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Pembrolizumab-Induced Lichen Planus in a Patient with Metastatic Pulmonary Giant Cell Carcinoma: A Case Report and Literature Review

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Abstract

Immune checkpoint inhibitors (ICIs) have revolutionized the management of advanced cancers. Nevertheless, the oncologic response is often achieved at the cost of immune-related adverse events (irAEs). We present a case of an immune-mediated lichen planus (LP) and a literature review of similar cases.

A 60-year-old man, who is being treated with pembrolizumab for a pulmonary giant cell carcinoma since April 2022, presented in November 2022 with a pruritic eruption that appeared two weeks ago. Examination showed bright purple confluent scaly papules on wrists, proximity of limbs, back and buttocks and palmar keratoderma made of violaceus papules covered with reticular white striae. Histological examination revealed an epidermal hyperplasia, vacuolization of the basal layer, necrotic keratinocytes and a band-like subepidermal lymphocytic infiltrate with many eosinophils. The diagnosis of an immune-related LP was retained. Pembrolizumab was withheld because of the severity and the extension of the lesions. Superpotent topical steroids were prescribed with a significant improvement of the rash within 3 weeks.

Immune-mediated lichenoid euptions represent one of the most frequent dermatologic irAEs. In our patient, the onset seven months after the initiation of ICIs, the infiltrate rich in eosinophils, and the rapidly diffused character are indications of an immuno-mediated LP.

Keywords: Lichen planus; Pembrolizumab; Anti-PD1; Immunotherapy; Drug reactions

Abbreviations: ICI: Immune checkpoint inhibitors, LP: lichen planus

Introduction

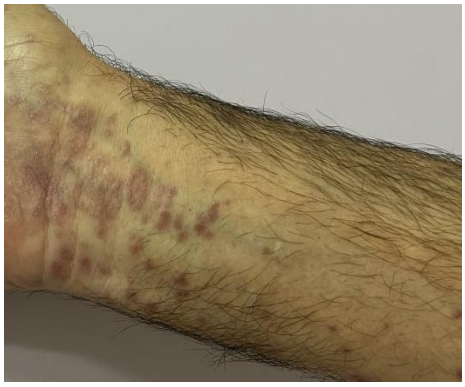
Immune checkpoint inhibitors (ICIs) have revolutionized the management of advanced cancers in dermatology as well as in other disciplines **[1]**. Pembrolizumab is one of the most frequently used ICIs, with a growing list of approved indications including non-small-cell lung cancers, metastatic melanoma, and advanced squamous cell cancer. It is an anti-Programmed Death protein 1 (Anti-PD-1) agent. Blocking the inhibitory signals of cytotoxic T cells, ICIs allow the upregulation of the antitumor immune response **[2]**. Nevertheless, the immune-mediated oncologic response is often achieved at the cost of immune-related adverse events

(irAEs) that may potentially affect any organ. Dermatologic irAEs (dirAEs) are among the most common and are observed in about 40% of all treated patients. These include maculopapular, psoriasiform, lichenoid, vitiligoid and eczematous rashes, auto-immune bullous disorders, pruritus, hair, nail and mucosal changes, as well as a few severe life-threatening drug reactions **[3]**.

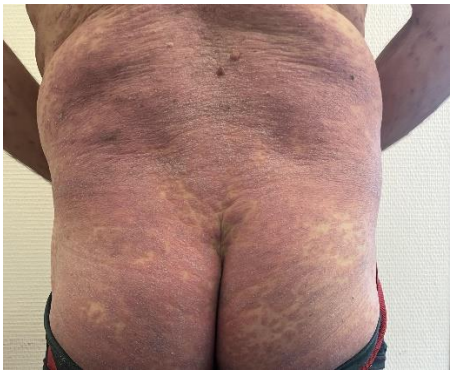
Herein we describe a case of an immune-mediated lichenoid eruption in a patient being treated with pembrolizumab for a pulmonary giant cell carcinoma.

Case Report

A 60-year-old Caucasian man, with a history of hypothyroidism supplemented for years, and who is being treated with pembrolizumab for a stage IV pulmonary giant cell carcinoma since April 2022, presented in November 2022 with a pruritic eruption that appeared two weeks ago. The eruption started with confluent papules of the wrists then extended to the limbs and the trunk. The patient did not have any other relevant history. Skin examination showed polygonal, bright purple, confluent, and scaly papules on wrists, proximity of limbs, back and buttocks and palmar keratoderma made of violaceus and confluent papules covered with reticular fine whitish streaks **(Figure A)**. These lesions were symmetrically distributed. Mucosal and nail examination was normal. The standard biological tests were within normal values. The patient had no history of unprotected sexual intercourse, and staining for syphilis antibodies was negative. Differential diagnosis included lichen planus (LP) and lichenoid drug eruption. Light microscopic evaluation of skin biopsy of the back revealed histological features of LP: Hypergranulosis, vacuolization of the basal layer with apoptotic keratinocytes, and a band-like subepidermal lymphocytic infiltrate. The presence of numerous eosinophils did not rule out the diagnosis of a lichenoid drug reaction **(Figure B)**. The diagnosis of a grade 3 immune-related lichenoid eruption was then retained. A multidisciplinary consultation meeting led to anti-PD-1 therapy withdrawal because of the severity and the extension of the lesions. Superpotent topical steroids were prescribed with a significant improvement of the pruritus and the rash within three weeks. Given the stability of the cancerous disease, checkpoint inhibitors were not reintroduced. At the fourth month follow-up, all skin lesions have healed.



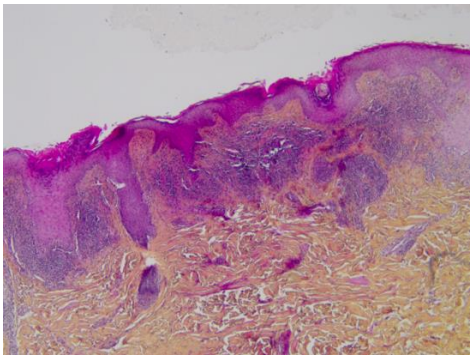
A.1



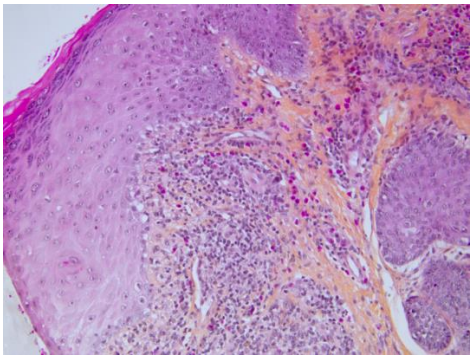
A.2

A.3

Figure A: Bright purple confluent scaly papules on wrists **(A.1)**, back and buttocks **(A.2)**, Palmar keratoderma **(A.3)**



B.1



B.2

Figure B: Hematoxylin Eosin Coloration X 10 showing epidermal hyperplasia, vacuolization of the basal layer, band-like subepidermal lymphocytic infiltrate **(B.1)** Hematoxylin Eosin Coloration X 20 showing rich lymphocytic and eosinophilic infiltrate **(B.2)**.

Discussion

LP is a T cell-mediated, inflammatory skin condition that affects between 0.5 and 1% of the population. Classic LP typically presents as a symmetrically distributed pruritic, polygonal, violaceous papules. It is suggested that the pathogenicity of LP involves the autoimmune-mediated lysis of basal keratinocytes by CD8 + lymphocytes. Yet, definitive etiological triggers are still unknown. An association between LP and the following has been observed : chronic active hepatitis (hepatitis C particularly); primary biliary cirrhosis; complication of hepatitis B vaccination; viral and bacterial antigens; medications; trauma (Koebner phenomenon); metal ions; and some autoimmune diseases such as autoimmune thyroiditis, alopecia areata, vitiligo, and autoimmune polyendocrinopathy **[4]**.

Lichenoid eruptions are among the most frequent manifestations of anti-PD-1 cutaneous toxicity. PD-1 is a membrane receptor. Its activation is responsible for self-tolerance during immune response. Increased expression of PD-L1 and PD-L2 by tumour cells thus leads to inhibition of T cells and tolerance toward malignant cells. Blockade of this pathway is transforming the prognosis of many cancers. However, the inhibition of the same pathway may lead to disruption of loss of self-tolerance and induce immune mediated diseases **[2]**. T cell-mediated autoimmune response secondary to PD-1 inhibition induces cell apoptosis, including basal layer keratinocytes apoptosis, and plays an important role in the pathogenesis of lichenoid reactions.

According to a recent study, LP or lichenoid eruption is 10.7-fold more likely to develop in patients treated with nivolumab or pembrolizumab than the general population **[5]**. Although lichenoid reactions have emerged as an important dirAEs, immune-induced LP have been infrequently described in the literature. So far, 26 cases of LP and 21 cases of LP pemphigoid induced by anti-PD1 have been reported, with the first description appearing in 2016 **[6,7]**. Among LP cases, 14 patients had a classic form (Cutaneous LP: 7 cases; cutaneo-mucosal LP: 7 cases), seven patients had bullous LP, four patients had hypertrophic LP mimicking early invasive squamous cell carcinomas, one patient had LP pilaris, and one patient had erosive LP **[6-12]**. The patient with LP pilaris also had lesions of classic cutaneous LP **[13]**. Delay of onset from the beginning of treatment ranged from two weeks to 18 months **[11,12]**. A delay of seven months was observed in our patient. This latency period is of particular interest as cutaneous toxicities can present even after withdrawal of ICIs **[3]**. In the majority of the reported cases, as in our patients, lesions were clinically and histologically indistinguishable from classic LP. However, a consistent chronology, an infiltrate rich in eosinophils and an eruptive and rapidly diffused character may be indicators of an immuno-mediated LP.

The majority of patients were treated with either oral or topical corticosteroids. Hydroxychloroquine was prescribed, in association with oral prednisone and topical steroids, in one of the patients presenting with a hypertrophic LP, with a complete resolution **[14]**. In the patient with LP pilaris, anti-inflammatory dose of doxycycline initially slowed the progression. However, control of infammation has been obtained only with systemic steroids and hydroxychloroquine, with a remaining scarring alopecia **[13]**. Withdrawal of anti-PD-1 treatment was considered in seven

patients. Pembrolizumab was temporarily suspended in two patients **[15,16]**. Cases of LP associated with anti-PD1 are summarized in **Table A**.

In conclusion, immunotherapy is increasingly becoming the standard treatment for many malignancies. ICIs are actually reshaping the prognosis of many cancers. These new treatments are bringing new hope to patients, but also a whole new spectrum of toxicities for clinicians to manage. Immune-induced LP represents one of the most frequent dirAEs. Several variants have been reported in the literature such as hypertrophic LP, bullous LP, and LP pilaris. However, immune-related classic cutaneous LP is the most frequently described. Treatment is based on topical steroids. Systemic steroids are often proposed in severe reactions. Withdrawal of ICIs may be indicated in refractory cases, in the framework of a multidisciplinary consultation meeting.

Table A: Reported cases of LP associated with anti-PD1

	Age (Years)	Sexe	History of LP before ICIs	Variant of LP	Treatment	Primary disease	Delay from start of treatment to onset of symptoms	Management
Wakade et al., 2016 [17]	71	Female	Unspecified	Bullous LP	Pembrolizumab	non-small-cell lung cancer	1 month	Topical steroids Acitretin 0.2 mg/kg/d
	49	Female	Unspecified	Bullous LP	Pembrolizumab	Metastatic melanoma	3 weeks	Withdrawal of ICIs Bolus IV methylprednisone followed by systemic steroids Acitretin 0.2 mg/kg/d
	86	Male	Unspecified	Bullous LP	Pembrolizumab	non-small-cell lung cancer	15 weeks	Topical steroids ICIs discontinued (Stable malignancy/Respiratory failure)
Komori et al., 2016 [18]	67	Female	Unspecified	Classic cutaneous LP	Nivolumab + Radiotherapy	Breast cancer with hepatic metastasis	Unspecified	Withdrawal of nivolumab Topical steroids
Hofmann et al., 2016 [16]	87	Male	Unspecified	Classic mucosal LP	Pembrolizumab	Metastatic melanoma	48 weeks	Topical steroids Systemic steroids ICIs temporarily suspended
	69	Male	Unspecified	Classic cutaneo-mucosal LP	Pembrolizumab	Metastatic melanoma	49 weeks	Topical steroid Systemic steroids Withdrawal of ICIs
	79	Male	Unspecified	Classic cutaneo-mucosal LP	Pembrolizumab	Metastatic melanoma	49 weeks	Withdrawal of ICIs Topical steroids Systemic steroids
	65	Female	Unspecified	Classic cutaneo-mucosal LP	Pembrolizumab	Metastatic melanoma	43 weeks	Topical steroids Topical pimecrolimus Mouthwash steroids
	74	Male	Unspecified	Classic cutaneo-mucosal LP	Pembrolizumab	Metastatic melanoma	49 weeks	Topical steroids Mouthwash steroids
	46	Male	Unspecified	Classic cutaneous LP	Pembrolizumab	Metastatic melanoma	24 weeks	Topical steroid Levocetirizine 5 mg/d
	80	Male	Unspecified	Classic cutaneous LP	Pembrolizumab	Metastatic melanoma	21 weeks	Topical steroids Levocetirizine 5 mg/d

Komori et al., 2017 [19]	67	Female	Unspecified	Erosive LP	Nivolumab + Radiotherapy	Breast cancer with hepatic and lymph node metastasis	5 months	Topical steroids Systemic steroids
Massey et al., 2017 [20]	70	Female	Unspecified	Hypertrophic LP	Pembrolizumab	Squamous-cell lung cancer	3 months	Topical steroids
Zhao et al., 2018 [15]	67	Man	No	Bullous LP	Pembrolizumab	Metastatic melanoma	12 months	Topical steroids Systemic steroids ICIs temporarily suspended
Biolo et al., 2018 [21]	77	Man	Unspecified	Linear bullous LP	Nivolumab	Metastatic renal carcinoma	8 months	Topical steroids Systemic steroids
Maarouf et al., 2018 [22]	51	Man	Yes	Hypertrophic LP	Nivolumab	Non-small-cell lung cancer, stage IV	2 weeks	Topical steroids
Fontecilla et al., 2018 [23]	79	Man	Yes	Hypertrophic LP	Pembrolizumab	Non-small-cell lung cancer, stage IV	6 weeks	Systemic steroids
Denny et al., 2018 [24]	46	Man	No	Classic cutaneous LP	Pembrolizumab	Metastatic melanoma	6 months	Topical steroids Systemic steroids
Coscarat et al., 2020 [13]	78	Female	No	Hypertrophic LP	Pembrolizumab	lung adenocarcinoma	6 months	Topical steroids Systemic steroids Hydroxychloroquine
Economopoulou et al., 2020 [9]	66	Male	Yes	Classic cutaneo-mucosal LP	Nivolumab	metastatic oral cavity cancer	8 months	Topical steroids
De Lorenzi et al., 2020 [8]	68	Male	No	Bullous LP	Nivolumab	Metastatic clear cell renal cell carcinoma	3 months	Systemic steroids Withdrawal of ICIs
Yilmaz et al., 2020 [10]	27	Female	No	Classic cutaneous LP	Nivolumab	Metastatic renal clear cell carcinoma	5 months	Topical steroids
Ferguson et al., 2020 [11]	73	Female	Unspecified	Classic cutaneo-mucosal LP	Nivolumab	Metastatic renal clear cell carcinoma	18 months	Topical steroids Betamethasone mouthwashes Systemic steroids Withdrawal of ICIs
Uthayakumar et al., 2021 [14]	62	Female	Unspecified	LP pilaris + Classic cutaneous LP	Pembrolizumab	Metastatic melanoma	9 months	Topical steroids Topical tacrolimus Doxycycline 100 mg: Initially slowed the progression Hydroxychloroquine Systemic steroids
Hanamie et al., 2022 [12]	74	Female	Unspecified	Classic cutaneous LP	Nivolumab	Non small cell lung cancer	6 weeks	Topical steroids
	81	Male	Unspecified	Bullous LP	Pembrolizumab	Non small cell lung cancer	6 months	Topical steroids Oral antihistamine
Our case	60	Male	No	Classic cutaneous LP	Pembrolizumab	Pulmonary giant cell carcinoma	7 months	Topical steroids Withdrawal of ICIs

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References

1. Martins F, Sykiotis GP, Maillard M, Fraga M, Ribi C, et al. (2019) New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. Lancet Oncol. 20(1): e54-64.
2. Boussiotis VA. (2016) Molecular and Biochemical Aspects of the PD-1 Checkpoint Pathway. N Engl J Med. 375(18): 1767-1778.
3. Apalla Z, Nikolaou V, Fattore D, Fabbrocini G, Freites-Martinez A, et al. (2022) European recommendations for management of immune checkpoint inhibitors-derived dermatologic adverse events. The EADV task force « Dermatology for cancer patients » position statement. J Eur Acad Dermatol Venereol JEADV. 36(3): 332-350.
4. Weston G, Payette M. (2015) Update on lichen planus and its clinical variants. Int J Womens Dermatol. 1(3): 140-149.
5. Le TK, Kaul S, Cappelli LC, Naidoo J, Semenov YR, et al. (2022) Cutaneous adverse events of immune checkpoint inhibitor therapy: incidence and types of reactive dermatoses. J Dermatol Treat. 33(3): 1691-1695.
6. Schaberg KB, Novoa RA, Wakelee HA, Kim J, Cheung C, et al. (2016) Immunohistochemical analysis of lichenoid reactions in patients treated with anti-PD-L1 and anti-PD-1 therapy. J Cutan Pathol. 43(4): 339-346.
7. Madan V, Marchitto MC, Sunshine JC. (2023) Pembrolizumab-Induced Lichen Planus Pemphigoides in a Patient with Metastatic Adrenocortical Cancer: A Case Report and Literature Review. Dermatopathology. 10(3): 244-258.
8. de Lorenzi C, André R, Vuilleumier A, Kaya G, Abosaleh M. (2020) Bullous lichen planus and anti-programmed cell death-1 therapy: Case report and literature review. Ann Dermatol Vénéréologie. 147(3): 221-227.
9. Economopoulou P, Nicolatou-Galitis O, Kotsantis I, Psyrri A. (2020) Nivolumab-related lichen planus of the lip in a patient with head and neck cancer. Oral Oncol. 104: 104623.
10. Yilmaz M, Mese SG, Celik U. (2020) Nivolumab-induced lichen planus. J Oncol Pharm Pract Off Publ Int Soc Oncol Pharm Pract. 26(3): 758-760.
11. Ferguson L, Ho B, Weir J, Francis N, West K, et al. (2020) Extensive mucocutaneous, oesophageal and otic lichen planus secondary to nivolumab therapy. Skin Health Dis. 1(1): e8.
12. Y Hanami, TYamamoto. (2024) Bullous and Non-Bullous Lichen Planus During Anti PD-1 Therapy for Lung Cancer. 113(10): 1014-1016.
13. Uthayakumar AK, Rudd E, Noy M, Weir J, Larkin J, et al. (2021) Severe progressive scarring pembrolizumab-induced lichen planopilaris in a patient with metastatic melanoma. Australas J Dermatol. 62(3): 403-406.
14. Coscarart A, Martel J, Lee MP, Wang AR. (2020) Pembrolizumab-induced pseudoepitheliomatous eruption consistent with hypertrophic lichen planus. J Cutan Pathol. 47(3): 275-279.
15. Zhao CY, Hwang SJE, Consuegra G, Chou S, Fernandez-Peñas P. (2018) Anti-programmed cell death-1 therapy-associated bullous disorders: a systematic review of the literature. Melanoma Res. 28(6): 491-501.
16. Hofmann L, Forschner A, Loquai C, Goldinger SM, Zimmer L, et al. (2016) Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer Oxf Engl 1990. 60: 190-209.
17. Wakade DV, Carlos G, Hwang SJE, Chou S, Hui R, et al. (2016) PD-1 inhibitors induced bullous lichen planus-like reactions: a rare presentation and report of three cases. Melanoma Res. 26(4): 421-424.
18. Komori T, Honda T, Irie H, Otsuka A, Kabashima K. (2017) Lichen Planus in Irradiated Skin During Nivolumab Treatment. Acta Derm Venereol. 97(3): 391-392.

19. Komori T, Honda T, Irie H, Otsuka A, Kabashima K. (2017) Multiple erosive lichen planus preceded by solitary lichen planus after combination therapy with nivolumab and radiation. J Eur Acad Dermatol Venereol JEADV. 31(8): e382-384.
20. Massey PR, Jones KM, Fox MC. (2017) New Yellow Plaques in a Patient Taking Pembrolizumab. JAMA Oncol. 3(1): 119-120.
21. Biolo G, Caroppo F, Salmaso R, Alaibac M. (2019) Linear bullous lichen planus associated with nivolumab. Clin Exp Dermatol. 44(1): 67-68.
22. Maarouf M, Alexander C, Shi VY. (2018) Nivolumab reactivation of hypertrophic lichen planus, a case report and review of published literature. Dermatol Online J. 24(1): 13030
23. Fontecilla NM, Kittler NW, Lopez A, Yang C, Geskin L. (2018) Programmed cell death protein-1 inhibitor-induced granuloma annulare and hypertrophic lichen planus masquerading as squamous cell carcinoma. JAAD Case Rep. 4(7): 636-639.
24. Denny J, Chong H, Akhras V. (2018) Lichen planus in a patient treated with pembrolizumab for metastatic malignant melanoma. Clin Exp Dermatol. 43(3): 354-356.