

Papulonodules on the Ankle in a Patient with Lung Cancer

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A 75-year-old woman presented to the dermatology department with well-circumscribed, round, hyperkeratotic papulonodules on the ankle of 3 months' duration (top). The papulonodules also were evaluated by dermoscopy, which highlighted in greater detail the hyperkeratosis seen grossly (bottom). The patient had a history of chronic obstructive pulmonary disease and metastatic lung cancer and had been taking pembrolizumab for the past 2 years. The lesions initially appeared on the medial right foot and slowly spread proximally. Most of the lesions resolved spontaneously except for 2 on the right ankle. At the current presentation, one lesion was slightly tender to palpation, but both were otherwise asymptomatic. A lesion was biopsied and sent for dermatopathologic evaluation.

WHAT'S YOUR DIAGNOSIS?

- cutaneous metastasis of lung cancer
- hypertrophic lichen planus
- pembrolizumab-induced eruptive squamous proliferation
- psoriasis
- squamous cell carcinoma

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THE DIAGNOSIS:

Pembrolizumab-Induced Eruptive Squamous Proliferation

Histopathology showed a broad squamous proliferation with acanthosis of the epidermis. Large glassy keratinocytes were seen with scattered necrotic keratinocytes (Figure), and a dense lichenoid band of inflammation was present subjacent to the proliferation. Notably, no hypergranulosis, remarkable keratinocyte atypia, or increased mitotic figures were seen. Based on the patient's medical history and biopsy results, a diagnosis of pembrolizumab-induced eruptive squamous proliferation was made. The diagnosis was supported by a growing body of evidence of this type of reaction in patients taking programmed death 1 (PD-1) inhibitors.^{1,2} Conservative treatment with clobetasol ointment 0.05% was initiated with complete resolution of the lesions at the 2-month follow-up appointment. Other common treatments include topical steroids, injected corticosteroids, or cryosurgery to locally control the inflammation and atypical proliferation of cells.³

Pembrolizumab is a humanized IgG4 monoclonal antibody targeting the PD-1 receptor that has been utilized for its antitumor activity against various cancers, including unresectable and metastatic melanoma, head and neck cancers, and non-small cell lung cancer (NSCLC).^{1,4,5} While this drug has extended the lives of many patients with cancer, there are adverse reactions associated with PD-1 inhibitors (eg, pembrolizumab, nivolumab). Skin toxicity to PD-1 inhibitors is the one of most common immune-mediated reactions worldwide, occurring in approximately 30% of patients.^{6,7} Reactions can occur while a patient is taking the inciting drug and can continue up to 2 months after treatment discontinuation.⁸ Skin reactions associated with PD-1 inhibitors vary from lichenoid reactions and vitiligo-like patches to psoriasis or eczema flares and are organized into 4 categories: inflammatory, immunobullous, alteration of

keratinocytes, and alteration of melanocytes.⁹ Our patient demonstrated alteration of keratinocytes, which is characterized by overlapping features of hypertrophic lichen planus and early keratoacanthoma.

The differential diagnoses for pembrolizumab-induced eruptive squamous proliferation include squamous cell carcinoma (SCC), psoriasis, hypertrophic lichen planus, and cutaneous metastasis of NSCLC. Hypertrophic lichen erythematosus also is a well-documented reaction to use of immune-checkpoint inhibitors.¹⁰ Direct immunofluorescence could have helped differentiate hypertrophic lichen erythematosus from an eruptive squamous proliferation in our patient; however, due to her response to treatment, no additional workup was done.

Squamous cell carcinoma, which is the most common type of skin cancer in Black patients in the United States,¹¹ has been shown to manifest after a PD-1 inhibitor is taken.¹² Although it typically has a more chronic persistent course, the clinical appearance of SCC can be similar to the findings seen in our patient. Histologically, SCC may demonstrate necrosis, but the atypical proliferations will invade the dermis—a feature not seen in our patient's histopathology.¹³

Lichen planus (LP) is an eruptive immune reaction of violaceous polygonal papules and plaques commonly seen on the ankles¹⁴ that has been shown to be an adverse effect of pembrolizumab.¹⁵ There are several subtypes of LP including hypertrophic versions, which can appear clinically similar to the findings seen in our patient. On dermoscopy, the classic finding of white lines, known as Wickham striae, is seen in all subtypes and can help diagnose this pathologic process. Under the microscope, LP can manifest with hyperkeratosis without parakeratosis, irregular thickening of the stratum granulosum, sawtooth rete ridges, and destruction of the basal layer.¹⁴

Psoriasis also has been shown to be exacerbated by anti-PD-1 therapy, although the majority of patients diagnosed with PD-1-induced psoriasis have a personal or family history of the disease.⁶ Clinically, psoriasis can have a hyperpigmented or violaceous appearance in patients with skin of color.¹⁶ The histopathology of psoriasis typically reveals confluent parakeratosis, neutrophils in the stratum corneum, regular acanthosis, thinning of the suprapapillary plates, and vessels in the dermal papillae.¹⁷

Although cutaneous metastasis of NSCLC may appear clinically similar to the current case, it is one of the rarer organ sites of metastasis for lung cancer.¹⁸ In our patient, biopsy quickly ruled out this diagnosis. If it had been a site of metastasis, histopathology would have shown a dermal-based proliferation of dysplastic cells without epidermal connection.¹⁹

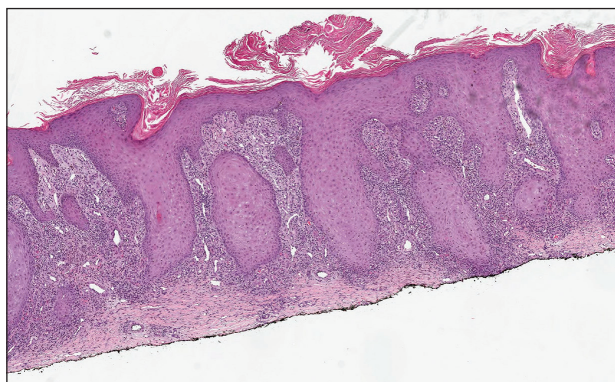


FIGURE. Shave biopsy of the lesion revealed acanthosis, large glassy keratinocytes, and necrotic keratinocytes in a background of chronic lichenoid inflammation (H&E, original magnification $\times 40$).

It is important for dermatologists to recognize eruptive squamous proliferations associated with pembrolizumab, as they often respond to conservative treatment and typically do not require dose reduction or discontinuation of the inciting drug.

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