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Case Report

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Successful Immunotherapy Rechallenge Without Recurrence of Hemophagocytic Lymphohistiocytosis in a Patient With Metastatic Endometrial Cancer Previously Treated With Dostarlimab

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal immune hyperactivation syndrome that can be induced by immune checkpoint inhibitors (ICIs). We report a case of a 72-year-old woman with metastatic endometrial carcinoma who developed HLH after dostarlimab treatment and underwent successful immunotherapy rechallenge with pembrolizumab-lenvatinib plus prophylactic corticosteroids without HLH recurrence. Close biological monitoring ensured no relapse of HLH during rechallenge.

Keywords: Hemophagocytic lymphohistiocytosis; Immune checkpoint inhibitors; Immunotherapy-related adverse events; Pembrolizumab; Dostarlimab; Endometrial cancer; Ruxolitinib; Corticosteroid prophylaxis

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive systemic inflammatory syndrome caused by excessive immune activation. Over the past decade, HLH secondary to immune checkpoint inhibitors (ICIs) has been increasingly recognized, representing a diagnostic and management challenge. Early identification and immunosuppressive treatment with corticosteroids and ruxolitinib are critical to improve outcomes. The literature on rechallenge with ICIs after HLH remains sparse but suggests possible safety with careful monitoring and prophylactic corticosteroids.

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Case Report

A 72-year-old woman was diagnosed with high-grade endometrial carcinoma with lymph node and bone metastases and was eligible for immunotherapy with dostarlimab in combination with carboplatin-paclitaxel chemotherapy. After a single dose of 500 mg dostarlimab, she developed HLH, confirmed clinically and biologically (bicytopenia, ferritin > 16,500 ng/mL, and bone marrow hemophagocytosis), a condition typically triggered by the excessive immune activation induced by this anti-programmed cell death-1 (anti-PD-1) therapy. Management with ruxolitinib 20 mg twice daily and methylprednisolone 80 mg daily led to significant clinical and laboratory improvement. After a gradual tapering, both treatments were discontinued. Immunotherapy was then discontinued to avoid recurrence of this severe syndrome [1].

In February 2024, 2 months after HLH diagnosis, oncologic treatment was resumed with carboplatin and paclitaxel only, without further immunotherapy.

In August 2024, the patient experienced nodal disease progression, prompting initiation of a new line of treatment combining pembrolizumab (another anti-PD-1) 200 mg every 3 weeks with 20 mg daily lenvatinib, administered with daily 5 mg prednisolone to mitigate potential reactivation of the inflammatory syndrome. Weekly monitoring of complete blood count (CBC), ferritin, fibrinogen, and triglycerides was performed, with all parameters remaining normal throughout the rechallenge period, facilitating early detection of any immune reactivation. Under prophylactic corticosteroid therapy, the patient did not experience any recurrence of HLH.

Unfortunately, in November 2024, her disease progressed with new metastases to the right adrenal gland, liver, bones, and brain. Pegylated liposomal doxorubicin was started as a third-line therapy. Due to large-volume brain lesions, focal brain radiotherapy was performed in January 2025.

By February 2025, her performance status had markedly deteriorated, preventing any further oncologic interventions.

The patient died at the end of March 2025 - approximately 15 months after the start of dostarlimab.

Discussion

Our case illustrates the complexity and severity of secondary HLH induced by ICIs, with successful management including rechallenge under prophylactic corticosteroids and close monitoring.

Differentiating HLH secondary to immunotherapy from HLH due to malignancy progression is critical. In our patient, HLH occurred shortly after first dostarlimab infusion, with stable disease confirmed on fludeoxyglucose-18-positron emission tomography (FDG-PET) imaging, consistent with a drug-induced etiology rather than malignancy-associated HLH. This aligns with criteria detailed in our prior publication [1].

Mortality associated with ICI-related HLH ranges from 20% to 27% within 1 month, underscoring the critical importance of prompt recognition and initiation of treatment [2, 3].

Ruxolitinib, a JAK1/2 inhibitor, has been increasingly validated in secondary HLH management, particularly in malignancy-associated and immunotherapy-related contexts. Rajapakse and colleagues conducted a multicenter retrospective analysis reporting overall response rates exceeding 70% with ruxolitinib, including significant reductions in cytokine levels and improved hematologic parameters [2]. Complementary case series and literature reviews by Wong and colleagues and Geusens and colleagues further support its pivotal role in controlling cytokine storm and immune hyperactivation in HLH patients [3, 4]. Our patient received ruxolitinib at 20 mg twice daily, resulting in rapid clinical and laboratory improvement after corticosteroid initiation, consistent with these findings. This evidence underscores ruxolitinib's utility especially in HLH cases refractory or insufficiently responsive to corticosteroids alone.

The use of low-dose corticosteroids (prednisolone 5 mg daily) during pembrolizumab-lenvatinib treatment was guided by emerging evidence supporting corticosteroid prophylaxis to reduce the recurrence of immune-related adverse events (irAEs) while preserving antitumor efficacy. Pollack and colleagues reported in a cohort study that patients receiving low-dose corticosteroids (≤ 10 mg prednisone equivalent) showed no significant reduction in ICI effectiveness compared to those receiving higher doses, with similar overall survival outcomes [5]. Similarly, Eldani and colleagues, in a systematic review and meta-analysis, found that low-dose corticosteroids did not compromise the efficacy of ICI rechallenge in patients with prior irAEs [6]. In line with these findings, Wong and colleagues and Geusens and colleagues described the use of prophylactic corticosteroids during ICI rechallenge as a feasible strategy to minimize irAE recurrence, especially in syndromes such as HLH or drug reaction with eosinophilia and systemic symptoms (DRESS), without compromising antitumor response [7, 8]. Our clinical experience supports this approach, as our patient tolerated pembrolizumab-lenvatinib with prednisolone 5 mg daily without HLH relapse.

Given the potential severity of HLH recurrence, rigorous weekly monitoring of hematologic and inflammatory parameters was conducted during rechallenge, including CBC, ferritin, fibrinogen, and triglycerides. All these parameters remained normal throughout pembrolizumab-lenvatinib therapy with corticosteroid prophylaxis, enabling timely detection and prevention of immune hyperactivation.

While corticosteroids are essential for managing irAEs, their impact on the efficacy of ICIs remains a subject of debate. High-dose corticosteroids - defined as doses greater than 10 mg prednisone equivalent - administered either at ICI initiation or for irAE treatment have been associated with reduced antitumor responses and poorer clinical outcomes [5, 9]. Conversely, studies indicate that low-dose corticosteroids (less than 10 mg prednisone equivalent) do not significantly impair ICI efficacy. Specifically, Zhao and colleagues demonstrated that patients receiving low-dose corticosteroids had comparable clinical outcomes to those not treated with steroids, whereas high-dose corticosteroid use correlated with shorter progression-free survival [9]. Furthermore, Larkin and colleagues emphasized the importance of balancing irAE management with preservation of immune-mediated tumor control by careful corticosteroid dosing [10]. Our clinical approach of administering prednisolone 5 mg daily during pembrolizumab-lenvatinib treatment aligns with these findings, effectively controlling irAEs without apparent compromise of antitumor efficacy.

Conclusion

This case highlights the possibility and challenges of safely rechallenging immunotherapy after HLH with corticosteroid prophylaxis and close biological monitoring. Prospective studies are needed to define optimal management strategies.

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Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained from our patient.

Author Contributions

Emilie Rollet was involved in bibliographic research and

drafting and proofreading of the article. Sebastien Puigrenier, Abeer Najem, and Benoit Desgrousilliers were involved in bibliographic research and proofreading of the article. Pierre Riviere suggested this clinical case. He was involved in bibliographic research and drafting, proofreading, and submission of the article. All authors attest they meet the ICMJE criteria for authorship.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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