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Letter to the Editor

Prurigo nodularis and pembrolizumab: A therapeutic challenge

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To the Editor

Over the recent years, immunotherapy has become one of the most important innovations in cancer treatment, especially for patients with advanced, recurrent and metastatic malignancy. Cancer cells are able to inhibit antitumour lymphocytes by turning immunosuppressive molecules to their advantage and thus avoiding destruction by the immune system. Immune checkpoint inhibitors are monoclonal antibodies directed against inhibitory immune receptors cytotoxic T-lymphocyte antigen 4 (ipilimumab and tremelimumab) or programmed cell death 1 receptor/programmed death ligand-1 (PD1/PD-L1) pathways (nivolumab, pembrolizumab and atezolizumab) reactivating cytotoxic T cells to destroy tumour cells with significant clinical benefit in multiple cancer types. These treatments have also been associated with development of autoimmune manifestations known as immune-related adverse events (irAEs). Such side effects are mediated by the triggering of cytotoxic CD4+/CD8+ T cell activation and by the imbalance of the immune system [1]. Cutaneous toxicities appear to be one of the mostly prevalent irAEs. The most common cutaneous irAEs are general maculopapular rashes, pruritus and lichenoid skin reaction, but several uncommon toxicities have been reported such as the development of bullous pemphigoid, dermatomyositis and others autoimmune diseases [2]. We present the first case of prurigo nodularis (PN) triggered during pembrolizumab therapy and treated with calcipotriene and betamethasone dipropionate foam plus lidocaine-prilocaine cream and narrow-band ultraviolet B.

1. Case report

A 60-year-old woman presented to our outpatient clinic for oncological patients with hyperkeratotic and excoriated firm nodules varying in size from 0.5 to 3 cm, weeping or crusted erosions of few millimetres in diameter, prevailing on the back and limbs (Figs. 1 and 2),

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associated with a maculopapular rash grade II—as per the National Cancer Institute's Common Terminology Criteria for Adverse Events criteria and confined to the trunk. She complained of intense burning and itching with important impairment of quality of life. No underlying skin or autoimmune disorders were revealed from the anamnestic collection. Three months before presentation, the patient started treatment with pembrolizumab (2 mg/kg every 3 weeks) for a metastatic non-small cell lung cancer. Laboratory analysis revealed erythrocyte sedimentation rate 46 mm and C-reactive protein 26,5 mg/L. Other serological tests, such as antinuclear antibodies, hepatitis B and C, HIV, were negative. A skin biopsy specimen taken from a new lesion revealed hyperkeratosis with parakeratosis and orthokeratosis, hypergranulosis and psoriasiform epidermal hyperplasia. The papillary dermis showed thickening of collagen with coarse collagen bundles and vertical streaks. There was a variable inflammatory infiltrate around the superficial vascular plexus with lymphocytes, histiocytes, and eosinophils. A diagnosis of PN was made by highly compatible clinical presentation and supported by histologic features. Pembrolizumab was not discontinued because of the antitumour efficacy found in our patient. Over the next 2 months, the pruritic rash progressively worsened, despite the use of emollients, topical fusidic acid plus betamethasone valerate cream, triamcinolone ointment and ebastine. Because of the patient's important diminished quality of life, we decided to treat her with narrow-band ultraviolet B, two times a week and topical therapy with calcipotriene and betamethasone dipropionate foam and lidocaine-prilocaine cream, with noticeable reduction of pruritus and improvement of the quality of life in the following 4 weeks (Figs. 3 and 4).

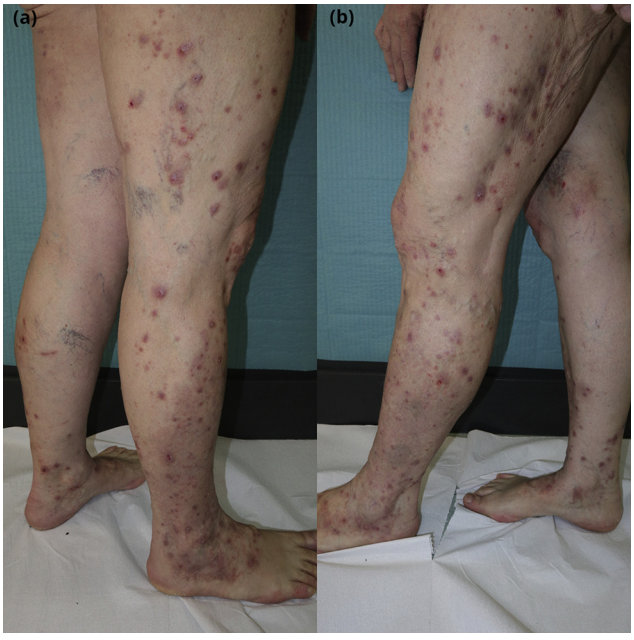

Fig. 1. (A, B) Multiple, intensely pruritic, excoriated nodules erupting on the extensor surfaces of the lower limbs.

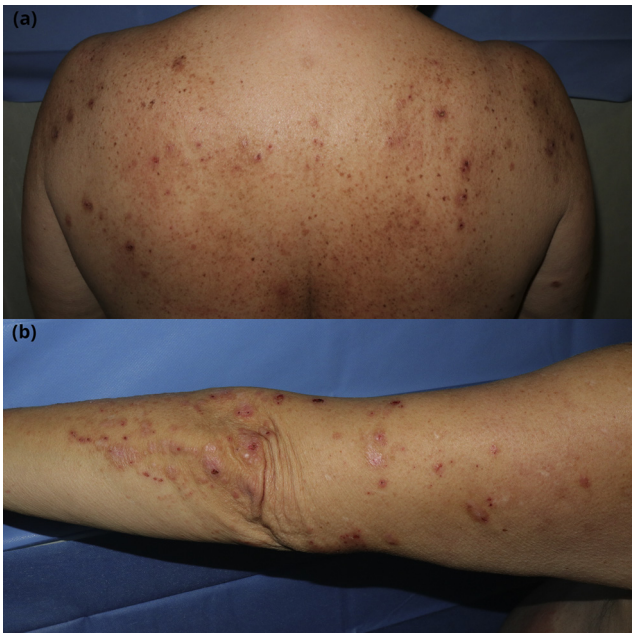

Fig. 2. Excoriated firm nodules and weeping or crusted erosions on the back (A) and extensor surfaces of the left arm (B).

2. Discussion

Antibodies such as pembrolizumab that block programmed death 1 protein are used as immune checkpoint inhibitors that are approved for the treatment of various cancers. Cancer cells can evade T-cell response, expressing the PD-1 ligand, called PD-L1 or PD-L2. Monoclonal antibodies directed against PD1/PD-L1 pathways block the interaction between PD-1 receptor and its ligands to allow antitumour activity of cytotoxic T cells [3]. Although they present a favourable risk/benefit ratio, immune checkpoint blockade therapies cause persistent activation of the immune system and, consequently, irAEs. So far, PN is not commonly described in patients receiving pembrolizumab. PN is a chronic, inflammatory, severely pruritic skin disease with erythematous, slightly keratotic papules and firm nodules usually 0.5–3.0 cm in diameter. The lesions occur mainly on the extremities and upper back secondary to prolonged and severe scratching. In long-standing disease, lesions may develop a verrucous, lichenified or fissured surface. Multiple excoriations, postinflammatory hyperpigmentation and superficial scarring are also often observed. The pathogenesis of PN is not completely understood. The interaction between cutaneous nerve fibres and immune cells plays an important role [4]. Inflammation caused by T lymphocytes, eosinophilic granulocytes and mast cells is involved in the development and chronification of PN and worsened by the persistent activation of the immune system induced by pembrolizumab.

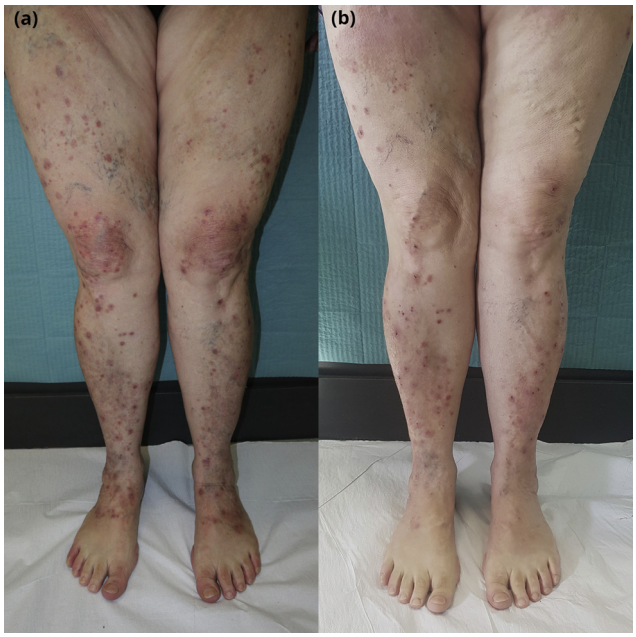

Fig. 3. Widespread firm, hyperkeratotic prurigo nodules and excoriations on the lower extremities present at time 0 (A) decreased in size and number by week 4 (B) of therapy.

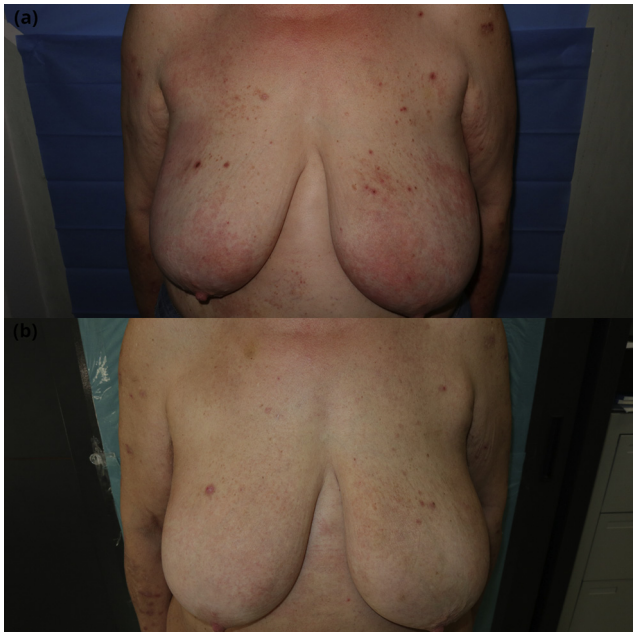

Fig. 4. (A, B) Clinical improvement of the rash and noticeable reduction of nodules the trunk after 4 weeks of therapy.

Currently, there is no approved therapy for PN. Existing used therapies are as follows: topical steroids, calcineurin inhibitors, capsaicin, UV therapy, antihistamines, anticonvulsants, μ-opioid receptor antagonists and immunosuppressants [5].

In milder forms of PN, topical treatment may be sufficient, but generalised therapy-resistant cases require often combined sequential treatments to reduce the number of exacerbations and improve quality of life. Although the pathogenesis of pruritus is still not fully understood, growing evidence suggests that the central nervous system is involved in the genesis and maintenance of itching. Lidocaine and prilocaine, sodium channel blockers, may inhibit abnormal activity in peripheral nerve endings and could be useful in patients who are resistant to conventional antipruritic medications [6].

Ways of minimising the damage from scratching also play an important role in the treatment of secondary reactive conditions. Psychocutaneous interventions aimed at reducing tension and stress can also be useful, especially in cancer patients. Side effects of anticancer therapy come in addition to the stress of the primary pathology, which leads to a significant reduction in quality of life.

Clinicians are progressively treating new types of irAEs with increasingly pleomorphic presentation. To the best of our knowledge, this is the first case report to detectPN during PD-1 blockade therapy. The clinical course of our patient was very challenging, with recurring severe pruritus and strong impairment of quality of life. We support the use of lidocaine–prilocaine cream in PN unresponsive to topical therapy, suggesting a selective inhibition of key components involved in the pathophysiological processes of irAE without compromising cancer immunotherapy efficiency. Therefore, close collaboration between dermatologists and oncologists is essential to allow the patient to continue the antitumour therapy, despite the cutaneous irAE.

Conflict of interest statement

None declared.

Funding sources

None.

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