Pembrolizumab-induced lichenoid dermatitis treated with dupilumab

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Immune checkpoint inhibitor (ICI) therapies have revolutionized cancer treatment and are being increasingly used for many cancer subtypes. However, the development of cutaneous immune-related adverse events (cirAEs) can severely impact quality of life and result in discontinuation of ICI therapy. Lichenoid dermatitis is a cirAE that typically occurs due to anti−PD-1 and anti−programmed death receptor ligand 1 therapy and rarely with anti−cytotoxic T-lymphocyte-associate antigen 4 treatment, and, although pruritus is common, the clinical presentation can be broad.[1] In addition to systematically characterizing ICI-induced cirAEs,[2] molecular phenotyping approaches, such as RNA in situ hybridization (RISH),[3] have the potential to better personalize cirAE diagnosis and treatment selection. We report 2 cases of recalcitrant ICI-induced lichenoid dermatitis found to have type 2 inflammatory cytokine interleukin-13 (*IL-13*) on biopsy using RISH and successfully treated with dupilumab.

Abbreviations used:

cirAE:	cutaneous immune-related adverse events
ICI:	Immune checkpoint inhibitor
IL:	interleukin
PD-1:	programmed death 1
RISH:	RNA in situ hybridization

CASE 1

Patient 1 is a 68-year-old woman with seropositive rheumatoid arthritis on adalimumab, hydroxychloroquine, and intermittent prednisone, in whom pancreatic adenocarcinoma developed and she was treated with PD-1 inhibitor pembrolizumab. Subsequently, an extensive pruritic rash developed in the patient. Physical examination demonstrated pink-violaceous, scaly papules coalescing into plaques scattered on the chest, back, arms, hands, and legs (Fig 1, *A*). Biopsies from the right side of the left thigh and dorsal aspect of the right hand showed a band of lichenoid infiltrate of lymphocytes with abundant eosinophils that obscures the dermoepidermal junction, which was consistent with anti−PD-1-induced lichenoid dermatitis (Fig 1, *B*). She was treated with acitretin 17.5 mg topical halobetasol and prednisone, but the rash and itch persisted. Pembrolizumab was held due to worsening rash. RISH staining results of the patient's biopsy samples showed expression of the cytokine *IL-13* (Fig 1, *C*). RISH staining for type 1 cytokine interferon gamma (*IFN-γ*), type 2 cytokine *IL-4*, and type 3 cytokine *IL-17A* were negative. She started receiving dupilumab, which resulted in sustained improvement of rash and itch (Fig 1, *D*), and the patient was able to restart her ICI therapy. She remains on pembrolizumab and dupilumab.

CASE 2

Patient 2 is a 77-year-old man with metastatic clear cell renal cell carcinoma, in whom lichenoid dermatitis developed on pembrolizumab, resulting in discontinuation of ICI therapy. Physical examination demonstrated pink papules coalescing into large confluent plaques on flanks, abdomen, thighs, and

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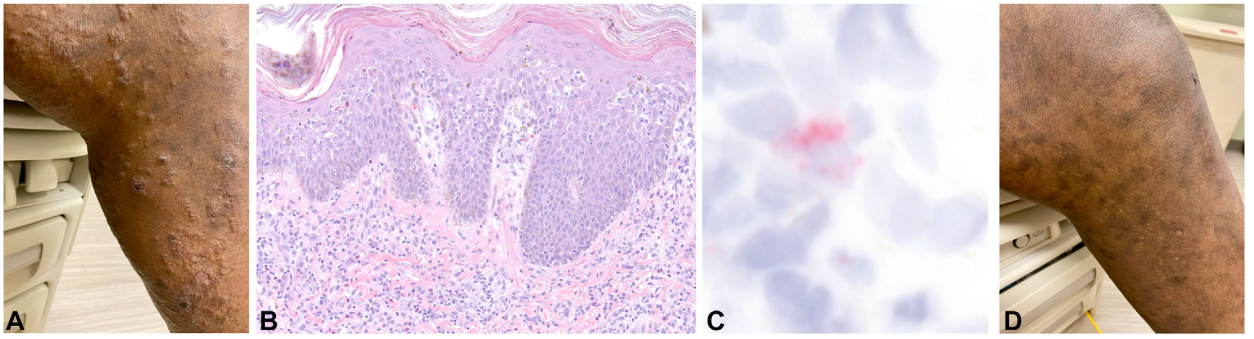

Fig 1. Patient 1. **A**, Clinical image of lichenoid dermatitis on the left thigh. **B**, Histology showing lichenoid infiltrate of lymphocytes and eosinophils that obscure the dermoepidermal junction, vacuolar alteration with necrotic keratinocytes, and saw-tooth hyperplasia. **C**, *IL-13* RISH staining in *red*. **D**, Response to treatment with dupilumab. *IL-13*, Interleukin-13; *RISH*, RNA in situ hybridization. (**B**, Hematoxylin-eosin; original magnification: ×20).

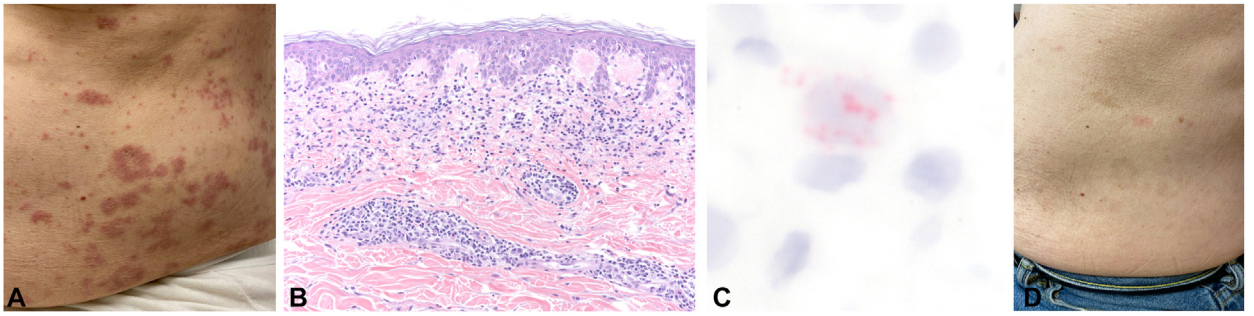

Fig 2. Patient 2. **A**, Clinical image of lichenoid dermatitis on the left side of the abdomen. **B**, Histology showing lichenoid infiltrate of lymphocytes and a few eosinophils, vacuolar alteration focal subepidermal clefts, and mild spongiosis. **C**, *IL-13* RISH staining in *red*. **D**, Response to treatment with dupilumab. *IL-13*, Interleukin-13; *RISH*, RNA in situ hybridization. (**B**, Hematoxylin-eosin; original magnification: ×20).

buttocks (Fig 2, *A*). Biopsy from the abdomen showed a band-like infiltrate concerning for possible PD-1 induced lichenoid dermatitis (Fig 2, *B*) and RISH analysis results showed *IL-13* staining (Fig 2, *C*). RISH staining for type 1 cytokine *IFN-γ*, type 2 cytokine *IL-4*, and type 3 cytokine *IL-17A* were negative. Past treatment with topical halobetasol daily and methotrexate 12.5 mg weekly was unsuccessful. He was started on dupilumab, and the rash cleared within 1 month (Fig 2, *D*) and pembrolizumab was reinstated. He remains on pembrolizumab and dupilumab.

DISCUSSION

In this case series we describe the use of dupilumab, which is a IL-4 receptor α-antagonist that blocks both IL-4 and IL-13 signaling,[4] for the treatment of lichenoid dermatitis in the setting of ICI therapy. Although there are substantial variability in the manifestation of skin-oriented toxicities based on factors including specific agent administered and underlying malignancy,[5] lichenoid reactions are among the most common cirAEs and, when severe, cause interruption or discontinuation of immunotherapy treatment.[2,6] Therefore, there is a need to identify pathogenesis-based targets to expand the therapeutic armamentarium for patients with refractory cirAEs beyond steroids and ICI therapy discontinuation. Certain features may help distinguish ICI-induced lichenoid dermatitis from classic lichen planus, such as the presence of eosinophils,[7] but the precise underlying pathophysiology remains unclear,[8] although one study has demonstrated phenotypic similarities between cutaneous acute graft versus host disease and anti—PD-1 interface cirAEs, suggesting potentially shared pathophysiologic mechanisms.[9] We found that *IL-13* is expressed in patient biopsies, suggesting that type 2 inflammation may play a role in the pathogenesis of ICI-induced lichenoid dermatitis and provides a molecular rationale for treatment with IL-4Rα antagonism. To our knowledge, this is the first report on

the use of dupilumab for treatment of ICI-induced lichenoid dermatitis, demonstrating safe, rapid, and sustained improvement. Importantly, initiation of dupilumab therapy allowed for reinitiation of ICI cancer therapy. In classic cutaneous lichen planus, there are elevated levels of *IFN-γ*, *IL-4*, and *IL-13* compared with psoriasis and a recent report of dupilumab treatment in a patient with cutaneous lichen planus.[10,11] In our 2 patients with pembrolizumab-induced lichenoid dermatitis, there was no RISH staining for *IFN-γ*, which may reflect potentially distinct mechanism of pathogenesis between classic cutaneous lichen planus and pembrolizumab-induced lichenoid dermatitis. However, more studies are needed to compare these overlapping, but distinct entities. Dupilumab has also been used with efficacy and tolerability in patients with classic bullous pemphigoid,[12] indicating its relevance for use in other cirAE subtypes, including immunobullous. Altogether, these cases highlight the value of molecular phenotyping with technologies such as RISH to guide treatment selection, and suggest that dupilumab may be an effective therapeutic strategy for treating cirAEs without interrupting ICI therapy; however, further studies are necessary to validate these results.

Conflicts of interest

Dr Vesely's spouse is an employee of Regeneron Pharmaceuticals, the maker of dupilumab. Dr Damsky is a consultant for Pfizer, Eli Lilly, and TWi Biotechnology, has received research funding from Pfizer, and receives licensing fees from EMD/Millipore/Sigma. Drs J. Park and E. Park have no conflicts of interest to declare.

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