

# Diffuse Papular Eruption With Erosions and Ulcerations

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A 70-year-old man presented with a painful, pruritic, diffuse eruption on the trunk, legs, and arms of 2 months' duration. He had a history of stage IV pleomorphic cell sarcoma of the retroperitoneum and was started on pembrolizumab therapy 6 weeks prior to the eruption. Physical examination revealed violaceous papules and plaques with shiny reticulated scaling as well as multiple scattered eroded papules and shallow ulcerations. The oral mucosa and genitals were spared. The patient endorsed blisters followed by open sores that were both itchy and painful. He denied self-infliction. Both the patient and his wife denied scratching. Two biopsies for direct immunofluorescence and histopathology were performed.

## WHAT'S YOUR DIAGNOSIS?

- DRESS syndrome
- drug-induced bullous pemphigoid
- immunotherapy-related lichenoid drug eruption
- lichen planus pemphigoides
- Stevens-Johnson syndrome

PLEASE TURN TO **PAGE E16** FOR THE DIAGNOSIS

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The authors report no conflict of interest.

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## THE DIAGNOSIS:

## Immunotherapy-Related Lichenoid Drug Eruption

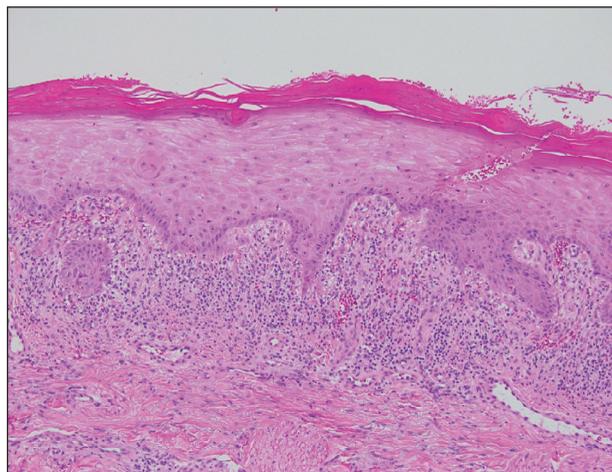
Direct immunofluorescence was negative, and histopathology revealed a lichenoid interface dermatitis, minimal parakeratosis, and saw-toothed rete ridges (Figure 1). He was diagnosed with an immunotherapy-related lichenoid drug eruption based on the morphology of the skin lesions and clinicopathologic correlation. Bullous pemphigoid and lichen planus pemphigoides were ruled out given the negative direct immunofluorescence findings. Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) was not consistent with the clinical presentation, especially given the lack of mucosal findings. The histology also was not consistent, as the biopsy specimen lacked apoptotic and necrotic keratinocytes to the degree seen in SJS/TEN and also had a greater degree of inflammatory infiltrate. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome was ruled out given the lack of systemic findings, including facial swelling and lymphadenopathy and the clinical appearance of the rash. No morbilliform features were present, which is the most common presentation of DRESS syndrome.

Checkpoint inhibitor (CPI) therapy has become the cornerstone in management of certain advanced malignancies.<sup>1</sup> Checkpoint inhibitors block cytotoxic T lymphocyte-associated protein 4, programmed cell death-1, and/or programmed cell death ligand-1, allowing activated T cells to infiltrate the tumor microenvironment and destroy malignant cells. Checkpoint inhibitors are approved for the treatment of melanoma, cutaneous squamous cell carcinoma, and Merkel cell carcinoma and are being investigated in various other cutaneous and soft tissue malignancies.<sup>1-3</sup>

Although CPIs have shown substantial efficacy in the management of advanced malignancies, immune-related adverse events (AEs) are common due to nonspecific immune activation.<sup>2</sup> Immune-related cutaneous AEs are the most common immune-related AEs, occurring in 30% to 50% of patients who undergo treatment.<sup>2-5</sup> Common immune-related cutaneous AEs include maculopapular, psoriasiform, and lichenoid dermatitis, as well as pruritus without dermatitis.<sup>2,3,6</sup> Other reactions include but are not limited to bullous pemphigoid, vitiligo-like depigmentation, and alopecia.<sup>2,3</sup> Immune-related cutaneous AEs usually are self-limited; however, severe life-threatening reactions such as the spectrum of SJS/TEN and DRESS syndrome also can occur.<sup>2-4</sup> Immune-related cutaneous AEs are graded based on the Common Terminology Criteria for Adverse Events: grade 1 reactions are asymptomatic and cover less than 10% of the patient's body surface area (BSA), grade 2 reactions have mild symptoms and cover 10% to 30% of the patient's BSA,

grade 3 reactions have moderate to severe symptoms and cover greater than 30% of the patient's BSA, and grade 4 reactions are life-threatening.<sup>2,3</sup> With prompt recognition and adequate treatment, mild to moderate immune-related cutaneous AEs—grades 1 and 2—largely are reversible, and less than 5% require discontinuation of therapy.<sup>2,3,6</sup> It has been suggested that immune-related cutaneous AEs may be a positive prognostic factor in the treatment of underlying malignancy, indicating adequate immune activation targeting the malignant cells.<sup>6</sup>

Although our patient had some typical violaceous, flat-topped papules and plaques with Wickham striae, he also had atypical findings for a lichenoid reaction. Given the endorsement of blisters, it is possible that some of these lesions initially were bullous and subsequently ruptured, leaving behind erosions. However, in other areas, there also were eroded papules and ulcerations without a reported history of excoriation, scratching, picking, or prior bullae, including difficult-to-reach areas such as the back. It is favored that these lesions represented a robust lichenoid dermatitis leading to erosive and ulcerated lesions, similar to the formation of bullous lichen planus. Lichenoid eruptions secondary to immunotherapy are well-known phenomena, but a PubMed search of articles indexed for MEDLINE using the terms *ulcer*, *lichenoid*, and *immunotherapy* revealed only 2 cases of ulcerative lichenoid eruptions: a localized digital erosive lichenoid dermatitis and a widespread ulcerative lichenoid drug eruption without true erosions.<sup>7,8</sup> However, widespread erosive and ulcerated lichenoid reactions are rare.



**FIGURE 1.** A biopsy obtained from a lichenoid plaque on the right thigh showed lichenoid interface dermatitis, minimal parakeratosis, and saw-toothed rete ridges (H&E, original magnification  $\times 40$ ).



**FIGURE 2.** Right leg with violaceous papules and plaques without erosions or ulcerations after 6 weeks of treatment consisting of cessation of immunotherapy and initiation of a systemic corticosteroid taper, acitretin, and narrowband UVB therapy.

Lichenoid eruptions most strongly are associated with anti-programmed cell death-1/ programmed cell death ligand-1 therapy, occurring in 20% of patients undergoing treatment.<sup>3</sup> Lichenoid eruptions present as discrete, pruritic, erythematous, violaceous papules and plaques on the chest and back and rarely may involve the limbs, palmo-plantar surfaces, and oral mucosa.<sup>2,3,6</sup> Histopathologic features include a dense bandlike lymphocytic infiltrate in the dermis with scattered apoptotic keratinocytes in the basal layer of the epidermis.<sup>2,4,6</sup> Grades 1 to 2 lesions can be managed with high-potency topical corticosteroids without CPI dose interruption, with more extensive grade 2 lesions requiring systemic corticosteroids.<sup>2,6,9</sup> Lichenoid eruptions grade 3 or higher also require systemic corticosteroid therapy CPI therapy cessation until

the eruption has receded to grade 0 to 1.<sup>2</sup> Alternative treatment options for high-grade toxicity include phototherapy and acitretin.<sup>2,4,9</sup>

Our patient was treated with cessation of immunotherapy and initiation of a systemic corticosteroid taper, acitretin, and narrowband UVB therapy. After 6 weeks of treatment, the pain and pruritus improved and the rash had resolved in some areas while it had taken on a more classic lichenoid appearance with violaceous scaly papules and plaques (Figure 2) in areas of prior ulcers and erosions. He no longer had any bullae, erosions, or ulcers.

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