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Dear Editor,

We report the case of a 51-year-old man with metastatic melanoma who presented with a cutaneous drug reaction consistent with acute localized exanthematous pustulosis (ALEP).

The patient was diagnosed with a BRAF wild type (NRAS Q61R mutant) metastatic melanoma following an admission for headache, blurred vision and left leg weakness. Multiple brain metastases were discovered on computed tomography imaging. Clinical examination revealed no evidence of cutaneous metastasis. Staging positron emission tomography scans revealed low volume positive axillary and hilar nodes, with no other extracranial disease. He was managed with excision of frontal, cerebellar and parietal masses, followed by whole brain radiotherapy and three-weekly infusions of Pembrolizumab. His medical history included diabetes, hypertension and dyslipidaemia.

Three months after commencing Pembrolizumab, he presented with erythematous macules and pustules on his palms and soles. The eruption was occasionally pruritic, but not painful. Although the eruption resembled palmoplantar pustulosis, he had no history of psoriasis.

Histopathological examination of a three-millimeter punch biopsy sample taken from the left palm showed an intraepidermal subcorneal vesicle containing a mild neutrophilic infiltrate and a few acantholytic keratinocytes (Figure 1). Adjacent epidermis showed mild spongiosis and there was a mild superficial dermal perivascular chronic inflammatory cell infiltrate.

Psoriasiform hyperplasia and suprapapillary plate thinning, characteristically seen in psoriasis was not detected. There was no subepidermal clefting, heavy eosinophilic infiltrate, dermal

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edema, leukocytoclasia or vasculitis. No viral cytopathic changes or fungal elements were detected either. **Histopathology examination of a right heel sample showed lichenoid inflammation consistent with a drug reaction.** Differential diagnoses based on histology included acute generalized exanthematous pustulosis (AGEP), pustular psoriasis or eczema with impetiginization. Based on clinical findings, the eruption was most consistent with a localized form of AGEP secondary to Pembrolizumab.

The patient was commenced on betamethasone dipropionate ointment used under occlusion and maintained on Pembrolizumab. At four months follow-up, he reported improvement with intermittent use of topical steroids with no further pustules seen and only mildly scaly plaques.

AGEP is a rare cutaneous eruption characterized by disseminated non-follicular sterile pustules on a background of erythematous skin. AGEP is typically drug-induced, with antibiotics being the commonest offending agent.[1] ALEP is a localized and milder variant of AGEP with similar histopathological features.[2] Clinical and histological distinction between pustular psoriasis and AGEP/ALEP is often difficult.

Pembrolizumab is a humanized monoclonal IgG4 antibody which functions as a T-cell checkpoint inhibitor, targeting the programmed cell death 1 receptor (PD-1). Pembrolizumab is currently approved for the treatment of advanced melanoma and non-small cell lung cancer. Cutaneous adverse reactions to pembrolizumab are common and usually mild; a retrospective study reported 42% of patients experienced a cutaneous reaction. Common skin reactions to anti-PD-1 agents include macular and papular eruptions, pruritus and hypopigmentation.[3, 4]

There are no cases of AGEP/ALEP secondary to any of the approved anti-PD-1 antibodies (Nivolumab and Pembrolizumab) in the medical literature; although unspecified pustular eruptions have been reported.[3, 5] Based on clinicopathological correlation, we propose that this case likely represents a drug reaction to Pembrolizumab on the AGEP/ALEP spectrum.

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Figure Legend

Figure 1A: Haematoxylin and eosin stain section of a punch biopsy from the left palm at 5x magnification showing an intraepidermal subcorneal pustule with a neutrophilic infiltrate. The adjacent epidermis is acanthotic. A superficial perivascular chronic inflammatory cell infiltrate consisting of lymphocytes and histiocytes is present within the dermis.

Figure 1B: Clinical photograph of patient's right palm demonstrating multiple pustules.

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