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Cutaneous type IV hypersensitivity reaction following tebentafusp treatment for uveal melanoma

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Abstract

Tebentafusp is a bispecific protein that recently underwent FDA approval for the treatment of metastatic uveal melanoma that functions by redirecting cytotoxic T cells to glycoprotein-100, a protein highly expressed in melanoma. Although clinical trials have demonstrated that rashes are common in the first few days of treatment, little is known about skin reactions that develop later in the treatment course. Herein, we describe a type IV hypersensitivity reaction and vitiligo-like depigmentation that developed six weeks into treatment and discuss the possible mechanisms underlying these reactions. The type IV hypersensitivity reaction resolved without intervention within seven weeks of onset, suggesting that tebentafusp can be safely continued in select patients who develop this cutaneous reaction.

Keywords: depigmentation, drug reaction, hypersensitivity, type IV, uveal melanoma, vitiligo

Introduction

Tebentafusp is a recently FDA-approved immunotherapy that has been shown to improve overall survival in metastatic uveal melanoma. It is a bispecific protein comprised of a soluble T cell receptor (TCR) fused to an anti-CD3 effector molecule that redirects cytotoxic T cells to glycoprotein-100 (gp100), a protein overexpressed in melanoma [1]. In a phase III trial, rash was the most common treatment-related adverse event and typically occurred in the first few days of treatment [2]. Herein, we present a patient with metastatic uveal melanoma who developed three distinct skin reactions while on tebentafusp, including a cutaneous type IV hypersensitivity reaction and vitiligo-like depigmentation beginning six weeks into treatment. Our case highlights the spectrum of cutaneous reactions associated with this medication.

Case Synopsis

A 49-year-old man with metastatic uveal melanoma was referred to the Columbia University Comprehensive Skin Cancer Center for evaluation of a papular rash on the arms and legs of six weeks' duration. He was initially diagnosed with uveal melanoma nine years prior to presentation. At that time, he underwent laser treatment with good response, but developed locally progressive disease five years later requiring enucleation. After several years of expectant observation, he developed metastases to the gallbladder, liver, and possibly lymph nodes. His disease progressed on multiple chemo- and immunotherapy treatments including temozolomide, bevacizumab, and pembrolizumab, along with combination of systemic therapy with

transarterial chemoembolization using cisplatin and fotemustine. He was HLA-A*02:01 positive and began treatment with tebentafusp. He received 20μg on day 1, 30μg on day 8, 68μg on day 15, and then 68μg once weekly thereafter.

He reported self-limited, recurrent mild rashes with associated fevers several hours after tebentafusp doses which resolved in less than 24 hours. His rash severity and duration diminished with additional doses of tebentafusp. After six weeks of treatment, he developed widespread depigmented macules and patches. He also noticed mildly pruritic papules that initially began on his left foot but progressed to involve his bilateral hands, arms, and legs over several weeks. The papules were intermittent, lasted a week or two, and recurred in the same regions but not the same location each time. He otherwise felt well with a negative review of systems.

On examination, he had widespread, well-demarcated depigmented macules and patches over most body surfaces, most noticeable in photoexposed areas, consistent with vitiligo-like depigmentation. There were several discrete 2mm×2mm pink-orange, non-vesicular, scattered papules with surrounding edge of scale located on right lateral index finger, trunk, arms, and legs (**Figure 1**).

A biopsy of a left forearm papule showed a very focal perivascular lymphocytic infiltrate with attendant red cell extravasation. There was endothelial cell swelling with mural edema and exocytosis of lymphocytes into the epidermis. There was an overlying scale containing sebum and degenerated leukocytes. Superficially, there was prominent red cell extravasation with intraepidermal erythrocyte entrapment. Focal eosinophilic spongiosis and interface dermatitis were also present. Angulated parakeratotic scale was absent (**Figure 2**).

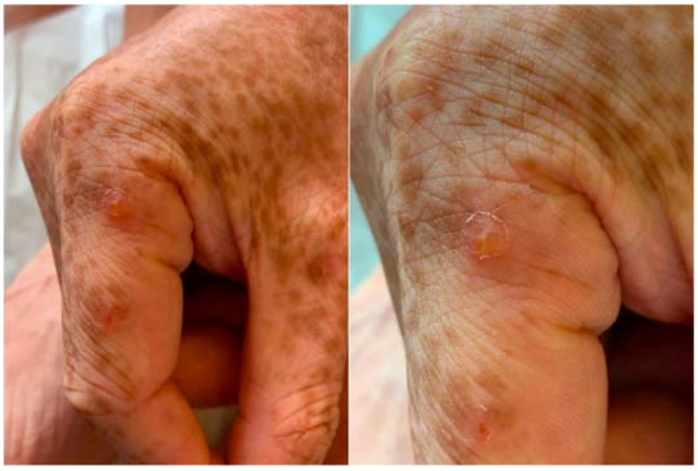

Figure 1. *Pink-orange papules with a surrounding edge of scale located on right lateral index finger on a background of depigmented macules and patches.*

The low-grade lymphocytic vasculitis with concomitant interface and eczematous epidermal changes were most compatible with a cutaneous type IV hypersensitivity reaction, likely tebentafusp-induced. Treatment of the rash was deferred as the patient was unbothered by it. He had complete resolution without intervention within 7 weeks of onset despite continuing to receive tebentafusp. His vitiligo-like depigmentation remained stable.

Case Discussion

Tebentafusp is part of a novel class of molecules termed immune-mobilizing monoclonal T cell receptors against cancer (ImmTAC). The TCR domain recognizes a peptide from gp100, a protein strongly upregulated in melanoma cells but also present in normal melanocytes. The anti-CD3 domain binds to and activates polyclonal CD3+ T cells, regardless of their TCR specificities, potentiating their secretion of cytotoxic mediators that kill target tumor cells [1].

In a phase I/II trial of tebentafusp in metastatic cutaneous and uveal melanoma, 69/82 (82%) patients developed a rash within the first few days of treatment. Patients with a rash in the first 21 days of treatment had longer survival than those who did not, suggesting that cutaneous reactions may be a biomarker for anti-tumor immune responses induced by the drug [3]. In a phase III trial, development of a rash within one week of initiating tebentafusp was associated with, but not independently predictive of, longer survival. Vitiligo was reported separately from rash in the trial and was seen in 40/245 (16%) of patients [2].

Our patient had three clinically distinct but likely pathogenetically-related skin reactions while on tebentafusp: a mild exanthematous drug eruption

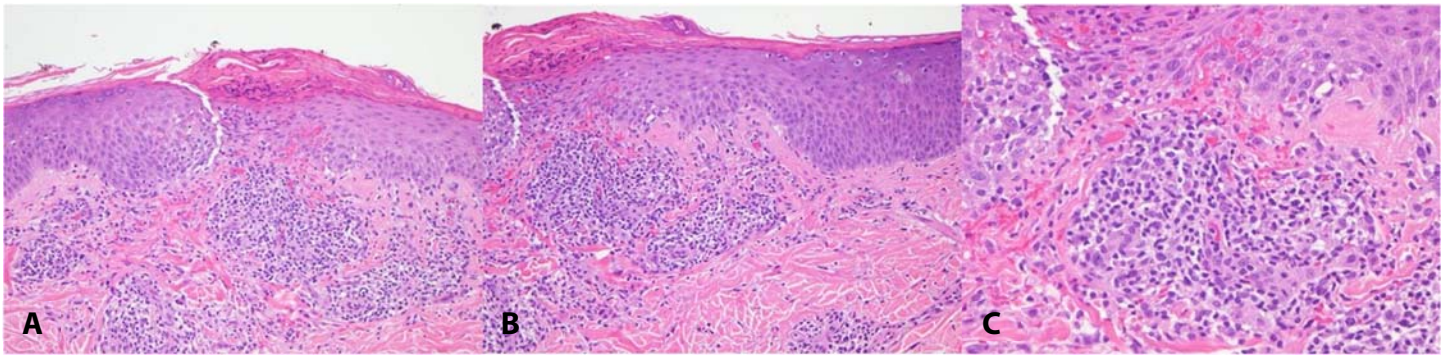

Figure 2. *H&E histopathology of skin biopsy of a forearm papule.* ***A)*** *A superficial perivascular lymphocytic infiltrate in association with overlying eczematous alterations revealed by lymphocytic exocytosis and an overlying serum imbued parakeratotic scale, 200×.* ***B)*** *The eczematous and interface epidermal changes are highlighted, 200×.* ***C)*** *A conspicuous finding on the biopsy is one of brisk angiocentric lymphocytic infiltration along with accompanying red cell extravasation including intraepidermal erythrocyte entrapment, 400×.*

after initial doses, a papular drug-induced type IV hypersensitivity reaction, and a post-inflammatory leukoderma recapitulating vitiligo, the presumptive sequelae of the robust inflammatory exanthematous and papular skin rashes. Although the mechanisms driving tebentafusp-related skin reactions are unknown, we offer the hypothesis that the drug redirects effector T cells towards gp100-expressing epidermal melanocytes, damaging melanocytes but also keratinocytes as innocent bystanders. Exposure of neoantigens through lymphocyte-mediated injury could further propagate the inflammatory cascade through epitope spreading. Evidence for this hypothesis is the significant reduction in melanocyte density within the zone of intraepidermal inflammation.

It is important to acknowledge that tebentafusp cannot be identified as the unequivocal trigger for the patient's hypersensitivity reaction. However, the development of this rash in temporal association with drug initiation and in the absence of new exposures or medications, suggests a relationship. The patient's vitiligo-like depigmentation is almost certainly a sequelae of the antecedent adaptive type IV immune response targeting melanocytes. The mechanism of vitiligo-like lesions in the setting of immune checkpoint inhibitors is pathogenetically different and more likely represents a cutaneous immune adverse effect due to preferential inhibition of regulatory T cells allowing the emergence of autoreactive T cell populations [4,5].

Conclusion

Given the recent FDA-approval of tebentafusp for metastatic uveal melanoma, dermatologic toxicities associated with this drug remain poorly characterized. Our report highlights the diversity of skin-related reactions that can occur with tebentafusp. Our patient's type IV hypersensitivity rash was minimally symptomatic and resolved without treatment within seven weeks. Although more research is needed to characterize the prognosis and management of skin reactions to tebentafusp, our case suggests that tebentafusp may be continued in the setting of minimally symptomatic cutaneous type IV hypersensitivity reactions in select patients.

Potential conflicts of interest

LJG has served as an investigator for and/or received research support from Helsinn Group, J&J, Mallinckrodt, Kyowa Kirin, Soligenix, Innate, Merck, BMS, and Stratpharma; on the speakers' bureau for Helsinn Group and J&J; and on the scientific advisory board for Helsinn Group, J&J, Mallinckrodt, Sanofi, Regeneron, and Kyowa Kirin. RDC discloses Consulting: Alkermes, BMS, Castle Biosciences, Delcath, Eisai, Hengrui, Ideaya, Immunocore, InxMed, Iovance, Merck, Novartis, Oncosec, Pierre Fabre, PureTech Health, Regeneron, Sanofi Genzyme, Sorrento Therapeutics, Trisalus; Clinical/Scientific Advisory Boards: Aura Biosciences, Chimeron, Rgenix. LMF, CMS, DEM, and CMM have no conflicts of interest to declare.

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