Genital lichen sclerosus after nivolumab

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To the Editor:

We report a patient with metastatic melanoma undergoing treatment with nivolumab who developed genital lichen sclerosus. Nivolumab is a human IgG4 monoclonal antibody that inhibits PD1 (programmed cell death protein 1) activity. Even though nivolumab has a relatively good tolerance profile, it may induce severe immunologic toxicities. Immuno-related adverse events can affect several organs including the endocrine system, digestive system, kidneys, peripheral and central nervous systems, eyes, and skin. Cutaneous toxicities include vitiligo, lichen planus, psoriasis, and bullous pemphigoid. A history of genital symptoms should be considered as part of routine history in patients treated with nivolumab.

Lichen sclerosus (LS) is a chronic, inflammatory disease which mainly affects the ano-genital area. The estimated prevalence of this disease is 1:300-1:1.000. Lichen sclerosus exhibits a bimodal distribution in incidence, with the first peak occurring before puberty in pre-adolescents and the second peak arising in middle to late adulthood, specifically after menopause for women, and between 30-50 years of age in men. The etiopathogenesis of LS is not fully understood. However, it seems that genetic and autoimmune background may have the strongest influence on its development. In 10-21% of cases, LS is associated with other autoimmune diseases including pernicious anemia, alopecia areata, thyroid disease, morphea, and vitiligo [1]. A relationship with infections, hormonal disorders, and chronic irritation of the genitals is also suggested. We report a patient with genital LS that presented after treatment with nivolumab for metastatic melanoma.

A 50-year-old woman was examined for itching and pain of the vulvar region. On physical examination, extensive reddish patches, affecting the genitocrural folds, perianal skin, labia majora, and outer labia minora were seen (**Figure 1**). Cigarette-paper atrophy was also noted. Histological examination of a biopsy taken from the perianal skin confirmed histological features of LS (**Figure 2**). The patient reported that she had started therapy with nivolumab (3mg/kg) for metastatic melanoma 5 months prior to the itching and rash appearance. The patient had no previous history of autoimmune disease or dermatologic conditions. Therapy with topical clobetasol propionate 0.05% (once a day for four weeks and then once daily on alternate days for 8 weeks) was initiated with considerable improvement of itching.

Nivolumab is a human IgG4 monoclonal antibody that inhibits the binding of PDL1 and PDL2 to the PD1 receptor. The binding of these ligands to PD1 receptors on T cells impedes T cell proliferation, activation and cytokine production, thus inhibiting the immune response to tumors. Although nivolumab has a relatively good tolerance profile, it may induce severe immunologic toxicities. The exact underlying mechanism is still not fully understood, but it is postulated to be largely T cell-mediated reactions. Cutaneous toxicities are usually mild, reversible, and conservatively manageable. They occur in 4-27% of patients and include vitiligo, lichen planus, psoriasis, and bullous pemphigoid [2].

Figure 1. *Extensive reddish plaques affecting vulvar, perineal, and perianal skin in a patient with lichen sclerosus.*

The association between nivolumab treatment and LS was reported in only four cases: a 67-year-old woman with extragenital LS after 7 months of treatment with nivolumab for metastatic melanoma of the back, a 74-year-old woman with vulvar, perineal, and perianal LS after 6 months of treatment with nivolumab for a metastatic melanoma of the right upper arm [3], a 48-year-old woman with extragenital LS after four months of treatment with nivolumab for a metastatic uveal melanoma [4], and a 63-year-old man with LS of the glans after four months of treatment with nivolumab for a bladder cancer with multiple bone metastases [5].

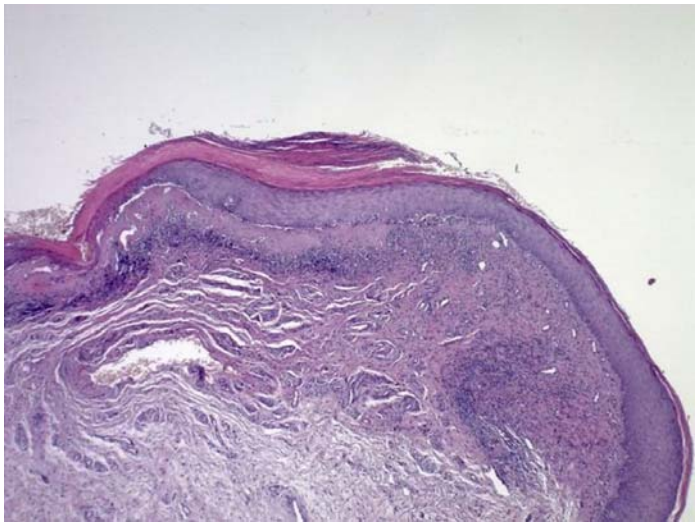

Figure 2. *Skin biopsy: orthokeratotic and parakeratotic hyperkeratosis, thinning of the epidermis, vacuolar alteration of the basal layer and a broad zone of subepidermal homogenization of collagen. The band-like, inflammatory infiltrate is pushed downwards. Also present is a perivascular infiltrate of lymphocytes, predominantly of T cell type in the mid dermis. H&E, 4×.*

Lichen sclerosus is an autoimmune disease characterized by autoreactive T cells, confirmed by the presence of increased levels of T helper 1-specific cytokines and dense T cell infiltrates [3]. In our case, its appearance can be justified, as for other autoimmune diseases, by the fact that nivolumab allows continued activation of T cells.

We report a patient with metastatic melanoma undergoing treatment with nivolumab who developed genital LS. This association has been rarely reported in the literature. A history of genital symptoms should therefore be considered as part of routine history in patients treated with nivolumab.

Potential conflicts of interest

The authors declare no conflicts of interests.

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