

# Disseminated blastomycosis in a patient on pembrolizumab for metastatic melanoma



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**Key words:** Blastomycosis; cell cycle checkpoints; immune checkpoint blockade; immunotherapy; melanoma; neoplasms; pembrolizumab; pseudoprogression.

## BACKGROUND

Although previously reported immunologic complications from immune checkpoint blockade have been autoimmune, we report a case of disseminated blastomycosis infection in the setting of pembrolizumab therapy. This unexpected infectious complication confounded monitoring of our patient's metastatic melanoma and had important consequences for his continued cancer therapy.

## CASE PRESENTATION

A previously healthy 77-year-old man presented to his primary care physician in Missouri with a new right axillary mass. Computed tomography (CT) found an enlarged right axillary lymph node and several right lower lobe pulmonary nodules. CT-guided needle biopsy was performed of the axillary mass and the largest pulmonary nodule and showed metastatic melanoma in both cases. Stage IV metastatic melanoma of unknown primary was diagnosed, and the patient was started on single-agent pembrolizumab (200 mg) every 3 weeks.

Repeat positron emission tomography (PET)-CT at the time of his fourth cycle of pembrolizumab found marked improvement in right axillary disease, but increased size and extrapleural extension of right pulmonary disease, and a new hypermetabolic pulmonary nodule in the lingula. At the time of his seventh pembrolizumab cycle, he complained of a tender lesion of the left lower eyelid. Examination found a crusted plaque on the left lower eyelid (Fig 1), a new and tender 3-cm erythematous fluctuant nodule on the upper chest, and a crusted, tender erythematous 1 cm papule on the left forearm. Biopsy specimens were obtained of all 3 sites.

### Abbreviations used:

CT:	computed tomography
PD-1:	programmed cell death receptor
PET:	positron emission tomography
Th:	helper T cell

Repeat staging by PET-CT found progression of the lingula mass with a new-onset pleural effusion and multiple hypermetabolic left axillary lymph nodes. Pembrolizumab was held in the setting of possible treatment failure. Given the mixed response, a fine-needle aspirate was obtained of an axillary lymph node to confirm the diagnosis of metastatic melanoma. Review of skin histology and fine-needle aspiration cytology found a mixed inflammatory cell infiltrate, granulomatous changes, and rare broad-based budding yeast consistent with a *Blastomycosis* sp. A diagnosis of blastomycosis dermatitidis with disseminated disease was made. He was treated with voriconazole 200 mg twice daily for 6 months with resolution of his skin lesions (Fig 2). Follow-up CT imaging and PET-CT imaging likewise found improvement in his pulmonary consolidation and axillary adenopathy.

## DISCUSSION

Blastomycosis is a systemic pyogranulomatous fungal infection endemic in regions of North America, including the Mississippi River Basin, acquired through inhalation of airborne conidia from soil. Clinical manifestations range from asymptomatic infection to pneumonia to extrapulmonary disease involving the skin, bones, or genitourinary

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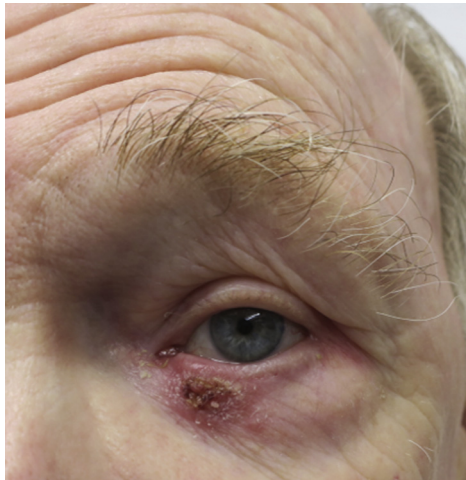
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**Fig 1.** Crusted plaque on the left lower eyelid.

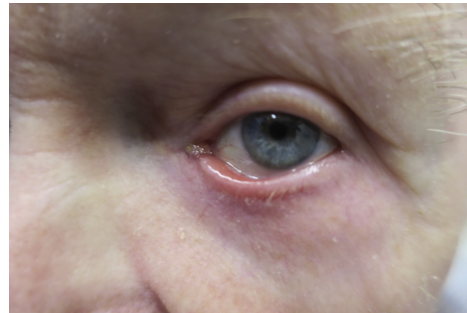
system. Skin involvement is reported in 40% to 80% of cases.<sup>1</sup> Classic lesions of cutaneous blastomycosis include crusted plaques and suppurative nodules.

Programmed cell death receptor 1 (PD-1) is an immune checkpoint receptor present on T cells, which, when activated, limits T-cell effector functions. Melanomas commonly upregulate PD-1 ligands to suppress T-cell-mediated killing of tumor cells. Pembrolizumab prevents binding of PD-1 to these ligands, thus potentiating the T-cell-mediated immune response against tumor cells.<sup>2</sup>

Immune-related adverse events from checkpoint inhibitor therapy are commonly inflammatory.<sup>3</sup> A recent study of 740 melanoma patients receiving immune checkpoint blockade, including 83 patients receiving pembrolizumab, found no serious infections in the pembrolizumab group.<sup>4</sup> Indeed, serious infections were limited to those patients receiving immunosuppressant medications (eg, corticosteroids, tumor necrosis factor- $\alpha$  inhibitors) for inflammatory adverse effects from ipilimumab and/or nivolumab.

Our patient lived in Missouri, an endemic region, but worked as a computer programmer and did not report regular high-risk outdoor exposures. He received no immunosuppressant medications during the course of pembrolizumab therapy and had no history of other immunosuppressed state.

Despite the widely acknowledged inflammatory effect of immune checkpoint blockade, the occurrence of disseminated infection in our case highlights a more nuanced immunomodulatory mechanism to



**Fig 2.** Healed skin lesion on the left lower eyelid after treatment with voriconazole.

PD-1 inhibitor therapy. Results of animal studies suggest that the immunomodulatory effects of PD-1 inhibitors include alterations, both activating and inhibitory, of the helper T cell (Th)1, Th2 and Th17 responses<sup>5</sup> and may impede T-cell expansion.<sup>6</sup> Such alterations may have allowed this patient's infection to escape T-cell-mediated suppression and surveillance. Alternatively, PD-1 inhibition may have promoted an exaggerated immune response to nascent fungal colonization resulting in clinically and radiologically apparent lesions. Additional functional studies are required to determine the exact mechanistic effects of immune checkpoint blockade on blastomycosis infection in patients.

This case represents a previously unreported complication of PD-1 inhibition and highlights the importance of recognizing classic-appearing lesions in unanticipated clinical contexts.

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