Hemophagocytic Lymphohistiocytosis after Initiation of Combined Immunotherapy for Metastatic Melanoma

Gambichler T*, Rached NA, Nowack N, Behle B and Susok L.
Department of Dermatology, Ruhr-University Bochum, Germany

*Corresponding author: Thilo Gambichler, Department of Dermatology, Ruhr-University Bochum, Gudrunstrasse 56, 44791 Bochum, Germany

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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, is predominantly caused by infections, hematological malignancies, and autoimmune conditions. 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

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.

Discussion

The present case clearly fulfilled the diagnostic criteria for...
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
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