Acute localized pustular drug reaction to pembrolizumab

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To the Editor:

We describe a patient with esophageal adenocarcinoma treated with pembrolizumab who developed a localized truncal pustular drug eruption. This eruption recurred with subsequent pembrolizumab infusions but was controlled with local topical corticosteroids.

Anti-programmed cell death 1 (ant-PD1) inhibitors have become a mainstay in the treatment of advanced malignancies. Tumor cells overexpress the receptor programmed cell death ligand-1 (PDL1) and bind T cells via the PD1 receptor resulting in immune tolerance in the tumor microenvironment and suppression of the antitumor response. Inhibition of this local suppression by anti-PD1 immune checkpoint inhibitors results in a significant anti-tumor T cell response [1]. As the skin harbors the majority of effector memory T cells in the body, collateral activation of cutaneous lymphocytes by drugs of this class makes cutaneous adverse reactions predictably frequent. Maculopapular, psoriasiform, and lichen planus-like eruptions are most common whereas pustular eruptions are only infrequently reported [2,3].

A 69-year-old man presented with a history of a rash on the chest. He had been diagnosed with esophageal adenocarcinoma 9 months prior and began treatment with pembrolizumab. He received 5 infusions at 3-4 week intervals and then treatment was paused while the patient underwent coronary artery bypass graft surgery. Pembrolizumab therapy was resumed two months later and within a week of the second infusion, the patient developed a moderately pruritic pustular eruption consisting of 3-5mm pustules on the chest and upper abdomen (**Figure 1**). Most of the pustules were non-follicular though some were follicle-based clinically. There was diffuse, poorly marginated, background macular erythema but no other lesions. Bacterial culture of a pustule was negative. A punch biopsy was performed. There was a focal collection of neutrophils present in the dermis with no signs of infection, vasculitis, or folliculitis (**Figure 2**). Some evidence of leukocytoclasia was also present within the dense, diffuse infiltrate of neutrophils in the dermis. Based on these histopathological findings paired with the clinical presentation, a diagnosis of

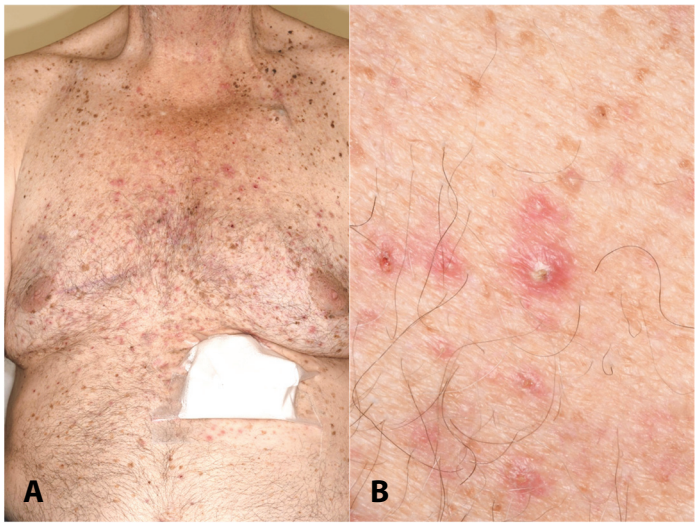

Figure 1. ***A)*** *Pustular eruption localized to the chest extending onto the abdomen.* ***B)*** *Close up of pustules.*

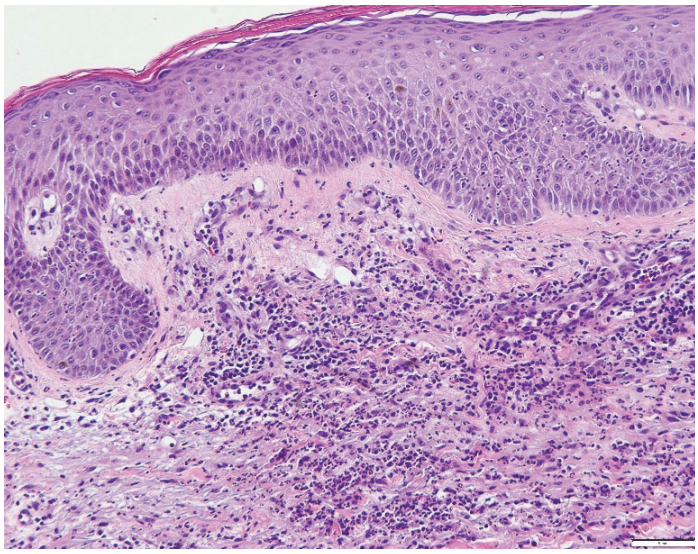

Figure 2. *A focal collection of neutrophils is present within the dermis. H&E, 10×.*

neutrophilic dermatosis as a result of checkpoint inhibitor therapy was made. The patient responded well to clobetasol 0.05% cream twice daily with a decrease in pruritus and near complete resolution of the pustular eruption in two weeks. He continues to respond well to pembrolizumab but develops new pustules in the same area after subsequent infusions. These eruptions continue to respond to use of intermittent topical clobetasol 0.05% cream.

Neutrophilic eruptions are less commonly reported adverse drug reactions related to immune checkpoint inhibitor therapy but have been reported with nivolumab and ipilumab (with or without combination chemotherapy) more frequently than with pembrolizumab [3]. Acute generalized exanthematous pustulosis (AGEP) has been reported with ipilumab, nivolumab, and pembrolizumab. One previous report of a localized palmoplantar pustular eruption to pembrolizumab was identified in the literature [4]. Our patient demonstrated limited truncal and no acral involvement. The patient's tumor continues to respond to pembrolizumab at 14 months of therapy. He continues to develop new pustules in the same location on the chest following subsequent infusions of pembrolizumab but these improve with 1-2 weeks of topical clobetasol cream and no interruption of cancer treatment has been required.

In the setting of AGEP it has been demonstrated that drug-specific T cells produce a significant amount of CXCL8, a neutrophil chemoattractant [5]. It has also been demonstrated that drug-specific CD4+ and CD8+ T cells are activated and cytotoxic within the skin allowing vesicle formation [6]. More recently, neutrophil recruitment into target tissue has been shown to be very complex involving not only CXCL8, but 6 other chemokines, including CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, and CXCL7, two neutrophil CXCR receptors, and G-protein and B-arresting-coupled signaling pathways [7]. The extent and distribution of cutaneous involvement with pustular drug reactions likely depends on the combination of chemotactic cytokines produced and subsequent receptors that are inadvertently activated by upregulated T cells in response to checkpoint inhibitor therapy. Local differences in the cutaneous immune microenvironment could explain whether patients develop a generalized cutaneous pustulosis such as AGEP or cutaneous pustulosis localized to only specific areas, such as limited truncal or palmoplantar regions.

Potential conflicts of interest

The authors declare no conflicts of interest.

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