Resolution of pembrolizumab-associated lichenoid dermatitis with a single dose of methotrexate

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Abstract

We present a 53-year-old woman with severe lichenoid dermatitis secondary to pembrolizumab therapy that was refractory to both topical and oral steroids. After almost three months without improvement, the rash was effectively combated with a single 15mg dose of methotrexate. We hope this case will help guide the management of the cutaneous adverse effects of anti-PD1 immunotherapy.

Keywords: methotrexate, pembrolizumab, PD1 inhibitors, lichenoid dermatitis

Introduction

As our understanding of the immunologic pathways involved in melanoma has broadened, so have the available treatment options. Antibodies against programmed death-1 receptor (PD1), such as pembrolizumab and nivolumab, and its ligand programmed death ligand one (PDL1) are highly efficacious in the treatment of advanced melanoma. However, they are also associated with cutaneous reactions in more than 40% of treated patients, including morbilliform rash, lichenoid dermatitis, pruritus, vitiligo, psoriasiform eruptions, and bullous disorders, among others [1, 2]. These reactions can often present months after initiation of the therapy [3]. These complications are typically treated with topical steroids and antihistamines, with or without cessation of the offending PD1 inhibitor [3]. Lichenoid dermatitis, one of the most common cutaneous complications of anti-PD1 immunotherapy, has been successfully managed with topical or systemic corticosteroids and does not typically require cessation of immunotherapy [4].

Case Synopsis

A 53-year-old woman with hypertension, irritable bowel syndrome**,** and stage IIIa nodular melanoma of the right calf status-post excision, now on adjuvant pembrolizumab immunotherapy, presented three months following the initiation of pembrolizumab with pruritic, xerotic patches of the soles. In the face of emollients and a mid-potency topical corticosteroid, the rash progressed to involve the hands, feet, antecubital fossae, upper chest, and back with violaceous papules and associated edema of the hands and feet (**Figure 1**). The patient's pembrolizumab was held, and a trial of high-potency topical steroids and oral antihistamines failed. Biopsy at this time demonstrated a lichenoid interface dermatitis (**Figure 2**). Clinicopathologic correlation

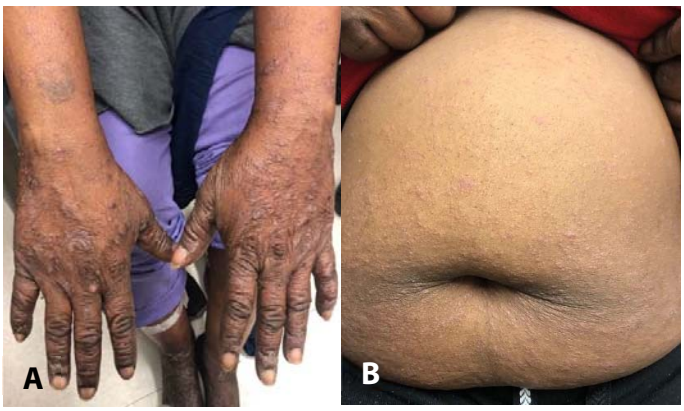

Figure 1. *Rash on the **A)** hands and **B)** trunk after failing multiple therapies***.**

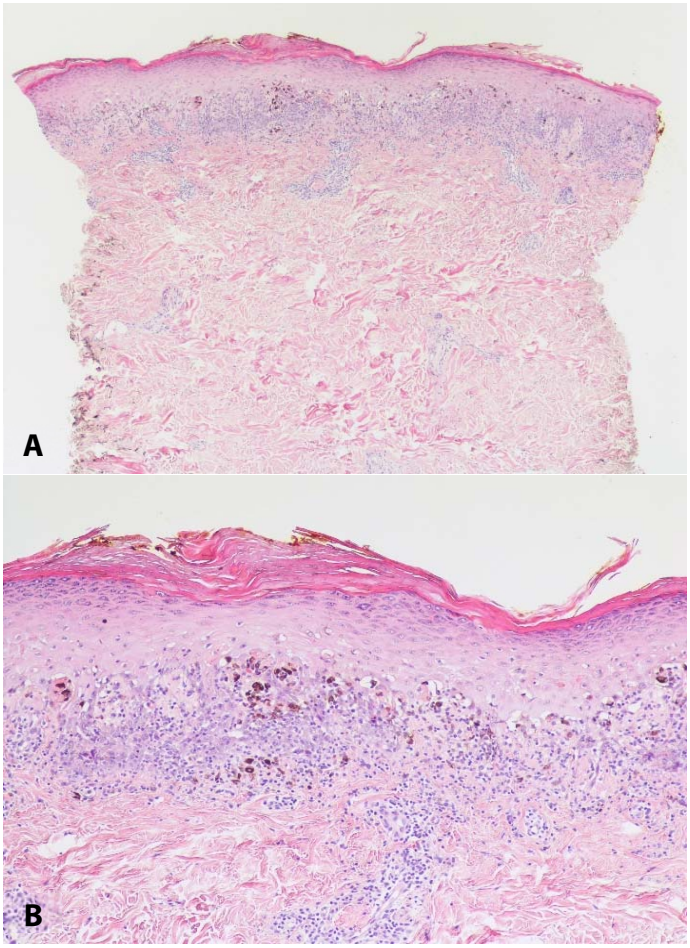

Figure 2. *Punch biopsy of the lower back, H&E.* ***A)*** *Lichenoid (band-like) lymphocytic infiltrate at the epidermal junction with overlying hyperkeratotic scale, 4×; and* ***B)*** *lichenoid infiltrate of the epidermal junction with colloid bodies and prominent pigment incontinence. No eosinophils are noted, 10×.*

favored the diagnosis of a lichenoid drug eruption, despite absence of eosinophils. Oral prednisone in conjunction with a topical mid-potency corticosteroid improved the patient's edema significantly, but only mildly reduced the pruritus. Moreover, upon completion of her prednisone course, the rash returned with severe pruritus.

In the search for a safe corticosteroid-sparing therapy, methotrexate 15mg weekly was prescribed after discussion with the patent's oncologist. Not only did the patient report a significant subjective improvement in her rash after a single dose of methotrexate, but there was a significant objective improvement visible on examination (**Figure 3**). The patient was advised to continue the methotrexate therapy for a total of three weeks. Although most patients can continue immunotherapy once the cutaneous reactions are managed, we opted not to restart the patient's pembrolizumab as it was being used as an adjuvant chemotherapy. [4].

Case Discussion

We present a case of a 53-year-old woman with severe lichenoid dermatitis secondary to pembrolizumab therapy that was refractory to both topical and oral corticosteroids. After almost three months without improvement, the eruption was effectively combated with a single 15mg dose of methotrexate. The patient completed three weekly doses of methotrexate in total, without recurrence of the rash or need for additional treatment since. Although there have been reports of pembrolizumab-associated psoriasiform and immunobullous eruptions responding to methotrexate therapy, this is the first instance of a corticosteroid-refractory pembrolizumab-associated lichenoid dermatitis being successfully resolved with methotrexate [2]. This speaks to the utility of methotrexate as a suitable option for cutaneous reactions to PD1 inhibitors. A previous report described the use of cyclosporine to clear a similar rash to that seen in our patient [5]. However, methotrexate may be a safer and cheaper alternative to consider once topical and systemic corticosteroid therapy has failed or if steroid-sparing therapy is preferred. Cyclosporine has a greater likelihood of causing major adverse effects (i.e., nephrotoxicity and hypertension) in short-term therapy than methotrexate [6]. Were methotrexate to fail, we considered a trial of apremilast given reports of this agent working well in lichen planus [7].

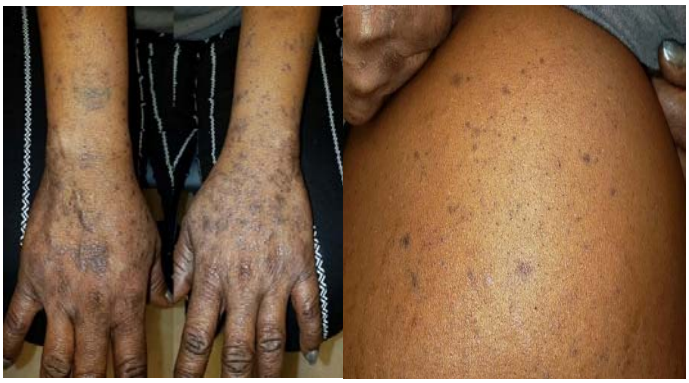

Figure 3. *Dramatic response of this patient's rash to methotrexate, Images depict a dramatic response of our patient's treatment-refractory pembrolizumab-associated lichenoid dermatitis to a single dose of methotrexate.*

Conclusion

We hope this case will help guide the management of the cutaneous adverse effects of anti-PD1 immunotherapy.

Potential conflicts of interest

Dr. Jacob Levitt was a consultant with Novartis, Abbvie, and Medscape; served on advisory boards for Janssen, Novartis, and Biofrontera; and was an investigator for the Corrona Psoriasis Registry.

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