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Omalizumab for treatment of refractory urticaria in a patient with metastatic uveal melanoma receiving tebentafusp

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Abstract

Tebentafusp is an immune-mobilizing monoclonal T-cell receptor approved for the treatment of metastatic uveal melanoma. While this agent improves outcomes in patients with unresectable or metastatic uveal melanoma, tebentafusp commonly results in dermatologic cutaneous toxicities. Herein, we present a case of a 32-year-old patient diagnosed with juxtapapillary choroidal melanoma of the left eye with metastases to the liver who developed a diffuse urticarial skin reaction to tebentafusp that was successfully treated with omalizumab.

Introduction

Tebentafusp is an FDA-approved bispecific protein composed of a T-cell receptor and an anti-CD3 fragment that redirects T-cells toward a glycoprotein (gp100) presented by human leukocyte antigen (HLA)-A*02:01 on uveal melanoma cells. It is the only treatment that improves survival for patients with this aggressive malignancy.[1] Despite its efficacy, tebentafusp is most commonly associated with immune-related cutaneous adverse events. In a phase 3 trial of 245 patients treated with tebentafusp for metastatic uveal melanoma, approximately 80% of patients developed rashes, 69% developed pruritus, and over 20% had erythema.[1,2] Prescribing guidelines recommend oral antihistamines and topical or systemic steroids, but there is limited knowledge regarding the management of refractory skin reactions using modern biologic agents. We present a case of a patient with metastatic uveal melanoma who developed antihistamine-refractory urticarial eruptions following tebentafusp infusions. These reactions were successfully treated with omalizumab, a monoclonal antibody against IgE that is FDA-approved for chronic spontaneous urticaria. This case highlights a potential treatment strategy for immune-related cutaneous reactions to tebentafusp.

Case Report

A 32-year-old healthy woman presented with blurred vision and was diagnosed with juxtapapillary choroidal melanoma of the left eye. She underwent I-125 plaque radiotherapy with transpupillary thermotherapy, achieving a good response. After three years of annual radiographic surveillance, metastases to the liver were detected on MRI. HLA testing showed she harbored the HLA-A*02:01 allele, indicating she was a candidate for tebentafusp. Approximately 5-6 hours after her first infusion of tebentafusp, the patient developed a grade 3 erythematous facial rash and chills, which were treated with oral antihistamine and resolved within 24 hours. For the following five infusions, the patient

was on a standing antihistamine regimen before and after infusions, and her rashes became increasingly tolerable and resolved within 48-72 hours post-infusion.

Within 6 hours following her seventh infusion, the patient developed diffuse, whole-body urticaria that was refractory to antihistamines. Despite standing regimens of cetirizine, loratadine, montelukast, famotidine, diphenhydramine, and topical clobetasol, she had persistent eruptions after each subsequent infusion, with associated pruritus and a reported negative impact on quality of life.

On dermatologic examination, she had diffuse urticarial papules and plaques of the trunk and bilateral extremities (Figure 1). She also had depigmentation of her eyelashes and eyebrows. Given the refractory nature of the urticaria, the patient was initiated on omalizumab 300 mg every 4 weeks. Within one week of initiation, she had improvement in her symptoms, and after two monthly doses, she experienced complete resolution. She continues weekly tebentafusp and monthly omalizumab 300 mg without recurrence of symptoms.

Discussion

We present a case of antihistamine-refractory urticarial eruptions triggered by tebentafusp that were successfully treated with omalizumab. Histological and molecular analyses of tebentafusp-related cutaneous reactions suggest that these reactions are mediated predominantly by $CD8^+$ T cells inadvertently targeting gp100-positive melanocytes at the dermal-epidermal junction, resulting in T-cell and immune activation.[3] In our case, the patient also developed depigmentation of her eyebrows and eyelashes, further supporting that melanocytes are targeted in these reactions. However, the urticarial presentation, the delayed onset of symptoms after the seventh infusion, and the absence of tachyphylaxis all suggest an alternative mechanism underlying our patient's cutaneous reaction.

Immune-mediated cutaneous adverse events are common with immune checkpoint inhibitors and human epidermal growth factor receptor 2 (HER2)-targeting monoclonal antibodies, including urticaria, eczema, maculopapular rashes, and bullous pemphigoid.[4] Elevated IgE levels have been observed, and IgE blockade is considered an appropriate therapeutic target for managing immune-mediated pruritus.[5] As such, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology include omalizumab as a treatment option for steroid-refractory immune checkpoint inhibitor-related skin reactions. Although the underlying mechanisms of these adverse events differ from tebentafusp-related cutaneous reactions, these findings provided initial support for the use of omalizumab as a therapeutic option in our case.

RNA sequencing of skin samples from patients who developed cutaneous adverse events while receiving tebentafusp revealed significant upregulation of interleukin (IL)-13 gene expression[3]. We hypothesize that this upregulation of IL-13 may have driven production of IgE in our patient, resulting in her clinical presentation and accounting for the excellent response to omalizumab. Of note, IgE levels were not measured in our patient; however, we suggest consideration of IgE as a potential biomarker to predict response to omalizumab in future patients with cutaneous adverse reactions to tebentafusp.

Conclusions

In summary, our report highlights a case of successful omalizumab use in treating tebentafusp-related urticarial reactions refractory to antihistamines and steroids. To our knowledge, this is the first published report of successful therapeutic management for these skin toxicities. As tebentafusp continues to be used for advanced uveal melanoma, expanding our understanding of the pathogenesis of its cutaneous adverse events and associated management is crucial for improving tolerability and long-term outcomes for these patients.

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Figure 1. Diffuse, erythematous patches on the dorsal forearm, infraumbilical region, dorsal wrist, and posterolateral thigh.