicians continue to explore the molecular mechanisms of the immune response in human body, it is expected that more treatment options will become available in the future for this life-threatening complication of ICI. Also, it is interesting to note that nivolumab, one of the ICIs that lead to HLH has also been identified as a potential therapy for EBV-associated HLH. Retrospective analysis of seven relapsed or refractory EBV-HLH patients who were treated with nivolumab on a compassionate-use basis at West China Hospital has led to complete response in five patients [27]. However, larger prospective clinical trials are warranted in this area.

Supplementary Material

Suppl 1. Main characteristics of the cases summarized in the database search.

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Conflict of Interest

The authors declare that they do not have any conflict of interest to disclose.

Author Contributions

Study conception and design, draft manuscript preparation: PR. Data collection: HA and PR. Analysis and interpretation of results: PR and HA. All authors reviewed the results and approved the final version of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

References

1. Coley WB. II. Contribution to the knowledge of sarcoma. Ann Surg. 1891;14(3):199-220.
2. Darvin P, Toor SM, Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors: recent progress and potential biomarkers. Exp Mol Med. 2018;50(12):1-11.
3. Zappasodi R, Merghoub T, Wolchok JD. Emerging concepts for immune checkpoint blockade-based combination therapies. Cancer Cell. 2018;33(4):581-598.
4. Li X, Shao C, Shi Y, Han W. Lessons learned from the blockade of immune checkpoints in cancer immunotherapy. J Hematol Oncol. 2018;11(1):31.
5. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. CA Cancer J Clin. 2020;70(2):86-104.
6. Puzanov I, Diab A, Abdallah K, Bingham CO, 3rd, Brogdon C, Dadu R, Hamad L, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5(1):95.
7. Noseda R, Bertoli R, Muller L, Ceschi A. Haemophagocytic lymphohistiocytosis in patients treated with immune checkpoint inhibitors: analysis of WHO global database of individual case safety reports. J Immunother Cancer. 2019;7(1):117.
8. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. J Blood Med. 2014;5:69-86.
9. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124-131.
10. Hakim NN, Chi J, Olazagasti C, Liu JM. Secondary hemophagocytic lymphohistiocytosis versus cytokine release syndrome in severe COVID-19 patients. Exp Biol Med (Maywood). 2021;246(1):5-9.
11. Osta BE, Hu F, Sadek R, et al. A meta-analysis of immune-related adverse events (irAE) of immune checkpoint inhibitors (ICI) from cancer clinical trials. Ann Oncol. 2016;27:vi369.
12. Takahashi H, Koiwa T, Fujita A, Suzuki T, Tagashira A, Iwasaki Y. A case of pembrolizumab-induced hemophagocytic lymphohistiocytosis successfully treated with pulse glucocorticoid therapy. Respir Med Case Rep. 2020;30:101097.
13. Kalmuk J, Puchalla J, Feng G, Giri A, Kaczmar J. Pembrolizumab-induced Hemophagocytic Lymphohistiocytosis: an immunotherapeutic challenge. Cancers Head Neck. 2020;5:3.
14. Chin CK, Hall S, Green C, Van Hazel G, Spagnolo D, Cheah CY. Secondary haemophagocytic lymphohistiocytosis due to checkpoint inhibitor therapy. Eur J Cancer. 2019;115:84-87.
15. Sadaat M, Jang S. Hemophagocytic lymphohistiocytosis with immunotherapy: brief review and case report. J Immunother Cancer. 2018;6(1):49.
16. Al-Samkari H, Snyder GD, Nikiforow S, Tolaney SM, Freedman RA, Losman JA. Haemophagocytic lymphohistiocytosis complicating pembrolizumab treatment for metastatic breast cancer in a patient with the PRF1A91V gene polymorphism. J Med Genet. 2019;56(1):39-42.
17. Mizuta H, Nakano E, Takahashi A, Koyama T, Namikawa K, Yamazaki N. Hemophagocytic lymphohistiocytosis with advanced malignant melanoma accompanied by ipilimumab and nivolumab: A case report and literature review. Dermatol Ther. 2020;33(3):e13321.
18. Delanoy N, Michot JM, Comont T, Kramkimel N, Lazarovici J, Dupont R, Champiat S, et al. Haematological immune-related adverse events induced by anti-PD-1 or anti-PD-L1 immunotherapy: a descriptive observational study. Lancet Haematol. 2019;6(1):e48-e57.
19. Bergsten E, Horne A, Arico M, Astigarraga I, Egeler RM, Filipovich AH, Ishii E, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood. 2017;130(25):2728-2738.
20. Imoto K, Kohjima M, Hioki T, Kurashige T, Kurokawa M, Tashiro S, Suzuki H, et al. Clinical Features of Liver Injury Induced by Immune Checkpoint Inhibitors in Japanese Patients. Can J Gastroenterol Hepatol. 2019;2019:6391712.
21. Chen LYC, Hayden A, Mattman A. Extreme hyperferritinaemia, soluble interleukin-2 receptor, and haemophagocytic lymphohistiocytosis. Br J Haematol. 2019;185(3):605-606.
22. Schram AM, Campigotto F, Mullally A, Fogerty A, Massarotti E, Neuberg D, Berliner N. Marked hyperferritinemia does not predict for HLH in the adult population. Blood. 2015;125(10):1548-1552.
23. Hayden A, Lin M, Park S, Pudek M, Schneider M, Jordan MB, Mattman A, et al. Soluble interleukin-2 receptor is a sensitive diagnostic test in adult HLH. Blood Adv. 2017;1(26):2529-2534.
24. McGinnis E, Medvedev N, Richards MJ, Chen LYC, Wong MP. Post-Transfusion Hemophagocytosis Without Hemophagocytic Lymphohistiocytosis. Mayo Clin Proc Innov Qual Outcomes. 2019;3(4):517-522.
25. La Rosee P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, Birndt S, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 2019;133(23):2465-2477.
26. Henter JI, Samuelsson-Horne A, Arico M, Egeler RM, Elinder G, Filipovich AH, Gadner H, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood. 2002;100(7):2367-2373.
27. Liu P, Pan X, Chen C, Niu T, Shuai X, Wang J, Chen X, et al. Nivolumab treatment of relapsed/refractory Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in adults. Blood. 2020;135(11):826-833.