**IL17A Blockade Successfully Treated Psoriasiform Dermatologic Toxicity from Immunotherapy**

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**Abstract**

Dermatologic toxicities are the most common immune-related adverse events (irAE) secondary to immune checkpoint inhibitors (ICI). First-line treatment for grade 3 or 4 skin irAEs is high-dose corticosteroids, which have their own side effects. Prolonged treatment with corticosteroids may abrogate antitumor ICI activity. The cellular causes of these dermatologic toxicities, which can manifest as a variety of clinical presentations, remain unclear. Beyond steroids, recommended treatment options are limited. We report a case of psoriasiform dermatologic toxicity, induced by inhibition of PD-1 with the mAb pembrolizumab, which resolved after treatment with systemic interleukin IL17A blockade. Introduction of IL17A blockade did not alter the patient's melanoma response to pembrolizumab. This case suggests a possible pathogenic role of Th17 cells in the irAE of the skin in this metastatic melanoma patient.

**Introduction**

Immune checkpoint inhibitors (ICI) have revolutionized cancer medicine by improving survival for patients with various malignancies (1–6). However, because these mAb agents block negative immune regulators, they can disrupt peripheral immune tolerance and cause autoimmune side effects termed immune-related adverse events (irAE; refs. 7, 8). ICI-associated irAEs can affect almost any organ, but most commonly include dermatologic toxicities (9, 10). The immune biology of ICI-associated irAEs is incompletely understood, which limits treatment options to broadly immunosuppressive strategies. Consensus guidelines recommend treating mild dermatologic irAEs with topical corticosteroids and moderate or severe cases with systemic corticosteroids (7, 11–14).

In clinical trials of ICIs, dermatologic toxicities are the most commonly reported irAE with an incidence ranging from 25% to 30% for monotherapy (anti-CTLA-4 or anti-PD-1/PD-L1) and up to 40% for combination therapy (anti-CTLA-4 and anti-PD-1/PD-L1; refs. 15, 16). In most cases, the reported skin manifestations involve macular rashes and vitiligo. However, more serious manifestations, such as toxic epidermal necrolysis/Stevens-Johnson syndrome, bullous pemphigoid, pustular psoriasis, and de novo Grover’s disease, have also been reported (17–22).

Here, we report a case of pembrolizumab (PD-1 mAb)–induced psoriasis-like dermatologic toxicity in a patient with advanced melanoma. This patient had no known previous clinical history of autoimmune diseases or family history of psoriasis. The patient demonstrated a complete skin response to IL17A inhibition (secukinumab) after inadequate benefit from treatment with systemic corticosteroids.

**Materials and Methods**

**Consents and permissions**

All analyses performed and patient information obtained for this project and other publications referenced in this article were conducted in accordance to the Declaration of Helsinki, HIPAA, and our institutional guidelines. The patient upon whom this case is focused and other patients from referenced case reports have given informed consent and consent to publish the clinical details that are contained within this report.

**Reagents**

IHC studies were performed on the Leica Bond autostainer with antibodies to the following proteins: CD3 (Agilent Technologies, catalog no. A045201-2, polyclonal, 1:100), CD4 (Leica Biotechnologies, catalog no. NCL-L-CD4-368, clone 4B12, 1:80), CD8 (Thermo Fisher Scientific, catalog MS-457s, clone C8/144B, 1:100; T-Bet, Cell Signaling Technology, catalog no. 13232S, clone D6N8B, 1:100), Gata-3 (Cell Signaling Technology, catalog no. 5852S, clone D13C9, 1:100), RORγt (Millipore, catalog no. MABF81, clone 6F3.1, 1:800), and phosphor-STAT3 (Tyr705; clone D3A7, Cell Signaling Technology, catalog no. 9145, 1:100).

**Case description**

An 80-year-old male presented with stage IIIC cutaneous melanoma of the right scalp and underwent surgical resection in...
March 2015. In September 2015, he developed bilateral lung nodules without other metastatic sites. Biopsy of the right lung confirmed metastatic melanoma, wild-type for BRAF<sup>V600</sup>, KIT, and NRAS. Therapy with pembrolizumab (2 mg/kg i.v. every three weeks) was initiated. Twelve weeks after the initial dose of pembrolizumab, restaging positron emission tomography (PET) imaging showed response of his melanoma to therapy. At this time, he also developed multiple pruritic, erythematous, and well-demarcated plaques with adherent scales on his back, abdomen, scalp, and bilateral upper/lower extremities without nail changes (Fig. 1). Prior to this, he had no personal history of skin rashes, autoimmune diseases, or family history of autoimmune disease. He was treated with topical triamcinolone cream and moisturizers with minimal symptom relief.

Because of persistent symptoms, pembrolizumab was discontinued and dermatology was consulted. A skin biopsy was performed that showed histopathologic features consistent with a psoriasiform reaction secondary to pembrolizumab (Fig. 2). The patient was subsequently started on oral acitretin (10 mg daily) and a short course of corticosteroids (50 mg prednisone tapered over total of 12 days). The rash improved, but recurred when steroids were discontinued. Acitretin dose was increased to 25 mg daily, but a severe rash persisted.

Because of persistent rash despite oral acitretin treatment, the patient started subcutaneous injections of secukinumab (300 mg once every two weeks), a fully human IL17A mAb, and discontinued acitretin. Four weeks after initiation of this therapy, the patient reported improved pruritus and near clearing of his skin

Figure 1.
Skin exam of the back with erythematous and well-demarcated plaques with adherent scales after therapy with pembrolizumab (A) and resolving after receiving secukinumab treatment (B).

Figure 2.
Histopathology of psoriasiform-like immune-related adverse event with acanthosis, hyperkeratosis with mounds of parakeratosis and dermal inflammation composed predominantly of lymphocytes and neutrophils [inset; hematoxylin and eosin (H&E), 40×, inset, 400×; A]. B, Munro microabscess with collection of neutrophils in the stratum corneum (H&E, 400×). C, Migration of neutrophils from dermal papilla into the epidermis with mild spongiosis (H&E, 400×).
Fig. 1. The patient continued secukinumab bi-weekly, but, after three treatments, he developed grade 1 thrombocytopenia, a known toxicity related to secukinumab treatment, which was therefore discontinued. Initially, our patient had a radiographic partial response by RECIST 1.1 criteria. However, after discontinuation of pembrolizumab and initiation of steroids, there was a recurrence of a 1.4-cm metastatic lung nodule. Twenty-eight weeks after secukinumab was administered, this lesion remained stable without reinitiation of pembrolizumab, and the patient did not develop any new lesions (Fig. 3).

Four weeks after secukinumab was discontinued in October 2016, the patient developed severe shortness of breath attributable to chronic obstructive pulmonary disease exacerbation and volume overload from preexisting and chronic renal failure. The patient was hospitalized and passed away shortly thereafter. No further melanoma progression or exacerbation of his skin toxicity was evident. Formalin-fixed paraffin embedded tissue samples from both the psoriasiform reaction and pre-pembrolizumab lung metastasis were analyzed by IHC to assess immune infiltrates. Histologic examination of the skin biopsy demonstrated both lymphocytic and neutrophil infiltrate in both epidermis and dermis (Fig. 2). Further immunophenotyping showed perivascular infiltrate of CD3+ T cells admixed with approximately 2:1 ratio of CD4+ T cells and CD8+ T cells, similar to the pre-pembrolizumab lung biopsy. Although there was scattered nuclear expression of the transcription factors T-Bet [characteristic of type 1 helper T cells (Th1)] and Gata-3 [characteristic of type 2 helper T cells (Th2)] and essentially negative stains for RORγt [characteristic of type 17 helper T cells (Th17)] in the tumor immune microenvironment, the inflamed skin tissue had more Gata-3+ cells with a subset exhibiting nuclear expression of RORγt (Fig. 4). In addition, the skin lesion appeared to have greater density of cells expressing phosphorylated STAT3 (pSTAT3), another nuclear marker associated with Th17 cell differentiation (Fig. 4), suggesting the immune infiltrate in the skin exhibited greater Th17 differentiation compared with the tumor immune infiltrate.

Discussion

This case illustrates another example of ICI-induced severe (grade 3 in the Common Terminology Criteria for Adverse Events) psoriasiform reaction, an infrequent irAE of the skin. Our patient developed biopsy-proven psoriasiform skin reaction within 12 weeks of initiation of pembrolizumab. A few cases of this type of dermatologic irAE have been reported (19, 21–22), and the underlying immune biology is not fully understood. Interest has focused on the integral role of Th17 and IL17 in the pathogenesis of psoriasis (23, 24). On the basis of two large phase III trials, secukinumab was approved by the FDA in 2015 for patients with moderate to severe plaque psoriasis (25). Our patient’s clinical history and response to secukinumab, together with histologic and immunologic data, suggest that his ICI-induced psoriasiform reaction may have arisen from pathogenesis through the Th17/IL17A axis, like other de novo cases of psoriasis.

Preclinical studies have shown that CD4+ T cells play an essential role in immune toxicity from ICIs. For example, CTLA-4-deficient mice develop an autoreactive lymphoproliferative disorder and die within 3 to 4 weeks of birth (26). Depletion of CD8+ T cells does not alter the onset or severity of this disorder, but CD4+ Th cell depletion prevents this lymphoproliferation (27). Th17 cells, which induce transcription of IL17
CD8+ diseases such as rheumatoid arthritis, psoriasis, and in subsets that has been implicated in a variety of autoimmune and lung biopsies exhibited immune infiltrates consisting of CD3+CD4-, CD8+T-bet, Gata-3, RORγt, and pSTAT3. Both skin and lung biopsies exhibited immune infiltrates consisting of CD3+, CD4-, CD8+, and T-Bet+ cells. Compared with the tumor microenvironment in the lung biopsy, the composition of immune cells in the psoriasiform-like irAE appeared to exhibit greater Gata-3+ cells with subset positive for RORγt and pSTAT3 (anti-CD3, 400x; anti-CD4, 400x; anti-CD8, 400x; anti-T-Bet, 400x; anti-Gata-3, 400x; anti-RORγt, 400x; pSTAT3, 400x).

Cytokines, are a CD4+ T-cell lineage distinct from Th1/Th2/Treg subsets that has been implicated in a variety of autoimmune diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease (28, 29). Associations between Th17 cells and IL17 with irAE development from ICIs have been reported. Both CTLA-4 and PD-1 blockade have been shown to increase peripheral blood Th17 cell expression in patients with melanoma and prostate cancer (30, 31). One study demonstrated that development and resolution of immune-related enterocolitis in patients treated with ipilimumab correlated with fluctuation in serum IL17 (32). These studies suggest that blockade of PD-1/PD-L1 and CTLA-4 can potentiate, in susceptible patients, a Th17-mediated immune response, which may induce some types of ICI-associated toxicity.

We sought to identify the predominant lymphocyte subsets within the immune infiltrate of our patient's skin toxicity biopsy and tumor biopsy. We found that markers associated with both Th2 and Th17 immune responses were more predominant in the inflamed skin tissue than in the tumor lymphocyte infiltrate. In addition, the predominance of neutrophils supports the role of IL17 in the pathogenesis of this severe psoriasiform dermatologic toxicity (29). There were limitations to our analysis including the unmatched timing of tumor and skin biopsies (the tumor biopsy occurred before ICI treatment) and lack of specificity with single-marker IHC for each CD4+ T-cell subtype. More accurate identification of Th17 cells requires multiple markers (such as CD45+CD3+CD8+FOXP3+RORγt+), which would require multiplex IHC (33).

Our patient had a suboptimal response to systemic corticosteroids, which are recommended as first-line treatment for grade 3 or 4 irAE dermatitis (12–14). Many patients with severe irAEs require prolonged corticosteroid exposure, which causes side effects and may hinder ICI antitumor activity (34, 35). Some patients do not respond to the steroids. Inflammatory cytokine blockade, such as by secukinumab, may not only be a useful treatment for steroid-refractory dermatologic irAEs, but may also be an effective steroid-sparing strategy.

Our group has also treated a different patient who had advanced melanoma and concomitant, refractory Crohn disease with pembrolizumab and tocilizumab, an IL6 receptor blocker (36). This strategy prevented exacerbation of the patient's Crohn's disease while allowing her to receive ICI therapy. Treatments that specifically target irAE inflammation may even be used concomitantly with immunotherapy to prevent recurrences when patients are rechallenged. These strategies need to be prospectively investigated in clinical trials.

A deeper understanding of the immune pathogenesis of irAEs may lead to improved, targeted treatments that do not inhibit the antitumor immune response. Another case has been reported of a patient with pembrolizumab-induced psoriasis flare successfully treated with secukinumab, although the authors suggested that the IL17 blockade led to loss of antitumor efficacy (37). This conclusion was based on a biochemical response and subsequent loss of response after introduction of secukinumab in a patient with mismatch repair–deficient metastatic colorectal cancer, but there was no radiographic evidence of initial response to pembrolizumab (37). Results from preclinical studies investigating the role of human Th17 cells in antitumor immunity have been conflicting. Tumor-specific Th17 cells have been shown to both reduce established B16 melanoma in mouse models through IFNγ production (38, 39) and recruit antitumor effector cells through Th1-type chemokines (40). However, IL17 also has pro-tumor activity through promotion of angiogenesis (41, 42) and promotion of tumor growth through the IL6–Stat3 pathway (43). Although the contribution of Th17 cells to tumor immunity is controversial, manipulation of the IL6/IL23/IL17 axis, which
contributes to chronic inflammation (44–46) as well as tumor growth, may be a promising strategy for the treatment of irAEs without compromising antitumor immunity.

Dermatologic toxicity from ICI therapy is common and its manifestations vary. ICI therapy–induced psoriasis is an infrequent dermatologic irAE, but its development can result in severe symptoms that respond poorly to corticosteroids. IL17A inhibition may represent a more effective, biologic therapy for patients with psoriasiform reactions from ICI and deserves further study. Our findings, although intriguing, are limited and purely descriptive. Studies evaluating the IL6/Th17/IL17 axis as a target to uncouple autoimmunity from tumor immunity are warranted in patients with cancer treated with ICIs.

Disclosure of Potential Conflicts of Interest

M.T. Tetzlaff is a consultant/advisory board member for Novartis, Myriad Genetics, Seattle Genetics. P. Hwu is a consultant/advisory board member for Sanofi and GlaxoSmithKline. No potential conflicts of interest were disclosed by the other authors.

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