CD30$^+$ lymphomatoid skin toxicity secondary to ipilimumab

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Key words: CD30; drug eruption; immune checkpoint therapy; ipilimumab; lymphoproliferative reaction; pseudolymphoma; skin toxicity.

INTRODUCTION

Ipilimumab is a monoclonal antibody that works by blocking the receptor cytotoxic T-lymphocyte–associated antigen-4 to increase T-cell activation and proliferation.[1] Although a morbilliform rash is a well-known dermatologic toxicity of ipilimumab, to the best of our knowledge, there are no reports of CD30$^+$ lymphoid skin reactions from ipilimumab.[1]

Abbreviation used:

CLL: chronic lymphocytic leukemia

CASE REPORT

A 63-year-old-man with history of stage IV metastatic melanoma and chronic lymphocytic leukemia (CLL) who received 3 cycles of ipilimumab presented to the dermatology department with a pruritic, erythematous papular eruption on his abdomen. His medical history was remarkable for diabetes mellitus, hypercholesterolemia, hypertension, squamous cell carcinoma, and 2 primary melanomas. The first was an invasive nodular melanoma, Clark level V, with a Breslow depth of 0.95 mm of the left neck with negative sentinel lymph node biopsies. A second primary tumor was an invasive lentigo maligna melanoma, Clark level II, with Breslow depth of a 0.19 mm melanoma of the left forearm. Metastatic melanoma developed in his lungs and extremities. Concurrent medications included losartan, 100 mg daily, metformin, 1000 mg twice daily, and glimepiride, 4 mg daily.

Five weeks after starting ipilimumab, he presented with 3- to 10-mm erythematous, pruritic papules coalescing into plaques along the midabdomen (Fig 1). A biopsy from the midabdomen was performed with concern for metastatic melanoma, leukemia cutis, primary cutaneous lymphoma, rare eruptive cutaneous neoplasms, infection, or drug reaction. Because his metastatic melanoma was responsive to ipilimumab, he completed 4 cycles total. Ten days later, the eruption progressed to diffuse, erythematous papules coalescing into plaques on his back, gluteal region, midabdomen, and posterior thighs (Fig 2) along with bilateral anterior uveitis. At this time, ipilimumab was discontinued. He was prescribed triamcinolone 0.1% cream for the affected areas and prednisolone acetate 1% drops for his eyes.

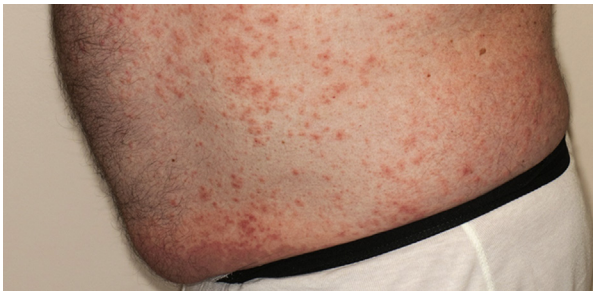

Fig 1. Clinical appearance of midabdomen rash prior to 4th cycle of ipilimumab. Three-to 10-mm erythematous, pink papules coalescing into plaques distributed along the midabdomen.

The biopsy found an atypical dermal lymphocytic infiltrate with increased CD30$^+$ cells in the papillary dermis. Sections showed psoriasiform epidermal

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Funding sources: None.
Conflicts of interest: None declared.

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JAAD Case Reports 2020;6:251-3.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2016.07.008

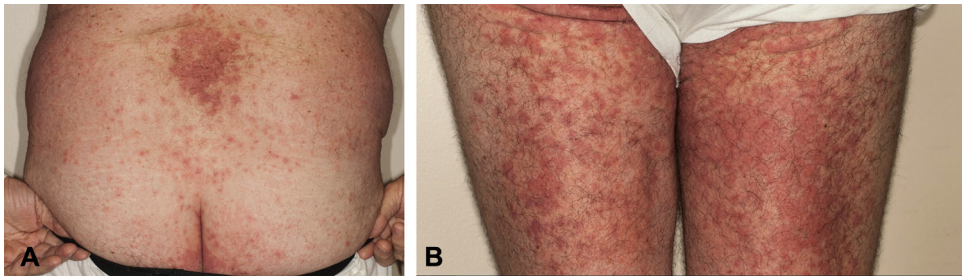

Fig 2. Clinical appearance of diffuse rash after 4th cycle of ipilimumab. **A**, Diffuse, erythematous, papules coalescing into plaques on patient's back and gluteal region. **B**, Diffuse, erythematous, papules coalescing into plaques on posterior thighs.

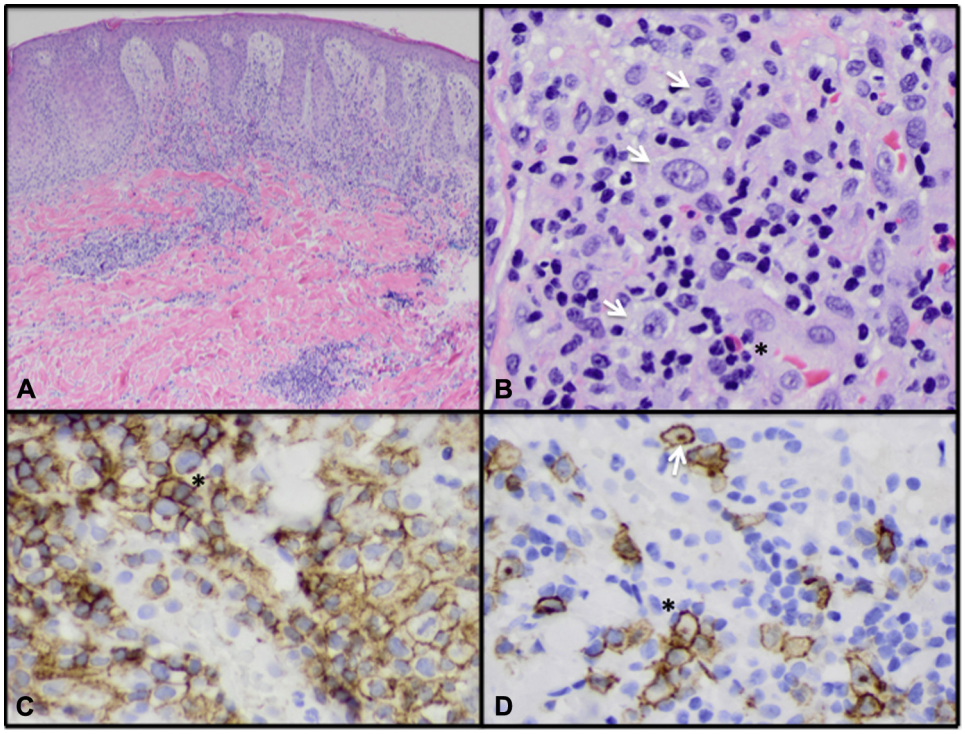

Fig 3. Photomicrographs of a biopsy specimen from midabdomen prior to 4th cycle ipilimumab. **A**, Skin punch with wedge shape pattern of atypical lymphocytic infiltrate involving the superficial and deep dermis. **B**, Scattered large atypical lymphocytes admixed with eosinophils, lymphocytes, and neutrophils (asterisk) **C**, Lymphoid infiltrate with predominance of $CD4^+$ T cells. Note the CD4 expression in the large atypical lymphocytes (asterisk). **D**, Increased clusters of $CD30^+$ cells (asterisk) with strong cytoplasmic membranous and perinuclear Golgi labeling (arrow). (**A**, Hematoxylin-eosin stain; **C**, Immunohistochemistry, anti-CD4; **D**, Immunohistochemistry, anti-CD30; original magnifications: **A**, ×40; **C** and **D**, ×400.)

hyperplasia, papillary dermal edema, and lymphocytic infiltrate composed of small- and largesized lymphocytes with eosinophils (Fig 3). Immunohistochemical studies found predominance of $CD4^+$ over $CD8^+$ T cells in the dermis, and *Pax5* was negative in the lymphocytic infiltrate (Fig 3). No monoclonal T-cell receptor γ or β gene rearrangements were detected by polymerase chain reaction analysis.

After discontinuing ipilimumab, his lesions began to resolve. At his 1-month follow-up appointment, only occasional residual papules remained. He had no other changes to his medications. At 1 year, the lesions have not recurred, and he is currently on surveillance for his melanoma.

DISCUSSION

$CD30^+$ lymphoid processes may be seen in a spectrum of cutaneous disorders, such as lymphomatoid papulosis, Hodgkin's disease, primary cutaneous anaplastic large T-cell lymphomas, and

mycosis fungoides.[2] The most common benign mimickers of CD30$^+$ cutaneous lymphoma, called *pseudolymphomas*, include viral and drug-induced reactions.[3] The drug-induced reaction develops after weeks to months and presents with papules, nodules, plaques, or widespread involvement such as erythema.[4] The reaction is secondary to increased production of T cells stimulated by the provoking agent, which typically resolves after cessation of the offending drug.[5] Case reports of such drugs include anticonvulsants, amlodipine, sertraline, gabapentin, metoprolol, cyclosporine, gemcitabine, and anti–tumor necrosis factor1-α inhibitors.[3-6]

Although most inciting factors causing pseudolymphomas are unknown, other known causes besides drugs include foreign agents, infections, and photosensitivities, all of which are well defined in the literature.[7] Classification of a pseudolymphoma depends on the predominant lymphocyte seen within the inflammatory infiltrate; thus, they are classically divided into B- and T-cell variants. The T-cell variants of pseudolymphomas are numerous and include, but are not limited to, lymphamotoid drug reactions, lymphomatoid contact dermatitis, idiopathic cutaneous T-cell pseudolymphoma, and actinic reticuloid.[7] Previous theories suggested that lymphomatoid drug eruptions were secondary to hypersensitivity reactions; however, newer evidence indicates that some drugs may cause decreased efficacy in immunosurveillance. This impaired surveillance may then allow for abnormal proliferation of lymphocytes and increased suppressor T-cell activity.[8] As was described in the biopsy of this patient, the generalized histologic pattern of T-cell pseudolymphomas is characterized by a bandlike infiltration of T lymphocytes within the dermis and evidence of epidermal changes including acanthosis.[9]

In this case, an extensive workup and subsequent biopsy were warranted to rule out potential metastasis of previously diagnosed malignant melanoma and CLL. The differential diagnosis at the time of presentation was constructed based on clinically relevant potential diagnoses (metastatic melanoma and leukemia cutis secondary to CLL). Common causes such as infection or drug reaction were considered. The addition of the more uncommon presentation of primary cutaneous lymphoma and rare eruptive cutaneous neoplasms were placed to complete a full differential diagnosis. Narrowing of the differential diagnosis began with evaluation of the lesion's histology (Fig 3), which was incongruent with metastatic melanoma. Staining for *Pax5*, a reliable marker for B cells in the setting of lymphoma, was negative, effectively eliminating a cutaneous manifestation of CLL and leukemia cutis from the differential diagnosis. Although diffusely positive for CD30, lymphomatoid papulosis was excluded because of a lack of recurrent, chronic lesions of similar morphology that is typical of its disease course.

This patient's CD30$^+$ cell infiltrate was most likely secondary to ipilimumab given the temporal relationship between administration of ipilimumab with the appearance and resolution of his skin rash upon withdrawal of medication. To our knowledge, this is the first case of CD30$^+$ lymphoid dermatologic toxicity secondary to ipilimumab, and physicians should be aware of this unusual side effect to new immunomodulatory drugs.

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