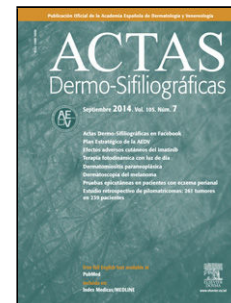


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Erupción cutánea lineal en un paciente con carcinoma escamoso de pulmón

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Casos para el diagnóstico

Erupción cutánea lineal en un paciente con carcinoma escamoso de pulmón

[[Translated article]]Linear cutaneous eruption in a patient with lung squamous cell carcinoma

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Clinical History

A 56-year-old man, with a past medical history of stage IIIA squamous cell carcinoma of the lung who had received 4 cycles of neoadjuvant chemotherapy (CT) with cisplatin-vinorelbine and radiotherapy. Ultimately, the tumor was deemed unresectable, and treatment with carboplatin, paclitaxel, and pembrolizumab every 3 weeks was initiated. Four weeks after initiation and after the 2nd cycle, he developed an asymptomatic rash on his left flank, leading to referral to our clinic with a clinical suspicion of herpes zoster.

Physical Examination

The physical examination revealed the presence multiple erythematous, shiny, flat papules on the left hemithorax, coalescing in a serpiginous pattern along Blaschko's lines. With dermoscopy, the lesions showed multiple red and gray dots (Fig. 1).

Histopathology

Histopathological examination showed a moderate inflammatory infiltrate with deep periannexial extension (Fig. 2A) and, at higher magnification, an epidermis with vacuolar degeneration of the basal layer and apoptotic keratinocytes. The inflammatory infiltrate was primarily lymphoplasmacytic, with perivascular and interstitial distribution, and with the presence of extravasated blood and melanophages (Figs. 2B and C).

What is the diagnosis?

Diagnosis

Lichenoid cutaneous eruption following the Blaschko's lines due to pembrolizumab.

Course of the Disease and Treatment

Treatment with topical betamethasone was initiated, and the patient completed a total of 4 cycles of CT-immunotherapy (IT), followed by maintenance treatment with pembrolizumab 200 mg every 3 weeks. The lesions resolved, leaving residual post-inflammatory hyperpigmentation, and have not recurred after seven additional cycles.

Comment

Lichenoid mucocutaneous eruptions are an immune-mediated cutaneous adverse effect primarily related to anti-PD1/PDL1 agents.¹ These eruptions show significant clinical variability, and a wide range of anatomical distributions has been reported, including localized, generalized, palmoplantar, mucosal, follicular, or ungual variants.¹ The onset of this cutaneous toxicity is usually late, weeks or months after treatment initiation.² However, this latency can be highly variable, ranging from a few days to more than a year.¹ In most cases, these are mild-to-moderate reactions and can be easily managed without discontinuing IT.²

Currently, only 3 cases of IT-related blaschkoid lichenoid cutaneous reactions have been reported (Table 1)³⁻⁵. However, other drugs such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or anti-TNF- α agents have been involved in the development of lichenoid eruptions with this distribution.⁶ Blaschko's lines reflect the migration of neural crest cells during embryogenesis. Dermatoses that follow Blaschko's lines would, therefore, be the cutaneous expression of genetic mosaicism caused by a postzygotic mutation, leading to the appearance of genetically distinct cell populations in the same individual. The resulting clonal cells may have a different histocompatibility antigen profile and, consequently, be more susceptible to T-cell-induced cytotoxicity after appropriate endogenous or environmental stimuli.⁶ It could be hypothesized that anti-PD1 induced T-cell activation may have been the trigger that, in our patient, unmasked a latent subpopulation of abnormal keratinocytes.⁵

The differential diagnosis should include herpes zoster, as it can temporarily limit the continuity of treatment. In our case, the absence of pain, along with the non-metameric distribution and a more prolonged course of the disease, allowed us to rule it out. Furthermore, an acquired unilateral rash in the context of advanced cancer requires ruling out zosteriform metastasis. This possibility was excluded based on the distribution and histopathological analysis. Finally, it should be noted that there is a broad spectrum of acquired blaschkoid dermatoses, including adult inflammatory linear verrucous epidermal nevus, linear psoriasis, blaschkitis, or lichen striatus, among others. Specifically, there is clinical and histopathological overlap between the spectrum of lichen striatus/blaschkitis and linear lichen planus or drug-induced lichenoid eruptions.⁷ In this regard, spongiotic changes would favor the diagnosis of blaschkitis or lichen striatus. Nevertheless, the definitive diagnosis must be established based on a comprehensive clinicopathological correlation, taking into account age, distribution, clinical and histological findings, as well as drug history.

Conflicts of interest

None declared.

References

<BIBL>

<BIB>

1

S Shi F V.J.

S Rodic F N.

S Gettinger F S.

S Leventhal F J.S.

S Neckman F J.P.

S Girardi F M.<ET-AL>

AT Clinical and Histologic Features of Lichenoid Mucocutaneous Eruptions Due to Anti-Programmed Cell Death 1 and Anti-Programmed Cell Death Ligand 1 Immunotherapy

JT JAMA Dermatol

V 152

D 2016

P 1128-L 1136

DOI 10.1001/jamadermatol.2016.2226

<original_ref>[1] 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;152<I>(10)</I>:1128-1136. <DOI>10.1001/jamadermatol.2016.2226</DOI>.</original_ref>

</BIB>

<BIB>

2

S Apalla F Z.

S Papageorgiou F C.

S Lallas F A.

S Delli F F.

S Fotiadou F C.

S Kemanetzi F C.<ET-AL>

AT Cutaneous Adverse Events of Immune Checkpoint Inhibitors: A Literature Review

JT Dermatol Pract Concept

V 11

D 2021

DOI 10.5826/dpc.1101a155

C e2021155

<original_ref>[2] Apalla Z, Papageorgiou C, Lallas A, et al. Cutaneous Adverse Events of Immune Checkpoint Inhibitors: A Literature Review. Dermatol Pract Concept 2021;11(1): e2021155. <DOI>10.5826/dpc.1101a155</DOI>.</original_ref>

</BIB>

<BIB>

3

S Biolo F G.

S Caroppo F F.

S Salmaso F R.

S Alaibac F M.

AT Linear bullous lichen planus associated with nivolumab

JT Clin Exp Dermatol

V 44

D 2019

P 67-L 68

DOI 10.1111/ced.13700

<original_ref>[3] Biolo G, Caroppo F, Salmaso R, Alaibac M. Linear bullous lichen planus associated with nivolumab. Clin Exp Dermatol 2019;44<I>(1)</I>:67-68.

<DOI>10.1111/ced.13700</DOI>.</original_ref>

</BIB>

<BIB>

4

S Ogawa F T.

S Aitake F U.

S Matsuyama F M.

S Hizawa F N.

S Nomura F T.

AT T. Linear lichen planus in the lines of Blaschko suggestive of immune-related adverse event

JT J Cutan Immunol Allergy

V 5

D 2022

P 109-L 111

DOI 10.1002/cia2.12222

<original_ref>[4] Ogawa, T, Aitake, U, Matsuyama, et al., T. Linear lichen planus in the lines of Blaschko suggestive of immune-related adverse event. J Cutan Immunol Allergy 2022;5: 109–111. <DOI>10.1002/cia2.12222</DOI>.</original_ref>

</BIB>

<BIB>

5

S Gambichler F T.

S Kautz F O.

S Schacht F R.

S Boms F S.

AT Unilateral Blaschkoid-linear verrucous lichen planus under immunotherapy with pembrolizumab

JT J Eur Acad Dermatol Venereol

V 37

D 2023

P e624-L e625

DOI 10.1111/jdv.18759

<original_ref>[5] Gambichler T, Kautz O, Schacht R, Boms S. Unilateral Blaschkoid-linear verrucous lichen planus under immunotherapy with pembrolizumab. J Eur Acad Dermatol Venereol 2023;37<I>(5)</I>: e624-e625. <DOI>10.1111/jdv.18759</DOI>.</original_ref>

</BIB>

<BIB>

6

S Bonito F F.

S Alves F J.

S António F A.M.

S Sequeira F P.

S Nogueira F J.

AT A case of blaschkoid lichenoid drug eruption

JT J Cutan Pathol

V 49

D 2022

P 1-L 6

DOI 10.1111/cup.13835

<original_ref>[6] Bonito F, Alves J, António AM, et al. A case of blaschkoid lichenoid drug eruption. J Cutan Pathol 2022;49<I>(1)</I>:1-6.

<DOI>10.1111/cup.13835</DOI>.</original_ref>

</BIB>

<BIB>

7

S Müller F C.S.

S Schmaltz F R.

S Vogt F T.

S Pföhler F C.

AT Lichen striatus and blaschkitis: Reappraisal of the concept of blaschkolinear dermatoses

JT Br J Dermatol

V 164

D 2011

P 257-L 262

DOI 10.1111/j.1365-2133.2010.10053.x

<original_ref>[7] Müller CS, Schmaltz R, Vogt T, Pföhler C. Lichen striatus and blaschkitis: reappraisal of the concept of blaschkolinear dermatoses. Br J Dermatol

2011;164<I>(2)</I>:257-262. <DOI>10.1111/j.1365-2133.2010.10053.x</DOI>.</original_ref>

Figure 1. Clinical and dermoscopic findings. (A-D) Multiple flat, shiny, and erythematous papules along Blaschko's lines. Dermoscopic examination revealed red and gray dots on a brownish background.



Figure 2. (A) Punch biopsy including epidermis, dermis, and subcutaneous tissue. The superficial dermis shows a moderate inflammatory infiltrate with deep periannexial extension (hematoxylin-eosin [HE], $\times 20$). (B-C) Slightly hyperplastic epidermis, vacuolar degeneration of the basal layer, and occasional apoptotic keratinocytes. The inflammatory infiltrate is mainly lymphoplasmacytic, with an interstitial and perivascular distribution and lymphocytic exocytosis into the epidermal basal layer. Additionally, slight edema of the superficial dermis, extravasated blood, and melanophages are observed (hematoxylin-eosin [HE], $\times 80$ [b] and $\times 200$ [c]).

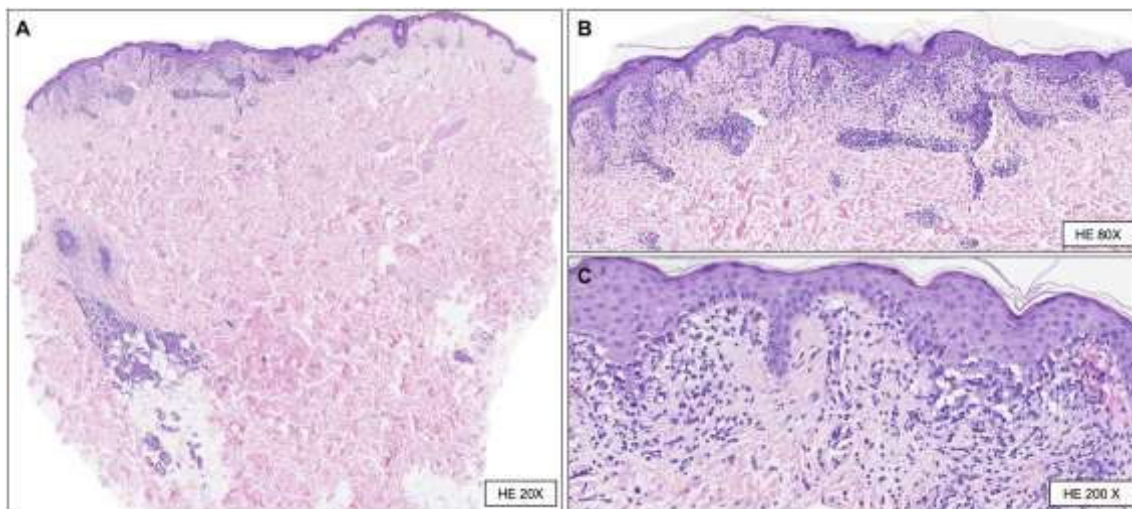


Table 1. Published Cases of Lichenoid Cutaneous Eruptions Following Immunotherapy-related Blaschko's Lines

Case	Age/Sex	Underlying Neoplasm	IT	Latency	Histopathology	Treatment	IT Interruption	Outcome
Biolo et al. ³	77/M	Renal cell carcinoma	NIV	8 months	Hyperkeratosis, hypergranulosis, Civatte bodies, subepidermal clefting, vacuolization of basal layer, band-like inflammatory infiltrate	Clobetasol, prednisone	NS	Complete remission
Ogawa et al. ⁴	79/F	Lung adenocarcinoma	PEM	10 months (6 months after PEM completion)	Hyperkeratosis, hypergranulosis, Civatte bodies, vacuolization of basal layer, lichenoid inflammatory infiltrate	Topical corticosteroids	NA	Improvement
Ganbichler et al. ⁵	39/M	Breast carcinoma	PEM	7 cycles	Compact orthokeratosis, acanthosis, scattered dyskeratosis, vacuolization of basal layer, band-like inflammatory infiltrate	Clobetasol	Yes	Clearance
Álvarez-Salafranca et al. (current case)	56/M	Squamous cell carcinoma of the lung	PEM	4 weeks (2 cycles)	Apoptotic keratinocytes, vacuolization of basal layer, lichenoid inflammatory infiltrate, dermal melanophages	Topical betamethasone	No	Resolution with post-inflammatory hyperpigmentation

IT: immunotherapy; M: male; F: female; NA: not applicable; NS: not specified; NIV: nivolumab; PEM: pembrolizumab.