Digital ulcerative lichenoid dermatitis in a patient receiving anti-PD-1 therapy

Permalink
https://escholarship.org/uc/item/8sm0j7t7

Journal
Dermatology Online Journal, 25(9)

Authors
Martínez-Doménech, Álvaro
García-Legaz Martínez, Marta
Magdaleno-Tapia, Jorge
et al.

Publication Date
2019

DOI
10.5070/D3259045515

Copyright Information
Copyright 2019 by the author(s). This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at https://creativecommons.org/licenses/by-nc-nd/4.0/

Peer reviewed
Digital ulcerative lichenoid dermatitis in a patient receiving anti-PD-1 therapy

Álvaro Martínez-Doménech MD, Marta García-Legaz Martínez MD, Jorge Magdaleno-Tapia MD, Cristian Valenzuela-Oñate MD, Gemma Pérez-Pastor MD PhD, Amparo Pérez-Ferriols MD PhD

Affiliations: Department of Dermatology, Consorci Hospital General Universitari de Valencia, Avenida Tres Cruces 2, Valencia, Spain

Corresponding Author: Marta García-Legaz Martínez, Avenida Tres Cruces 2, 46014, Valencia, Spain, Tel: 34-963131884, Email: martaglegazm@gmail.com

Introduction

Programmed cell death receptor 1 inhibitors (anti-PD-1) have been proven to be beneficial in treating several solid cancers, such as melanoma, renal cell carcinoma, non-small cell lung cancer, and squamous cell carcinoma of the head and neck [1]. The binding of PD-1 with its ligand (PD-L1) downregulates cytotoxic lymphocyte activity [2]. Programmed cell death ligand 1 is overexpressed in these tumors as a means of evading the immune system's response against them. Anti-PD-1 works by blocking this interaction. However, this immune response modulation is not tumor-specific, which explains why these medications may be associated with immune-related adverse events (irAE), [1, 3-5].

Cutaneous irAE are among the most common, appearing in up to 50% of patients [4, 5]. Several types of dermatologic irAE have been described, particularly vitiligo and lichenoid dermatitis, which has been reported with different cutaneous and mucosal presentations [1, 3, 4, 6]. However, these lichenoid reactions are yet to be fully characterized and the relationship with tumor response is still unclear [1, 2]. We present a case of digital ulcerative lichenoid dermatitis in a patient receiving pembrolizumab for squamous cell carcinoma of the oral mucosa.

Case Synopsis

A 77-year-old male consulted our clinic for a painful digital lesion. He had a history of verrucous squamous cell carcinoma of the oral mucosa. After
radical surgery, radiotherapy, and chemotherapy (cisplatin), he presented with lymph node metastasis and was started on pembrolizumab, 200mg every three weeks. After 18 months (25 cycles) he developed an intensely painful lesion that persisted for over two months despite topical antibiotic and zinc oxide ointment. He had no personal or familial history of dermatoses.

Physical examination revealed an ulcerated, indurated ulcer on the medial and palmar aspect of his right index finger (Figure 1). The lesion had a fleshy, exudative floor and hyperkeratotic borders. There were no other relevant findings.

Punch biopsy showed full-thickness epidermal ulceration and a dense lymphohistiocytic infiltrate with lichenoid disposition (Figure 2A). The epidermis on the borders showed marked orthokeratotic hyperkeratosis, irregular saw-tooth acanthosis, and secondary subepidermal clefting. Eosinophilic cytoid bodies were present in the papillary dermis, especially on the ulcerated portion. Immunohistochemical study showed intense positivity for CD8 lymphocytes with scattered exocytosis (Figure 2B) and CD163 histiocytes (Figure 2C), with milder positivity for CD3, CD4, CD68, and PD-L1.

Treatment was started with daily application of topical betamethasone dipropionate 0.5% and gentamycin sulfate 1% cream, and zinc oxide 16.6% water-based ointment. The lesion improved significantly after three weeks and completely resolved after three months. Although he required occasional re-treatments for milder recurrences during the following three months, there was no need for pembrolizumab discontinuation or dose reduction. Thereafter, the patient received 10 more cycles and one year after completing pembrolizumab therapy he remains free of disease progression.

**Case Discussion**

The spectrum of anti-PD-1-associated cutaneous irAE is wide and broadens every day. Pruritic rash, vitiligo, and lichenoid dermatitis are among the most frequent [1, 3, 4]. Efforts have been made to study the profiles of both vitiligo and lichenoid dermatitis, as
they seem to have different clinical and histological characteristics from their non-drug-related presentations [6-8]. To the best of our knowledge, there have been no reports of anti-PD-1-associated digital ulcerative lichenoid dermatitis resembling ulcerative cutaneous lichen planus (UCLP).

Certain issues arise when a patient under anti-PD-1 therapy presents with a skin reaction. Ideally, treatment for irAE should not interfere with the patient’s antineoplastic treatment, making certain systemic therapies suboptimal. Fortunately, most cutaneous irAE are manageable with topical treatment [1, 4, 7]. Furthermore, reactions that might be life-threatening must be promptly recognized, as they would justify immunotherapy discontinuation. On the contrary, unnecessary anti-PD-1 suspension or dose reduction should be avoided as they could hinder the cancer treatment.

Multiple types of lichenoid dermatitis in patients undergoing anti-PD-1 therapy have been reported. Some presented with palmar or plantar lichenoid papules and others with oral or genital erosions [1, 3, 4, 6]. However, UCLP-like irAE have not been described. Owing to the clinical features and delayed presentation of our patient’s irAE, metastatic disease was considered in the differential diagnosis. Histopathological examination ruled out malignancy and indicated grade 2 irAE instead. Despite the fact that idiopathic forms of UCLP are known to be recalcitrant to both topical and systemic therapy and that persistent painful lesions might motivate immunotherapy suspension [9], our patient’s irAE was manageable with topical therapy and without modification of pembrolizumab therapy.

Histologically, anti-PD-1-associated rashes are characterized by predominantly lymphocytic infiltrates with lichenoid disposition [7]. Schaberg et al. [7] compared histological and immunohistochemical characteristics of anti-PD-1-associated and non-drug-related lichenoid dermatitis. The former showed more prominent spongiosis; in addition, epidermal necrosis was observed with greater frequency. Immunohistochemically, they only differed in the presence of CD163 histiocytes, which was significantly higher in lesions associated with anti-PD-1. This could be a reactive response to greater epidermal destruction or a contribution to the inflammatory reaction secondary to a M2-to-M1 macrophage polarization switch derived from PD-1 pathway blockade [7]. In our case, immunohistochemical study showed intense positivity of CD163 histiocytes at the base of the ulcer with a decrease on the edges where the epidermis was still preserved. We also observed a comparatively milder positivity for CD68 macrophages. On the contrary, CD8 lymphocyte marking was predominant on the edges of the ulcer and less intense at its base.

The PD-1 pathway, as a mechanism for keeping cytotoxic lymphocytes from reacting against self-antigens, seems to be implicated in epidermal integrity preservation during inflammatory skin reactions [2]. In the context of anti-PD-1 therapy, these reactions have a prominent cytotoxic profile, exhibiting significant accumulation of CD8 lymphocytes in the dermoepidermal junction with accompanying exocytosis and marked keratinocyte apoptosis [2]. Our patient’s ulcerated plaque exhibited marked CD8 polarization of the lichenoid infiltrate, scattered exocytosis of CD8 lymphocytes, and abundant epidermal necrosis. This depicts an intense cytotoxic reaction against self-antigens present on the patient’s keratinocytes and suggests it is secondary to blockade of PD-1-mediated immune downregulation. Since our patient was started on pembrolizumab for squamous cell carcinoma of the oral mucosa, this could reflect cross-reactivity between shared epidermal antigens present both on the primary tumor’s cells and on epidermal cells on his finger. If so, this irAE could be associated with the favorable response to treatment, as he maintains progression-free-survival one year after completion. Analogously, a correlation between anti-tumor response and development of vitiligo as irAE in patients receiving anti-PD-1 for melanoma was reported [10].

**Conclusion**

Cutaneous irAE in patients undergoing anti-PD-1 therapy are common and increasingly diverse. This report adds an undescribed reaction that may simulate metastatic disease; management was surprisingly successful with topical treatments.
Further studies of these reactions are required to improve patient management and perhaps find a potential use as predictor of treatment response [1, 2, 5].

Potential conflicts of interest
The authors declare no conflicts of interests.

References