

## SHORT COMMUNICATION

**A Case of Hand-Foot Skin Reaction-like Eruption Associated with Pembrolizumab**

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## INTRODUCTION

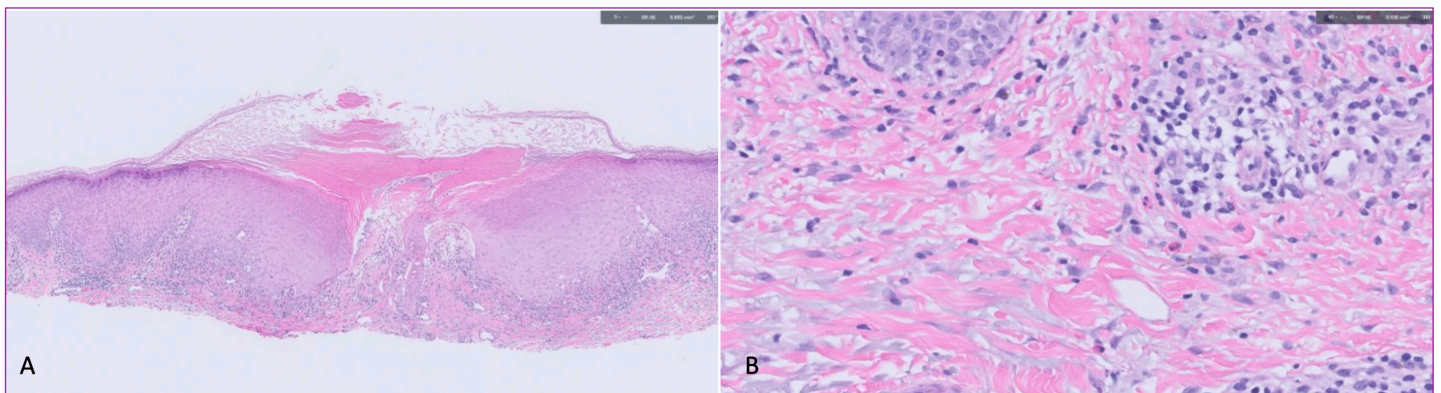
Skin toxicity poses a dose-limiting challenge in various cancer therapies. Hand-foot skin reaction (HFSR) is characterized by painful, occasionally pruritic, inflammatory hyperkeratotic plaques predominantly on palmoplantar surfaces. HFSR is predominantly observed in the context of targeted therapy, with an expanding list of implicated agents due to the growing arsenal of available cancer therapies. The most common causative agents are multikinase inhibitors. Up to 70% of patients on multikinase inhibitors report HFSR.<sup>1</sup> Additional agents will likely be associated as treatment options expand. Immune checkpoint inhibitors (ICIs) block inhibitory immune activity, activating the immune system and promoting anti-tumoral immunity.<sup>2</sup> Due to non-specific immune activation, ICIs are linked with systemic and cutaneous immune-related adverse events (irAEs). To our knowledge, there have been no previous reports of HFSR-like eruptions in association with an ICI.

## CASE REPORT

A patient in his 60s with locally invasive urothelial carcinoma presented with a two-month history of painful lesions on the palmar surfaces of his hands after seven cycles of pembrolizumab administered every three weeks. He was not receiving any concomitant cancer therapies. Previous cancer treatments included six cycles of gemcitabine plus cisplatin, which were discontinued in favor of pembrolizumab. Immune-related adverse events during pembrolizumab therapy included transaminitis six weeks after initiating treatment, resulting in a one-month interruption of therapy. The patient had no history of prior irAEs. Upon examination, hyperkeratotic papules and plaques with erythematous halos were observed on the palmar surfaces of both hands (**Figure 1**). Drainage attempts yielded no fluid. Considering the clinical presentation and onset during immunotherapy, a diagnosis of HFSR-like eruption was made. He was treated with clobetasol ointment 0.05% for



**Figure 1.** Hyperkeratotic plaques with erythematous halos on the palmar surfaces of the bilateral hands, consistent with hand-foot skin reaction.



**Figure 2.** Histopathological slides stained with hematoxylin and eosin staining. x50 magnification (A) shows epidermal hyperplasia with ulcer and perivascular and band-like infiltrate (lichenoid dermatitis) with parakeratosis. x400 magnification (B) shows an inflammatory infiltrate composed of lymphocytes and eosinophils.

symptomatic relief and urea 40% cream twice daily for keratolysis. At three-week follow-up, he presented with new lesions on the dorsal surfaces of the hands and progression of palmar involvement. A shave biopsy of a dorsal lesion revealed ulceration and lichenoid dermatitis with eosinophils, notable parakeratosis, and a band-like mixed infiltrate in the dermis consistent with HFSR histological features previously reported in the literature (**Figure 2**).<sup>3,4</sup> Pembrolizumab was held approximately three months after rash onset due to the progression of skin symptoms.

## DISCUSSION

HFSR is a dose-limiting side effect of cancer therapy.<sup>5</sup> The differential diagnosis for HFSR includes verruca vulgaris, callus, corn, and bullous pemphigoid. The pathogenesis is not completely understood. Its association with multikinase inhibitors, which possess anti-angiogenic properties, and the observed exacerbation of symptoms with concomitant anti-angiogenic agents suggest that angiogenic inhibition may contribute to HFSR development.<sup>4</sup> In this case, the HFSR-like eruption was secondary to pembrolizumab, an agent not previously reported in association with this condition. This suggests non-specific immune activation may lead to HFSR-like eruptions through an alternative mechanism.

Management strategies include keratolytics, topical steroids, acitretin, topical vitamin E, heparin ointment, and hydrocolloid wound dressings. Generally, therapies demonstrate the greatest success in low-grade disease, with efficacy largely not evaluated in controlled trials.<sup>1,4</sup> Preventative measures, such as pressure avoidance and regular emollient use, can help combat HFSR development.<sup>4</sup> While dose reduction or therapy cessation is often the most effective

management strategy for advanced HFSR, dermatologists can help reduce this by facilitating early recognition and management of this condition.

**Patient Consent:** Consent for the publication of all patient photographs and medical information is on file, stating that the patient gave consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

**Conflict of Interest Disclosures:** None

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