

# Angioimmunoblastic T-cell lymphoma associated with immune checkpoint inhibitor treatment



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## INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive lymphoma that accounts for approximately 18% of natural killer/T-cell lymphomas.<sup>1</sup> AITL typically affects older men and manifests at nodal and extranodal sites with B symptoms, lymphadenopathy, hematologic abnormalities, and, in up to 50% of cases, cutaneous manifestations.<sup>1-3</sup> We report a case of AITL with a severe skin eruption developing during checkpoint inhibitor therapy.

## CASE REPORT

A 78-year-old man developed spindle cell melanoma of the lip with biopsy-proven metastases to the lungs and mediastinal and hilar lymph nodes. He received surgeries, radiation, and pembrolizumab from September 2016 to June 2018. Disease progression was then treated with ipilimumab and transitioned to pembrolizumab for maintenance.

A surveillance positron emission tomography scan was conducted in February 2019 while the patient remained on maintenance pembrolizumab, with no known active disease. It demonstrated hypermetabolic lymphadenopathy concerning for melanoma recurrence. Subsequent excisional lymph node biopsy revealed a proliferation of atypical lymphocytes consistent with AITL, with no evidence of melanoma. Flow cytometry immunophenotyping demonstrated aberrant T lymphocytes with an increased CD4:CD8 ratio and decreased CD3,

### Abbreviations used:

AITL: angioimmunoblastic T-cell lymphoma  
PD-1: programmed death-1  
TCR: T-cell receptor

with coexpression of CD10. Immunohistochemistry demonstrated neoplastic lymphocytes positive for CD2<sup>+</sup>, CD3<sup>+</sup>, CD4<sup>+</sup>, and CD5<sup>+</sup> and partially positive for CD7. Bcl-2, CD10, and Bcl-6 were variably positive. CD21 revealed increased follicular dendritic cell meshworks with vascular structures. Scattered small-to-intermediate programmed death-1 (PD-1)<sup>+</sup> cells were detected in the areas of follicular dendritic cells. Pembrolizumab was discontinued because of the possibility that the lymphoma developed secondary to therapy effect. Active surveillance was chosen over chemotherapy given that he was asymptomatic and had few small avid nodes, normal blood counts, and a normal bone marrow biopsy result.

Four months after discontinuation of pembrolizumab, a restaging positron emission tomography/computed tomography showed spontaneous regression of the size and activity of lymph nodes, though there were some with activity suspicious for residual lymphoma. At 8 months, he developed extremely pruritic papules across the trunk, arms, and thighs (Fig 1). On presentation to our clinic, he had an outside diagnosis of Grover disease based on a biopsy showing acantholysis and had minimal

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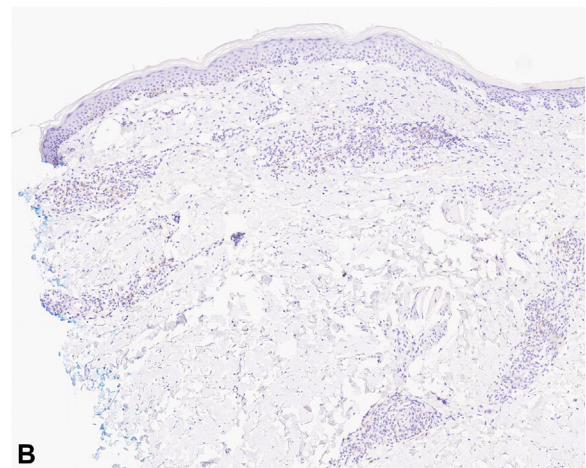
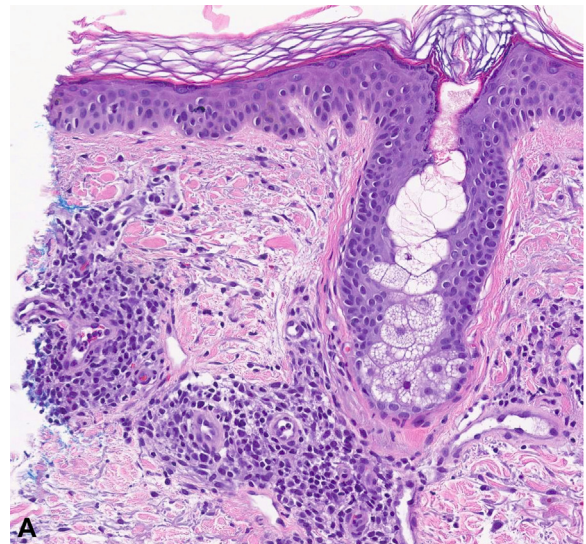
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**Fig 1.** Pink edematous papules across the chest and abdomen at the time of initial visit.

relief from antihistamines and topical steroids. The severity of itching was disproportionate to his rash. Repeat skin biopsies showed a superficial and deep perivascular lymphohistiocytic infiltrate. Numerous  $CD3^+$  T cells were predominately  $CD4^+$ , with a  $CD4:CD8$  ratio of approximately 5:1. Scattered cells were  $CXCL13^+$ . Scattered T lymphocytes were weakly positive for PD-1 and Bcl-6 (Fig 2). The infiltrate was interpreted as reactive to his AITL. A repeat positron emission tomography/computed tomography revealed a modest increase in the lymph node size, but overall the nodes remained low in volume and stable. Interdisciplinary discussion resulted in surveillance and skin management with aggressive topical therapy, methotrexate, gabapentin, and hydroxyzine.

Two months later, there was a significant evolution of his rash, with urticarial figurate erythematous patches and plaques and ulcerating nodules (Fig 3). Retrospective polymerase chain reaction–based analysis for the T-cell receptor (TCR) gamma gene in the previous lymph node and skin samples showed identical sizes of rearranged peaks for TCRV gamma 3 clones linking his cutaneous infiltrate and his nodal disease. Though his nodal disease remained stable, given his skin progression and intolerable pruritus, cyclophosphamide, Adriamycin, vincristine, and prednisone were started. After 6 cycles, the patient had complete resolution of his pruritus, rash, and nodal disease. The patient has been on observation for 6 months without evidence of lymphoma or melanoma recurrence.



**Fig 2.** Skin pathology findings. **A**, A perivascular lymphoid infiltrate composed of medium-sized cells with mild cytologic atypia is present. **B**, Scattered cells are  $PD-1^+$ . (**A**, Hematoxylin-eosin stain and **B**, Immunohistochemistry for PD-1; original magnifications: **A**,  $\times 400$ ; **B**,  $\times 400$ ). *PD-1*, Programmed death-1.

## DISCUSSION

This case posed numerous diagnostic and management challenges. The initial skin biopsy consistent with Grover disease did not explain his presentation. A high level of suspicion was required to broaden his workup and link his cutaneous complaints with his nodal disease. Peripheral T-cell lymphomas are often diagnostically challenging due to rarity, classification disagreements, and lack of reliable immunohistochemical markers.<sup>2,4</sup> Existing literature suggests that skin involvement occurs in 21%-50% of AITL patients.<sup>1,3,4</sup> Clinically, a wide range of morphologies have also been reported.<sup>3,4</sup> Histopathological presentations range from reactive-appearing to frankly malignant infiltrates.





**Fig 3.** Progression to urticarial figurate bright erythematous patches and plaques at follow-up.

Clonal TCR gamma gene rearrangements are frequently detected.<sup>4</sup> A retrospective study by Botros et al compared the skin biopsies of patients with known nodal AITL with cutaneous manifestations to those of control cases, observing a clinical evolution from early macular through papular to nodular stages. The maculopapular phase often eludes identification, while the nodular phase of cutaneous AITL can usually be discerned as lymphomatous. Lymph node biopsy confirmation remains mandatory.<sup>5</sup> Our patient's diagnosis of AITL in the lymph node was made on histology and immunohistochemistry. Molecular testing that revealed similar TCR clones between our patient's skin and lymph node was a critical tool in his diagnostic workup.

This patient's skin findings were disproportionately progressive compared with the overall presentation, and his discomfort ultimately spurred the initiation of chemotherapy. Although AITL is usually aggressive, our patient had stable lymph nodes with no other systemic concerns. This presentation, coupled with recent immunotherapy, made initiating cyclophosphamide, Adriamycin, vincristine, and prednisone a complicated decision. Interdisciplinary

discussions were essential to successfully and safely treat this patient.

Finally, this case is unique because of the development of AITL while on pembrolizumab. This case of AITL may be a clonal reactive immunophenotype, an entity that can also be seen in drug eruptions and inflammatory disorders. Drug-induced AITL has been reported with other medications, including sulfonamides, macrolides, and doxycycline. Cutaneous eruptions typically develop within months of initiation, with mixed results after drug cessation.<sup>4,6-8</sup> Immunotherapy-induced inflammatory dermatoses are common, but secondary T-cell lymphomas after PD-1 inhibitor therapy have rarely been reported.<sup>9</sup> Interestingly, AITL is often PD-1<sup>+</sup>. The mechanism for the development of immunotherapy-associated AITL is unconfirmed but is plausibly due to the activation of cytotoxic T cells. It is reasonable to postulate that pembrolizumab immunostimulation selected for a clone that led to the development of AITL, as seen in a similar case reported by Anand et al of the development of secondary T-cell lymphoma after PD-1 inhibitor therapy for an epithelial neoplasm.<sup>9</sup> A biconal T-cell lymphoproliferative lesion in a melanoma patient treated with ipilimumab and nivolumab has also been described and possibly attributed to the clonal expansion of lymphocytes, leading to a cutaneous lymphoproliferative disorder.<sup>10</sup> Further studies are needed to determine the role and mechanism of PD-1 inhibitors in peripheral T-cell lymphomas.

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