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

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Abstract

Programmed cell death receptor 1 inhibitors (anti-PD-1) constitute a form of immunotherapy for the treatment of several cancers. They are associated with cutaneous immune-related adverse events (irAE), occurring in up to 50% of patients. Lichenoid dermatitis is frequent and several presentations have been described. Although attempts have been made to study these reactions, they are yet to be fully characterized and the relationship with tumor response is unclear. We describe a case of digital ulcerative lichenoid dermatitis resembling ulcerative cutaneous lichen planus that occurred during pembrolizumab therapy for oral squamous cell carcinoma. The patient developed a painful ulcer on his index finger 18 months into therapy. Biopsy revealed epidermal ulceration with intense lichenoid dermatitis. Immunohistochemical study revealed intense CD8 positivity at the ulcer's edges and marked CD163 positivity at its base. Although idiopathic forms of this type of lichenoid dermatitis are particularly recalcitrant, our case was successfully managed with topical therapy and oncologic treatment did not require modification. One year after ending treatment the patient remains free of disease progression. It is unclear if this reaction is associated with his favorable oncologic response. This report adds an undescribed reaction to the increasing diversity of cutaneous irAE associated with anti-PD-1 therapy.

Keywords: programmed cell death 1 receptor, immunotherapy, pembrolizumab, lichenoid dermatitis, digital ulcerative lichen planus, immune-related adverse events, squamous cell carcinoma

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

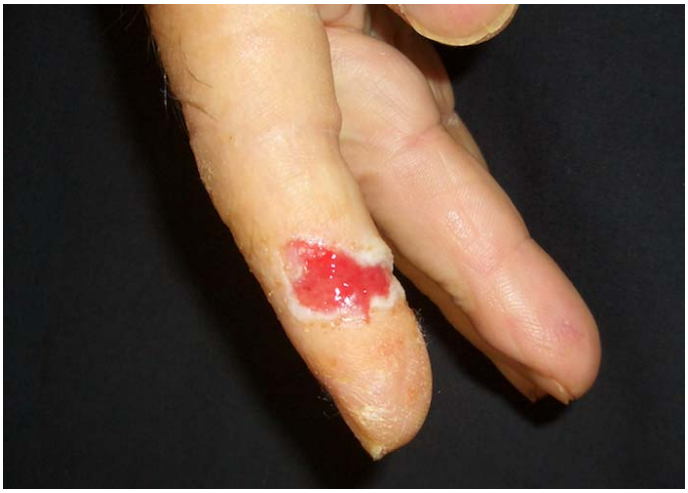

Figure 1. *Digital ulcerative lichenoid dermatitis associated with pembrolizumab therapy. Indurated ulcer with keratotic borders on the medial and palmar aspect of the right index finger.*

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

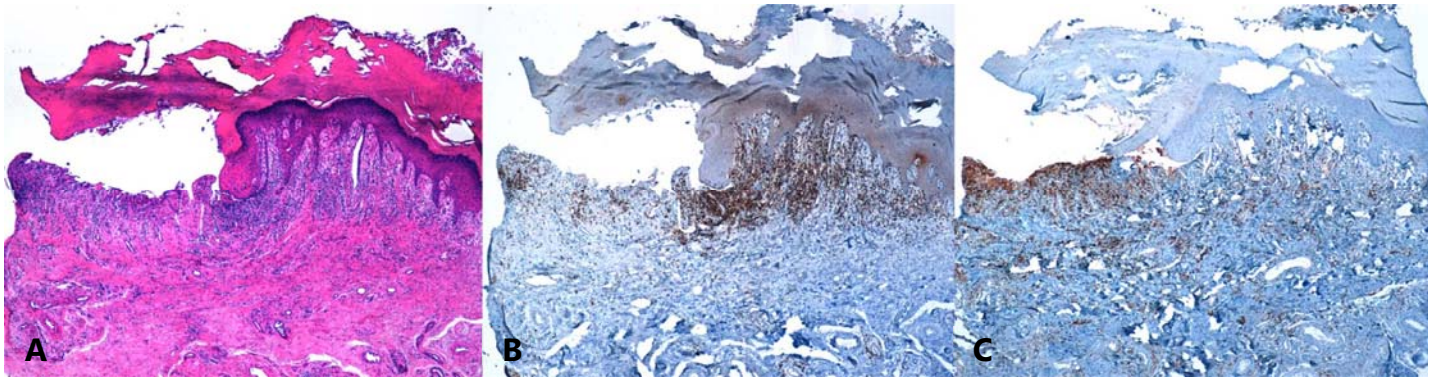

Figure 2. *Digital ulcerative lichenoid dermatitis associated with pembrolizumab therapy.* ***A)*** *Biopsy showing full-thickness epidermal ulceration. An underlying dense lichenoid lymphohistiocytic infiltrate is observed. Eosinophilic cytoid bodies are present in the papillary dermis at the base of the ulcer. The edges show hyperorthokeratosis, irregular acanthosis, and subepidermal clefting. H&E, 4×.* ***B)*** *CD8. Intense positivity for CD8 at the edges of the ulcer coupled with scattered exocytosis, 4×.* ***C)*** *CD163 immunohistochemistry. Intense positivity for CD163 at the base of the ulcer, 4×.*

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 immunohisto-chemical 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

1. Shen J, Chang J, Mendenhall M, et al. Diverse cutaneous adverse eruptions caused by anti-programmed cell death-1 (PD-1) and anti-programmed cell death ligand-1 (PD-L1) immunotherapies: clinical features and management. *Ther Adv Med Oncol*. 2018 Jan 22;10:1758834017751634. [PMID: 29383039].
2. Goldinger SM, Stieger P, Meier B, et al. Cytotoxic Cutaneous Adverse Drug Reactions during Anti-PD-1 Therapy. *Clin Cancer Res*. 2016;22:4023-9. [PMID: 26957557].
3. Hwang SJ, Carlos G, Wakade D, et al. Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: A single-institution cohort. *J Am Acad Dermatol*. 2016;74:455-61.e1. [PMID: 26793994].
4. Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer*. 2016;60:190-209. [PMID: 27085692].
5. Sanlorenzo M, Vujic I, Daud A, et al. Pembrolizumab Cutaneous Adverse Events and Their Association With Disease Progression. *JAMA Dermatol*. 2015;151:1206-1212. [PMID: 26222619].
6. Shi VJ, Rodic N, Gettinger S, et al. Clinical and Histologic Features of Lichenoid Mucocutaneous Eruptions Due to Anti-Programmed Cell Death 1 and Anti-Programmed Cell Death Ligand 1 Immunotherapy. *JAMA Dermatol*. 2016 Oct 1;152:1128-1136. [PMID: 27411054].
7. Schaberg KB, Novoa RA, Wakelee HA, et al. Immunohistochemical analysis of lichenoid reactions in patients treated with anti-PD-L1 and anti-PD-1 therapy. *J Cutan Pathol*. 2016;43:339-46. [PMID: 26762844].
8. Larsabal M, Marti A, Jacquemin C, et al. Vitiligo-like lesions occurring in patients receiving anti-programmed cell death-1 therapies are clinically and biologically distinct from vitiligo. *J Am Acad Dermatol*. 2017;76:863-870. [PMID: 28094061].
9. Weston G, Payette M. Update on lichen planus and its clinical variants. *Int J Womens Dermatol*. 2015;1:140-149. [PMID: 28491978].
10. Hua C, Boussemart L, Mateus C, et al. Association of Vitiligo With Tumor Response in Patients With Metastatic Melanoma Treated With Pembrolizumab. *JAMA Dermatol*. 2016;152:45-51. [PMID: 26501224].