

Pityriasis rubra pilaris–like erythroderma in the setting of pembrolizumab therapy responsive to acitretin



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Key words: acitretin; immune-related adverse event; pembrolizumab; pityriasis rubra pilaris.

INTRODUCTION

Numerous cutaneous adverse effects have been associated with programmed death 1 (PD-1) inhibitors including maculopapular eruptions, pruritus, eczema, lichenoid reactions, leukoderma, psoriasis, sarcoidosis, immunobullous disorders, and Stevens-Johnson syndrome.^{1,2} Here we report the first case, to our knowledge, of pityriasis rubra pilaris (PRP)-like erythroderma in the setting of anti-PD-1 therapy responsive to acitretin and topical steroids.

CASE REPORT

A 64-year-old man with stage IV squamous cell carcinoma of the lung had a diffuse, pruritic eruption 2 weeks after initiating pembrolizumab. The eruption began on the scalp and distal extremities then abruptly spread to the remainder of his body. He was treated with prednisone, 40 mg/d, which was tapered over 4 weeks without improvement. Pembrolizumab was permanently discontinued because of persistent and intolerable grade 3 skin toxicity, and the patient was subsequently treated with carboplatin and paclitaxel chemotherapy.

The patient was evaluated by at the Oncodermatology Clinic 1 month later for refractory skin disease. He had no personal or family history of psoriasis and no medication changes and denied joint pain, stiffness, or muscle weakness. Physical examination found erythroderma with confluent red-orange patches over the head, neck, torso, and upper and lower extremities with dry, desquamative scale (Fig 1, A). There was palmar-plantar

Abbreviations used:

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|-------|------------------------------|
| Th: | helper T cell |
| irAE: | immune-related adverse event |
| IL: | interleukin |
| PRP: | pityriasis rubra pilaris |
| PD-1: | programmed death 1 |

keratoderma with waxy scale (Fig 1, B and C). Two biopsies found acanthosis of the epidermis with orthokeratosis and parakeratosis, mild spongiosis, and an intact granular layer. There was a superficial perivascular inflammatory infiltrate in the dermis (Fig 2). Histopathology was consistent with a PRP-like eruption. The patient was treated with acitretin, 50 mg/d, and triamcinolone ointment. Four weeks later, his pruritus was resolved, and the plaques on his head, neck, torso, arms and legs were fading, while his plantar surfaces had markedly reduced keratoderma and scale (Fig 1, D).

DISCUSSION

Our case highlights a novel cutaneous reaction possibly associated with PD-1 axis inhibitor therapy. We postulate that pembrolizumab was the causative agent given the abrupt development of the eruption 2 weeks after initiating treatment. A paraneoplastic eruption was considered, but the onset of the rash after initial exposure to anti-PD-1 therapy and the multiple reports of other papulosquamous eruptions including lichenoid dermatitis,¹ psoriasis,² pityriasis lichenoides et varioliformis acuta,³ and pityriasis

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Funding sources: Ms. Coleman has funding support by the NIH for her Yale School of Medicine Medical Student Fellowship.

Conflicts of interest: Dr. Leventhal has served on an advisory board for Amgen. The rest of the authors have no conflicts to disclose.

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JAAD Case Reports 2018;4:669-71.
2352-5126

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<https://doi.org/10.1016/j.jidcr.2018.06.022>



Fig 1. Clinical presentation and response to treatment. **A**, Erythroderma with red-orange patches and dry desquamative scale at presentation. **B** and **C**, Orange-red plaques and keratoderma with waxy scale on the plantar feet and palms. **D**, Marked improvement of the palm after 8 weeks of treatment with acitretin and topical steroids.

lichenoides chronica-like eruption⁴ during anti-PD-1 therapy supported an immune-related adverse event (irAE). Additionally, unlike typical exanthematous eruptions to medications, which resolve shortly upon discontinuation of the causative drug, cutaneous irAE may persist even after cessation of anti-PD-1 therapy, and our patient's eruption required further management with acitretin, which subsequently resulted in a clinical response.

The pathomechanism of papulosquamous eruptions such as psoriasis in the setting immunotherapy is not fully elucidated. PD-1 blockade by

checkpoint inhibitors promotes a helper T cell (Th)1/Th17 response, with increased production of interferon- γ , interleukin (IL)-2, tumor necrosis factor- α , IL-6, and IL-17.⁵ PRP, like psoriasis, has been shown to have increased Th17 expression in lesional skin.⁶ Furthermore, PRP is associated with autoimmune conditions including myasthenia gravis, arthritis, and myositis, suggesting that its pathogenesis may in part be due to aberrant immune regulation.⁶ Psoriasiform and PRP-like eruptions in the setting of anti-PD-1 therapy may share a common pathomechanism.

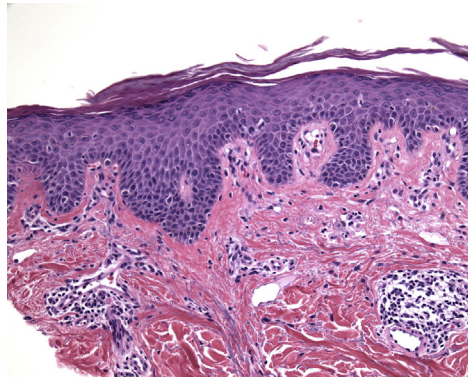


Fig 2. Histologic examination found epidermal acanthosis with orthokeratosis and parakeratosis, with an intact granular layer and mild spongiosis. There was a perivascular inflammatory infiltrate within the papillary dermis. (Hematoxylin-eosin stain; original magnification, $\times 200$.)

The differential diagnosis for PRP-like erythroderma in the setting of immunotherapy includes erythrodermic psoriasis or dermatitis, dermatomyositis with features of PRP (Wong variant), and erythrodermic drug hypersensitivity. A literature review identified a single case of erythrodermic psoriasis that developed in a patient with known plaque psoriasis on pembrolizumab,² which differs from our patient who lacked a history of psoriasis and who manifested with clinical (orange hue, waxy keratoderma) and histopathologic features resembling PRP.

Our case expands the spectrum of immunotherapy-associated papulosquamous irAE beyond lichenoid, eczematous, and psoriasiform reactions. Early recognition and management of cutaneous irAE by dermatologists and oncologists is important in the care of oncologic patients. Further studies are needed to investigate the frequency and pathomechanism of this unique cutaneous irAE.

REFERENCES

1. Curry JL, Tetzlaff MT, Nagarajan P, et al. Diverse types of dermatologic toxicities from immune checkpoint blockade therapy. *J Cutan Pathol.* 2017;44:158-176.
2. Bonigen J, Raynaud-Donzel C, Hureauux J, et al. Anti-PD1-induced psoriasis: a study of 21 patients. *J Eur Acad Dermatol Venereol.* 2017;31:e254-e257.
3. Mutgi KAJ, Milhem M, Swick BL, Liu V. Pityriasis lichenoides chronica-like drug eruption developing during pembrolizumab treatment for metastatic melanoma. *JAAD Case Rep.* 2016;2:343-345.
4. Voudouri D, Nikolaou V, Xydakis E, et al. Pityriasis lichenoides et varioliformis acuta (PLEVA) during therapy with immunomodulatory agent targeting PD1-A case report. *J Eur Acad Dermatol Venereol.* 2017;31:54.
5. Dulos J, Carven GJ, van Boxtel SJ, et al. PD-1 blockade augments Th1 and Th17 and suppresses Th2 responses in peripheral blood from patients with prostate and advanced melanoma cancer. *J Immunother.* 2012;35:169-178.
6. Feldmeyer L, Mylonas A, Demaria O, et al. Interleukin 23-helper T cell 17 axis as a treatment target for pityriasis rubra pilaris. *JAMA Dermatol.* 2017;153:304-308.