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Case Report

Hemophagocytic Lymphohistiocytosis after Initiation of Combined Immunotherapy for Metastatic Melanoma

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Abstract

Hemophagocytic Lymphohistiocytosis (HLH), which is a severe, potentially fatal condition characterized by T lymphocyte overactivation, is predominantly caused by infections, hematological malignancies, and autoimmune conditions. HLH due to therapy with Immune Checkpoint Inhibitors (ICI) has rarely been reported. We describe a 60-year-old male with metastatic melanoma who developed HLH after the initiation of nivolumab plus ipilimumab treatment. Prompt diagnosis and high-dose mono-prednisolone therapy resulted in rapid resolution of his subjective symptoms and laboratory findings. Apart from this case presentation we provide a brief overview on clinical characteristics of previously observed ICI-induced HLH cases. Given the increasing use of ICI in a variety of cancers, the frequency of HLH will very likely raise. HLH morbidity and mortality are often the result of delayed diagnosis and inappropriate treatment. Hence, HLH must be considered in ICI-treated cancer patients who present with symptoms such as fever, cytopenias and hyperferritinemia.

Keywords: Hemophagocytic lymphohistiocytosis; Metastatic melanoma; Immune checkpoint inhibitors

Introduction

The therapy paradigms and outcomes of patients with cancer have dramatically changed since the introduction of immunotherapy with Immune Checkpoint Inhibitors (ICI), including cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death protein (PD-1) and its ligand (PD-L1) antibodies. However, these agents can trigger immune-related Adverse Events (irAEs), which may be due to hyperactivation of T lymphocytes against self-antigens. Unlike the frequently described organ systems affected by irAEs, such as skin, gut, lungs, and endocrine system, hematologic toxicities have been poorly reported, probably due to their uncommon nature and lack of correct detection. One of these rare hematologic complications of ICI represents Hemophagocytic Lymphohistiocytosis (HLH), which is a severe, potentially fatal condition characterized by T lymphocyte overactivation that is measurable, for example, by soluble Interleukin-2 Receptor (IL-2R) determination in blood [1,2]. Primary or hereditary HLH (e.g., A91V mutation in PRF1) must be differentiated from secondary HLH, which is predominantly caused by infections, malignancies, and autoimmune conditions, frequently in the context of underlying immunodeficiency or immunosuppression. HLH is usually characterized by recurrent high fever, splenomegaly, pancytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, increased IL-2R, and hemophagocytosis on bone marrow assessment [1-10]. Here we report a patient with metastatic melanoma who developed HLH after initiation of anti-CTLA-4/PD-1 treatment and give a brief tabular overview on previously reported cases.

Case Presentation

We report a 60-year-old man with stage III BRAF-wildtype melanoma, who had received 8 cycles nivolumab (240mg fix dose every other week) in the adjuvant setting. Since he showed disease progress on Computed Tomography (CT), including left axillary, pre-pectoral, and mediastinal lymph node metastases, combined immunotherapy with nivolumab (1mg/kg three weekly) and ipilimumab (3mg/kg three weekly) was initiated. Nine weeks (three cycles) after the introduction of combi-immunotherapy, the patient was admitted to our skin cancer center with a history of high-spiking fever (>38.5°) and malaise. Blood cultures, procalcitonin, C-reactive protein, and virus serology for herpes simplex, herpes zoster, cytomegaly, HIV, and Epstein-Barr did not reveal evidence for an infection. PCR for SARS-CoV was negative on several test times. Remarkable laboratory findings included: Leukocytes 3670/µl (4600-9500), erythrocytes 3.8 mill/µl (4.6-6.2), thrombocytes 139.000/µl (150.000-400.000), ferritin 12.806ng/ml (30-400), fibrinogen 166mg/dl (200-400), IL-2R 5999 U/l (<710), lactate dehydrogenase 346 U/l (135-225), and up to 3-fold elevated liver transaminases. Antinuclear autoantibodies (ANA, dsDNA, ENA) were within the normal range. A CT-scan showed splenomegaly (14.8cm) and regredient lymph node metastases. Bone marrow biopsy did not show signs of phagocytosis. Hence, the patient met 6 of 8 diagnostic criteria of HLH according to the HLH-2004 guideline. His Hscore was 189 (almost 80% HLH probability). ICI was discontinued, and prednisolone was introduced in a tapered dose regimen (initial dosage 250mg), resulting in a rapid decrease of the patient's clinical complaints and improvement of laboratory findings. After two weeks the patient has been fully recovered. His following outpatient treatment was performed with orally administered prednisolone tapered down to 20mg/d for two weeks. Regular monitoring of his clinical performance and blood tests were carried out on a weekly basis.

Discussion

The present case clearly fulfilled the diagnostic criteria for

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Table 1: Characteristics of cancer patients (n=69) with Immune Checkpoint Inhibitor (ICI) induced Hemophagocytotic Lymphohistiocytosis (HLH) [1-10, present case].

Gender	
Male	n=50/69 (72.3%)
Female	n=19/69 (27.7%
Median age (years)	60 (26-81)
Cancer type	
Melanoma	n=39 (56.5%)
Lung cancer	n=9 (13%)
Bladder cancer	n=4 (5.8%)
Renal cell cancer	n=4 (5.8%)
Miscellaneous	n=13 (18.8%)
ICI at HLH onset	
Anti-CTLA-4	n=7 (10.1%)
Anti-PD-1	n=38 (55.1%)
Anti-PD-1/CTLA-4	n=16 (23.2%)
Miscellaneous	n=8 (11.6%)
Median time (weeks) of HLH onset after ICI initiation	6 weeks (1-428)
HLH deaths	11/68 (16.2%)

secondary HLH [1,2]. Supported by the current literature [1-10], we are convinced that ICI was the cause of HLH in the present case. Of course, we cannot fully exclude that HLH was mainly driven by the underlying malignancy [11-16]. However, malignancy-triggered HLH occurs most frequently in T- and NK-cell lymphoma or leukemia, diffuse large B-cell lymphoma, and Hodgkin's disease [15]. Solid tumors are rarely associated with HLH with only a 3% prevalence in adults. Whereas causes of secondary HLH, including malignancies, infections, and autoimmune diseases, are due to an underlying condition, ICI-induced HLH has been recognized as a new clinical challenge in cancer management. Notably, HLH was also reported in patients managed with chimeric antigen receptor T-cell therapy, further highlighting the association between T-cell activity modulation and HLH development [11-16].

Noseda et al. [1] and Dupré et al. [2] recently published data of ICI-induced HLH patients which extracted from large pharmacovigilance databases. Noseda et al. [1] searched the VigiBase including 49.883 ICI-related suspected adverse drug reactions and found 38 patients with HLH, whereas rates were highest in France (0.4%) and the lowest in the USA (0.03%). Dupré et al. [2] identified 5 ICI-induced HLH cases from a pharmacovigilance databases in the Parisian region. They published their 5 cases together with a review of the literature including 17 previously published patients [2]. Including the present case, we have studied new ICI-induced HLH cases recently published and collected the data with the aforementioned investigations as shown in Table 1 [1,2]. Remarkably, ICI-induced HLH is associated with a substantial male predominance, which was also observed in other clinical settings such as infection or malignancy-associated HLH [13,14]. In systematic review on ICI-induced irAEs [17], no differences in gender distribution have recently been found in hematologic irAEs. However, most cases were associated with irAEs such as hemolytic anemia and immune thrombocytopenic purpura [17]. Unsurprisingly, most patients with ICI-induced HLH had melanoma, for which ICI approvals exist much longer when compared to other cancer entities [1,2]. Table 1 also demonstrates that there is no difference between the immunotherapy agents (e.g., anti-PD-1, anti-CTLA-4) regarding the potency to cause HLH. Even though the onset of HLH may occur at any time under ICI treatment, it appears that early onset of HLH is more likely. Most importantly, however, fatal outcome was reported in 16.2% of ICI-induced HLH cases - a rate that seems to be smaller than the death rates (up to 50%) reported for patients with HLH associated with other causes [1-10].

Basic scientists recently found a reciprocal correlation between PD-1 expression and tumor-associated phagocytic activity of macrophages as well as an enhanced cancer cell phagocytosis by macrophages following PD-1/PD-L1 targeting [9,11]. As also demonstrated in the present case, some patients with ICI-induced HLH improve with corticosteroids alone not requiring cytoreductive regimens such as etoposide [18]. Treatment approaches for more severe HLH cases include anti-interleukin 6 (e.g., tocilizumab) and anti-CD25 antibodies. Paradoxically, ICI (e.g., nivolumab) treatment has also successfully been used to treat relapsed/refractory Epstein-Barr virus-associated HLH [19]. Re-challenge of ICI after HLH resolution is a difficult clinical decision. In most cases previously reported, ICI was permanently discontinued. In patients with progressive cancer, however, ICI must be reconsidered if no treatment alternatives are available.

Conclusion

In conclusion, HLH morbidity and mortality are often due to delayed diagnosis and inappropriate treatment. Hence, HLH must be considered in ICI-treated cancer patients who present with symptoms such as fever, cytopenias, and hyperferritinemia.

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Ethical Conduct of Research

The authors state that they have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participant involved.

Informed Consent Disclosure

The authors state that they have obtained verbal and written informed consent from their patient for the inclusion of his medical and treatment history within this case report.

Availability of Data and Materials

All crucial data generated or analyzed during this case study are

included in this published article.

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