



Dermatology Reports

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eISSN 2036-7406



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Società Italiana di Dermatologia
Chirurgica, Oncologica, Correttiva ed Estetica

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Please cite this article as:

Ambrogio F, Laface C, Castronovi C, et al. Pembrolizumab-related hand and foot skin reaction. Dermatol Rep 2026 [Epub Ahead of Print] doi: 10.4081/dr.2026.10184



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Received: 6 November 2024; Accepted: 2 October 2026.

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Pembrolizumab-related hand and foot skin reaction

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Key words: hand and foot skin reaction; pembrolizumab; HFSR.

Contributions: Francesca Ambrogio, Caterina Foti: conceptualization, supervision; Francesca Ambrogio: visualization; all authors contributed to data collection, writing – original draft, writing – review & editing. All authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no conflict of interest.

Ethics approval and consent to participate: not required.

Consent for publication: informed consent was obtained from the patient for publication of this case report and any accompanying images.

Availability of data and materials: all data underlying the findings are fully available.

Abstract

Hand and foot skin reaction (HFSR), usually associated with tyrosine kinase inhibitors, is characterized by painful erythema and hyperkeratosis at palmoplantar pressure points. HFSR differs from the more widely recognized chemotherapy-induced hand-foot syndrome (HFS) in terms of both clinical and histopathological features. Here we present the case of a 79-year-old man with advanced lung adenocarcinoma who developed grade 3 HFSR after receiving pembrolizumab, a PD-1 inhibitor. The patient initially presented with erythema, desquamation, and hyperkeratotic plaques on the palms and soles, followed by the development of vesiculobullous lesions. Histopathological findings supported the clinical diagnosis. Treatment included discontinuation of pembrolizumab, along with systemic and topical corticosteroids and salicylic acid, with marked improvement and resolution after about 2 months. Given the impact on quality of life and treatment continuity, clinicians should monitor for HFSR in patients receiving immune checkpoint inhibitors (ICIs) to allow for timely intervention.

Introduction

Hand and foot skin reaction (HFSR) is a frequent cutaneous adverse event (AE) consisting of erythema, vesicles, and hyperkeratosis, as well as dysesthesia and pain at the points of greatest friction (for example, soles of the feet and palms of the hands).^{1,2} HFSR is primarily associated with multikinase inhibitors (sorafenib, sunitinib, regorafenib, axitinib, pazopanib, cabozantinib) and BRAF inhibitors (including dabrafenib and vemurafenib), whereas classical hand-foot syndrome (HFS) is most commonly associated with cytotoxic agents such as capecitabine and doxorubicin.²⁻⁶ Usually, HFSR occurs within a few days or a few weeks of starting treatment.^{1,2}

Case Report

In this paper, we report a clinical case of a 79-year-old man who developed HFSR during pembrolizumab monotherapy for an advanced lung adenocarcinoma (*EGFR*, *ALK*, *ROS-1*, *BRAF* wild type, PD-L1 tumor proportion score 50%). The patient was not taking any other medications, as he had no associated comorbidities. After four cycles of pembrolizumab, a radiological assessment was carried out, resulting in a partial response. Therefore, pembrolizumab was continued. However, 2 weeks after the administration of the sixth cycle, the patient developed significant peeling of the palms and the soles associated with pain and itching. The physical examination revealed erythema, desquamation, and hyperkeratotic plaques without fissures localized to plantar and palmar pressure points (Figure 1 A,C), with no dorsal involvement. No lesions were observed elsewhere on the body. There were no clinical findings, such as small, intensely pruritic vesicular lesions, suggestive of pompholyx, nor was there a personal history of atopy to support a diagnosis of eczema. There was no

personal or family history of psoriasis, and no silvery-white scaly plaques or pustules suggestive of psoriasis were observed. Likewise, there was no violaceous discoloration or other clinical features consistent with lichenoid dermatitis.

Given the clinical presentation, which resembled previously reported cases of HFSR associated with other drugs, further investigations were performed, and a 6-mm punch biopsy was obtained from the sole of the right foot. Histological examination reported parakeratosis, hyperkeratosis, hypergranulosis, mild spongiosis, and occasional necrotic keratinocytes; furthermore, there was an active interface dermatitis with a moderate lymphomonocytic inflammatory component and some eosinophils (Figure 2 A,B). Overall, the clinical findings, histopathological features, and temporal association with treatment suggested a diagnosis of HFSR. The reaction was classified as grade 3 according to the Common Terminology Criteria for Adverse Events, version 5.0, due to severe skin involvement, pain, and functional impairment affecting self-care activities, requiring interruption of the ongoing treatment with pembrolizumab.⁷ No mucosal or systemic symptoms were observed.

Based on these findings, the patient was treated with systemic (prednisone 25 mg daily for 7 days, followed by gradual tapering over approximately 1 month) and topical therapy consisting of betamethasone and salicylic acid ointment applied twice daily for 14 days and then once daily for an additional 14 days. This treatment resulted in a marked improvement of the hyperkeratotic lesions; however, vesiculobullous lesions subsequently developed (Figure 1B). The Nikolsky sign was negative. Autoantibodies against DSG1/3, BP180/BP230, and direct immunofluorescence (DIF) were negative, making pemphigus and pemphigoid less likely. The patient did not receive any further oncological therapies due to the deterioration of his clinical condition, despite maintaining stable disease at subsequent evaluation. Complete resolution of the HFSR was achieved with clobetasol cream within 20 days. No further recurrences were observed after discontinuation of pembrolizumab.

Discussion

Immunotherapy was developed to reverse the immunological “escape” mechanisms implemented by the tumor to evade the immune system, thus reactivating the anti-tumor immune response. Given its high efficacy, this therapeutic strategy has transformed the treatment landscape for multiple solid and hematological neoplasms.⁸ Immune checkpoint proteins, including PD-1 and CTLA-4, trigger signaling pathways that suppress T cell function. CTLA-4 and PD-1 signaling pathways are tightly regulated to enable self-tolerance; however, tumor cells can use these pathways to evade the immune response and establish a microenvironment that allows tumor growth. Immune checkpoint inhibitors (ICIs) bind to immune checkpoint proteins to overcome this tumor-mediated inhibition of T cell function. Pembrolizumab is a humanized monoclonal antibody that binds to the PD-1 receptor and

blocks its interaction with the PD-L1 and PD-L2 ligands. The PD-1 receptor is involved in the negative regulation of T cell function. Pembrolizumab enhances T cell responses, including antitumor responses, through blocking PD-1 binding to PD-L1 and PD-L2, which are expressed on antigen-presenting cells and may be expressed by tumors or other cells in the tumor microenvironment. Disinhibition of T cell function by ICIs can lead to a spectrum of inflammatory side effects, called immune-related AEs (irAEs).⁸ Dermatologic toxicity is the most common irAE reported in patients who underwent therapy with ICIs.⁹ To be specific, dermatologic toxicities have been reported in a substantial proportion of patients treated with ICIs, although they are more frequently of low-grade severity.⁹ Presentation is varied and includes maculopapular or papulopustular rash, acneiform rash, skin hypersensitivity or photosensitivity reactions, Sweet's syndrome, dermatomyositis, pyoderma gangrenosum, drug reaction with eosinophilia and systemic symptoms (DRESS), psoriasis, bullous disorders, and vitiligo.^{9,10} However, the most reported dermatological irAEs are pruritus, maculopapular rash, and vitiligo. Severe toxicities, such as DRESS or Stevens-Johnson syndrome/toxic epidermal necrolysis, are rare.¹⁰ Reports of HFS or HFSR occurring during anti-PD-1 therapy are limited. Cases of HFS or HFSR have been reported in patients receiving pembrolizumab in combination with, or following treatment with, tyrosine kinase inhibitors, making it difficult to determine the specific contribution of immunotherapy to the development of these acral toxicities.¹¹⁻¹³ Hyperkeratosis, parakeratosis, and keratinocyte necrosis have been described in HFSR associated with multikinase inhibitors.¹⁴ In our patient, these findings were accompanied by hypergranulosis, mild spongiosis, interface dermatitis, and a lymphomonocytic inflammatory infiltrate with occasional eosinophils. Lichenoid dermatitis with eosinophils was also reported by Young *et al.* in a dorsal hand biopsy from a patient with a pembrolizumab-associated HFSR-like eruption.¹⁵ HFSR is a distinct clinical entity that shares some clinical features with the more widely recognized HFS, also known as palmar-plantar erythrodysesthesia, but differs in several important aspects. In particular, HFSR is characterized by localized hyperkeratotic lesions predominantly affecting pressure-bearing areas and may present with erythema, dysesthesia, vesicles, bullae, and desquamation. In contrast, HFS typically manifests as a more diffuse and symmetric erythema and edema of the palms and soles.^{2,3} In our patient, the predominance of localized hyperkeratotic plaques at palmar and plantar pressure points favored HFSR over classical HFS. The histopathological findings were interpreted in conjunction with the clinical presentation and were not considered diagnostic in isolation. Historically, HFS has been most commonly associated with fluoropyrimidines, anthracyclines, and taxanes. More recently, several cases have been reported in patients receiving pembrolizumab in combination with targeted agents such as anlotinib, lenvatinib, and apatinib.^{9,11-13} An HFSR-like eruption during pembrolizumab monotherapy has also been described by Young *et al.*, with initial palmar involvement followed by

extension to the dorsal hands.¹⁵ In the present case, lesions involved both palmar and plantar pressure points without dorsal involvement, and histopathological assessment was performed on a plantar lesion. Our patient had no previous or concomitant exposure to tyrosine kinase inhibitors. This case provides additional clinicopathological evidence of HFSR occurring during pembrolizumab monotherapy. As with other cutaneous irAEs, the HFSR experienced by our patient might also be mediated by various immune-mediated mechanisms. Specifically, ICI therapy generates autoreactive CD4⁺ T cells and activates cytotoxic CD8⁺ T cells against healthy tissues as a consequence of the diversification and expansion of autoreactive clones. Furthermore, ICI therapy can promote the expansion of autoreactive B cells, resulting in antibody-mediated cytotoxicity in target tissues. Immunotherapy may also induce the abnormal release of pro-inflammatory mediators, including chemokines and cytokines, thereby impairing Treg cell function and promoting systemic and organ-specific inflammation.

Moreover, the release of self-antigens from cancer cells following cytotoxic activity might determine antigenic cross-presentation and cross-reactivity to normal tissues.⁸ On the other hand, although the exact pathogenesis of tyrosine kinase inhibitor (TKI)-mediated HFSR is still unknown, the most accepted hypotheses do not concern immune-mediated mechanisms. In particular, TKIs probably reach the acral sweat glands, resulting in direct skin toxicity. Since the number of eccrine sweat glands is highest in the palms and soles, more cytotoxic agents will be excreted in the sweat and affect the region. However, this theory has not been proven, since TKIs were not found in the sweat produced by the eccrine glands. Another hypothesis refers to the TKI-mediated inhibition of the vascular endothelial growth factor receptor that could affect the vascular repair mechanisms in the body, leading to marked inflammation after any vascular damage. This effect could be highlighted in areas with high pressure and repeated subclinical trauma, such as the palms and soles.²⁻⁶

Conclusions

In conclusion, to the best of our knowledge, we describe a case of pembrolizumab-associated HFSR supported by both clinical and histopathological findings.

Our findings suggest that immune-mediated mechanisms may also contribute to the development of HFSR. Increased awareness of this potential AE is important to ensure accurate diagnosis and appropriate management. Careful pharmacovigilance is needed so that these reactions are not overlooked or mistakenly attributed to other causes. Early recognition may allow prompt implementation of supportive measures and topical therapies, improving patients' quality of life while minimizing interference with ongoing oncologic treatment.

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Figure 1. A, C) Hyperkeratotic plaques with erythema at the plantar and palmar levels. B) Disappearance of hyperkeratosis but occurrence of vesicles and bullae.

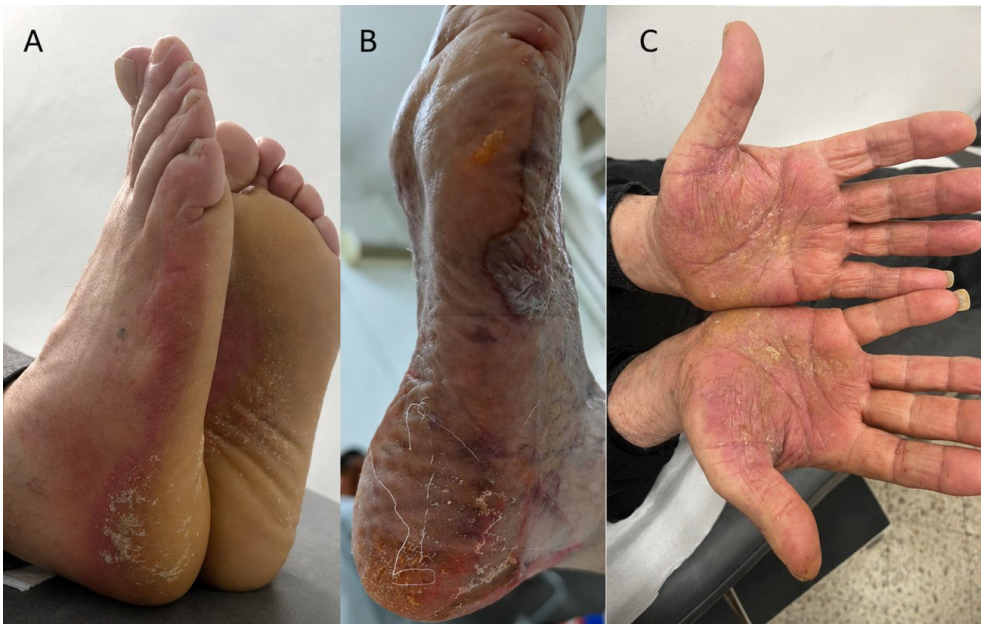


Figure 2. A) Histopathological photomicrograph showing hyperkeratosis, hypergranulosis, epidermal hyperplasia with occasional necrotic keratinocytes; furthermore, there is interface dermatitis with moderate inflammatory lymphoid infiltrate (Hematoxylin-Eosin, original magnification 5x). B) Photomicrograph showing necrotic keratinocytes, with active interface dermatitis and some eosinophils (Hematoxylin-Eosin, original magnification 40x).

