



## Nivolumab-associated extragenital lichen sclerosus et atrophicus

This is the peer reviewed (post-print) version of the following article:

*Original*

Nivolumab-associated extragenital lichen sclerosus et atrophicus / di Meo, N., Conforti, C., Corneli, P., Vezzoni, R., Retrosi, C., Pizzichetta, M.a., Magaton Rizzi, G., Zalaudek, I.. - In: CLINICAL AND EXPERIMENTAL DERMATOLOGY. - ISSN 0307-6938. - STAMPA. - 45:3(2020), pp. 350-352. [10.1111/ced.14092]

*Availability:*

This version is available at: 11368/2948790 since: 2019-09-10T13:22:37Z

*Publisher:*

*Published*

DOI:10.1111/ced.14092

*Terms of use:*

Some rights reserved. More details in the PostPrint rights section below.

*License:*

Digital Rights Management not defined

*Publisher copyright*

--

(Article begins on next page)

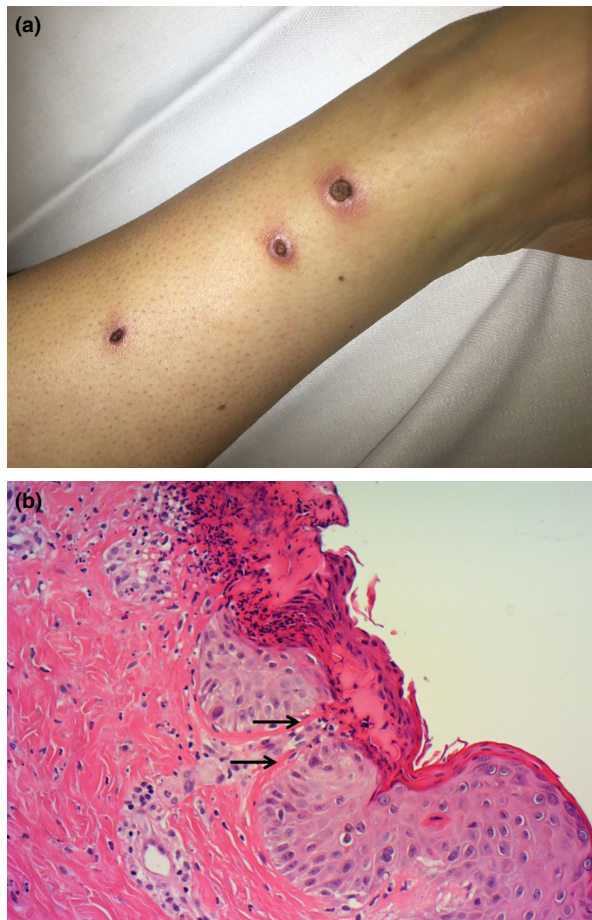


**Figure 1** (a) Erythematous keratotic papules and nodules on the anterior leg. (b) Elimination of collagen fibres vertically through the epidermis (indicated by black arrows) with a central plug of parakeratotic debris and inflammatory cells (haematoxylin and eosin, original magnification  $\times 200$ ).

the setting of interferon-alfa treatment for HCV infection.<sup>5</sup> However, given the well-recognized association between PD and HCV, interferon was unlikely to be the culprit in that case report. Hepatitis screening in our patient was negative.

In our case, observation of the clear chronological correlation between drug administration and skin eruption with complete resolution after treatment discontinuation compounded by the absence of a known cause leads to the high likelihood that interferon was the precipitant of APD. If so, this would not only establish another possible cause of APD but also add to the adverse effect profile of interferon. It has been postulated that endothelial damage, resulting in decreased blood flow and relative hypoxia in the dermis, may in part explain the pathogenesis of PD. Furthermore, >60% of the drugs reported to cause PD have inhibitory effects on vascular endothelial growth factor.<sup>6</sup> As interferon-alfa is thought to have anti-

angiogenic effects, within the dermis, this case might also add to our understanding of the pathogenesis of perforating dermatoses.

**I. Nicholls,<sup>1</sup> C. Wlodek<sup>1</sup> and D. Lamont<sup>1</sup>**

<sup>1</sup>Waikato District Health Board, Hamilton, New Zealand

E-mail: isabellenicholls2017@gmail.com

Conflict of interest: the authors declare that they have no conflicts of interest.

Accepted for publication 3 September 2019

## References

- 1 Pernet C, Pageaux GP, Guillot B *et al.* Telaprevir-induced acquired perforating dermatosis. *JAMA Dermatol* 2014; **150**: 1371–2.
- 2 García-Malinis AJ, Del Valle Sánchez E, Sánchez-Salas MP *et al.* Acquired perforating dermatosis: clinicopathological study of 31 cases, emphasizing pathogenesis and treatment. *J Eur Acad Dermatol Venereol* 2017; **10**: 1757–63.
- 3 Calista D, Morri M. Acquired reactive perforating collagenosis induced by indinavir in 2 patients with HIV disease. *Eur J Dermatol* 2008; **18**: 84–5.
- 4 Sleijfer S, Bannink M, Gool Van *et al.* Side effects of interferon- $\alpha$  therapy. *Pharm World Sci* 2005; **27**: 423.
- 5 Choi YJ, Shin MS, Ahn JY, Park MY. Acquired reactive perforating collagenosis in a chronic HCV hepatitis patient who was treated with interferon alpha. *Korean J Dermatol* 2008; **46**: 788–91.
- 6 Keeley JM, Pavlidakey P, Sami N. Perforating disorder secondary to leflunomide and review of the literature of medications associated with perforating disorder. *Dermatol Online J* 2018; **24**: pii: 13030/qt6167g2vr.

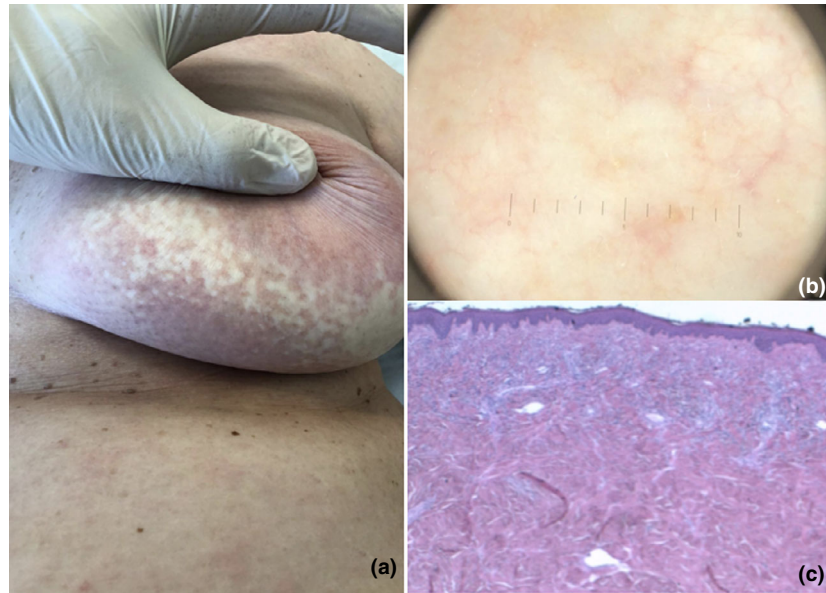
## Nivolumab-associated extragenital lichen sclerosus et atrophicus

Linked article Wernham AGH, Shah F, Velangi S. *Clin Exp Dermatol* 2019; **44**: e22–3

The first case of genital lichen sclerosus (LS) involving the vulval, perineal and perianal areas during treatment with nivolumab was published recently in *Clinical and Experimental Dermatology*.<sup>1</sup>

Nivolumab is a human monoclonal antibody, which was approved by the US Food and Drug Administration (FDA) in December 2014 for the treatment of metastatic melanoma (MM).<sup>2</sup> It works by inhibiting the interaction between programmed death (PD)-1 and PD ligand-1, whose unimpeded interaction downregulates T cells, allowing cancer cells to evade immune surveillance. This drug has subsequently earned a series of FDA approvals for diseases other than MM, including nonsmall cell lung

**Figure 1** (a) Left breast of the patient with lichen sclerosus (LS), showing the erythematous background and white atrophic lenticular areas tending to confluence. (b) Dermoscopic examination revealed an erythematous halo with well-demarcated borders (marker of inflammation activity in LS) (original magnification  $\times 40$ ). (c) Histologically, LS is characterized by dermal sclerosis, epidermal atrophy with loss of rete ridges, lymphocytic infiltrate and deep dermal fibrosis (original magnification  $\times 10$ ).



cancer, head and neck squamous cell cancer, urothelial cancer and classic Hodgkin lymphoma.

The use of PD-1 inhibitors is relatively recent, but adverse effects (AEs) and cutaneous reactions have already been described. The most frequent AEs are hepatitis, colitis, thyroiditis, bullous pemphigoid, lichen planus, psoriasis and morphoea.<sup>3–5</sup> The paper by Wernham *et al.*<sup>1</sup> described an association between nivolumab treatment and genital LS, but there are no cases in the literature on the association between PD-1 inhibitors and extragenital LS.

A 67-year-old woman presented with an itchy rash affecting her breasts. Primary melanoma (stage pT3b) had been surgically removed 1 year earlier from the patient's back and subsequent computed tomography staging had revealed the presence of pulmonary metastases. The melanoma was *BRAF* wildtype-positive and thus therapy with nivolumab 3 mg/kg had been initiated 7 months prior to the rash appearance. The rash affected the skin of the lower quadrants of her breasts and was reported to worsen after every administration of the drug. The patient had no history of skin disease.

Physical examination revealed a bilateral rash characterized by white atrophic scars affecting the lower quadrants of the breasts on an erythematous background (Fig. 1a).

Dermoscopic examination revealed an erythematous halo with well-demarcated borders (Fig. 1b).

The clinical and dermoscopic examinations supported the diagnosis of extragenital LS, which was further confirmed by histology revealing dermal sclerosis, epidermal atrophy with loss of rete ridges, lymphocytic infiltrate and deep dermal fibrosis (Fig. 1c).

Therapy with topical clobetasol propionate 0.05% was initiated. This was applied twice a day for the first week, then once a day for 1 week and then once daily on alternate days. This significantly improved the symptoms of itch and for this reason, a 5-day pulsed therapy with topical steroid after each infusion of nivolumab was recommended to avoid post-therapy discomfort. This approach prevented the progression of the rash during subsequent infusions.

Extragenital LS is an autoimmune disease characterized by autoreactive T cells, confirmed by the presence of increased levels of T helper 1-specific cytokines, dense T-cell infiltrates and enhanced BIC/miR-155 expression.<sup>4</sup> Nivolumab prevents the deactivation of T lymphocytes, thus promoting self-reactive T cells.

To our knowledge, our case is the first report of an association between extragenital LS and nivolumab. We would like to highlight this case so that in patients treated with nivolumab, this potential AE could be quickly recognized and we propose an approach with potent topical corticosteroids to prevent post-therapy discomfort and avoid disease progression.

N.diMeo,<sup>1</sup> C. Conforti,<sup>1</sup> P. Corneli,<sup>1</sup> R. Vezzoni,<sup>1</sup> C. Retrosi,<sup>1</sup> M. A. Pizzichetta,<sup>2</sup> G. M. Rizzi<sup>1</sup> and I. Zalaudek<sup>1</sup>

<sup>1</sup>Department of Dermatology, Maggiore Hospital, University of Trieste, Trieste, Italy and <sup>2</sup>Division of Medical Oncology – Preventive Oncology, Centro di Riferimento Oncologico, National Cancer Institute, Aviano, Italy

E-mail: corneli.paola@gmail.com

Conflict of interest: the authors declare that they have no conflicts of interest.

Accepted for publication 3 September 2019

## References

- 1 Wernham AGH, Shah F, Velangi S. Nivolumab PD-1 inhibitor immunotherapy associated with vulvar, perineal and perianal lichen sclerosis. *Clin Exp Dermatol* 2019; **44**: e22–3.
- 2 Wolchok JD, Chiarion-Sileni V, Gonzalez R *et al*. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2017; **377**: 1345–56.
- 3 Belum VR, Benhuri B, Postow MA. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer* 2016; **60**: 12–25.
- 4 Terlouw A, Santegoets LA, van der Meijden WI *et al*. An autoimmune phenotype in vulvar lichen sclerosis and lichen planus: a Th1 response and high levels of microRNA-155. *J Invest Dermatol* 2012; **132**: 658–66.
- 5 Barquín-García A, Molina-Cerrillo J, Garrido P *et al*. New oncologic emergencies: what is there to know about immunotherapy and its potential side effects? *Eur J Intern Med* 2019; **66**: 1–8.

## An unusual manifestation of X-linked hypohidrotic ectodermal dysplasia with palmoplantar keratoderma

We present a case of genetically confirmed X-linked hypohidrotic ectodermal dysplasia (XHED) with the unusual clinical manifestation of palmoplantar keratoderma.

A 63-year-old man, who had been born to unrelated parents, presented with the classic features of hypohidrotic ectodermal dysplasia (HED): sparse hair, delayed tooth eruption of a few conically shaped teeth, and absence of sweating, leading to heat intolerance, which had a profound impact on his life. He was a retired nurse, originally from Mauritius, and because of the heat intolerance, he had preferentially sought out night shifts while working, and avoided returning to Mauritius during the hotter months.

On physical examination, the patient was found to have frontal bossing, a saddle-nose deformity, periorbital hyperpigmentation and xerosis (Fig. 1a–c). He had symmetrical acral hyperkeratosis, which had been present since birth but had worsened over the past 3 years, becoming uncomfortable. He had plantar keratoderma with fissuring, sub-ungual hyperkeratosis and nail dystrophy (Fig. 1d–g); he used a metal scraper weekly on his feet.

The patient's sister had mild ectodermal dysplasia (ED) features, with only hypotrichosis (Fig. 2) and her son had similar clinical features to our patient, including keratoderma, suggesting X-linked inheritance.

Following informed consent, genetic testing was performed. This confirmed XHED with identification of a previously reported hemizygous pathogenic variant (c.766C>T) in the *EDA* gene,<sup>1</sup> which was a stop-gain



**Figure 1** (a–g) Typical features of hypohidrotic ectodermal dysplasia: (a) loss of eyebrows and eyelashes, and presence of saddle nose, periorbital wrinkling, (b) xerosis and (c) sparse, fine hair, with palmoplantar keratoderma of (d,e) the feet and (f) the hands, and (g) onychodysplasia.

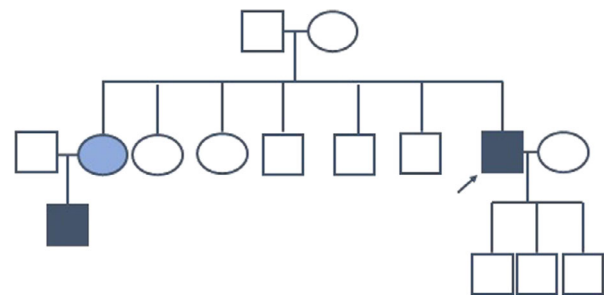


**Figure 2** The patient's family tree showing his affected nephew (including keratoderma) and mildly affected sister (hypotrichosis), suggesting that she is a carrier.

change, p(Gln156Ter), at the protein level, resulting in protein truncation.

The patient was prescribed topical salicylic acid and 10 mg acitretin daily, which is partially controlling his condition.

The EDs are a diverse group of rare conditions defined by congenital alteration in two or more ectodermal