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Letter to the Editor

Dramatic response of nivolumab-associated psoriasiform dermatitis to etoposide

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Dear Editor

There is a revolution in cancer therapy prompted by the resurgence of immunotherapy in the form of immune checkpoint inhibitors (ICPis) [1]. With the beneficial effects of this new understanding of how to harness the prowess of the immune system with therapeutic intent, it has also become clear that similar to other modalities of cancer therapy, there are important side-effects associated to their use [2]. These side-effects are known as immune-related adverse events (irAEs) and are the result of an immunological imbalance introduced by the disruption of the immune system homoeostasis. The inhibition of immune checkpoint receptor proteins, cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) expressed on the surface of cytotoxic T cells results in an imbalance favouring continuous activation of the cytotoxic T-cells resulting not only in the desired antitumour effect but also leading to the development of autoimmune manifestations. There is similarity of these side-effects to autoimmune disorders known to be associated with polymorphisms of PD-1 and CTLA-4 genes [3]. Although the frequency of side-effects with ICPis is of 90%, only 12%–15% meets the criteria for Grade III–V using the Common Terminology Criteria for Adverse Events of the NCI (National Cancer Institute) with a death rate of 0.3%–1.3% [2,4]. For most parts, short courses of steroids or temporal discontinuation of the ICPis result in control of the side-effects. However, for those patients with Grade III–V side-effects, use of full doses of immunosuppressants, mostly antiinflammatory steroids, alone or in combination with other immunosuppressant agents and permanent discontinuation of

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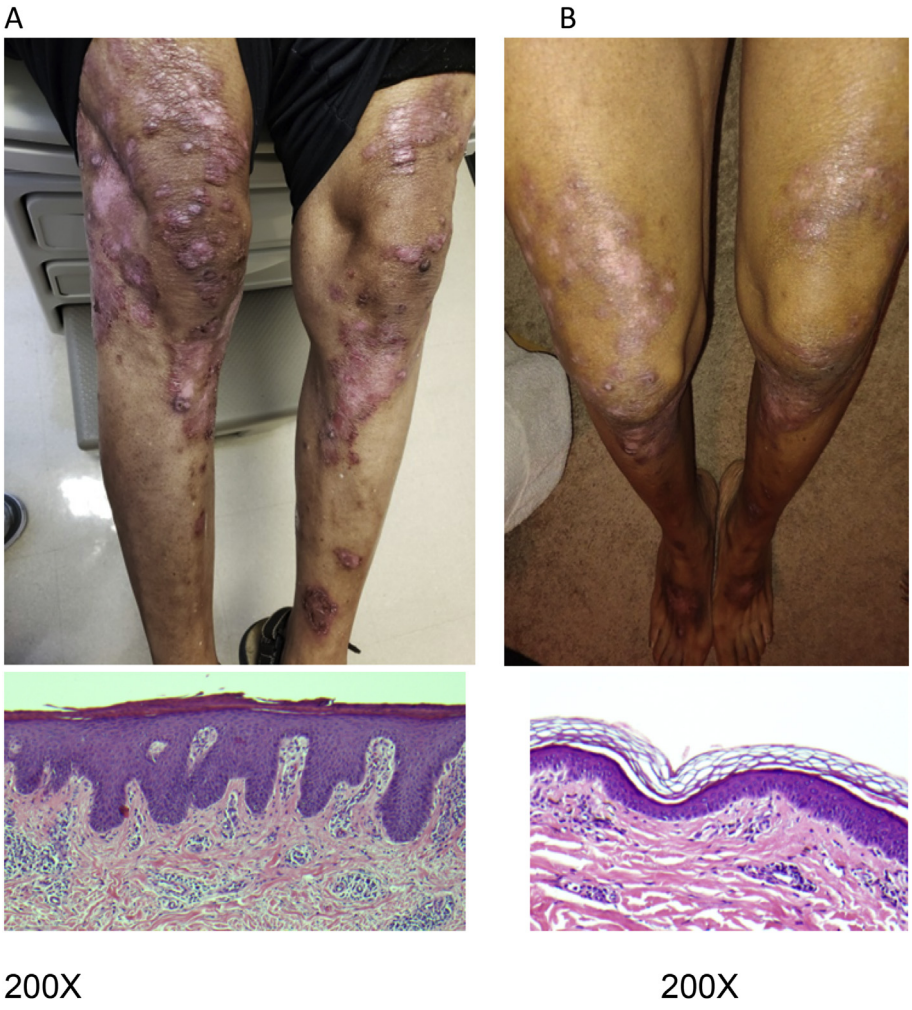

Fig. 1. Panel A shows the psoriasiform dermatitis as seen clinically. Below is the classical histological picture of psoriasiform dermatitis associated to ICPis with irregular acanthosis of the rete ridges, a hypogranular layer and confluent parakeratosis. Neutrophils and dilated blood vessels are seen in the papillary dermis. Panel B shows the clinical resolution of the psoriasiform dermatitis after 7 days of oral etoposide. Below is the image showing superficial perivascular lymphohistiocytic infiltrate with vacuolar changes and prominent melanophages. There was effacement of the rete ridges with basket-weave hyperorthokeratosis indicating histological resolution.

therapy are the only options [2]. As clinical experience rapidly accumulates with the explosive use of these agents, the prompt communication of clinical observations will assist in formulating an integrated approach to the development of systematic guidelines for the management and treatment of irAEs [5]. Here, we report the dramatic response of a Grade IV nivolumab-associated psoriasiform dermatitis to a short course of oral etoposide in a patient treated with this ICPi for a hepatoma. A 62-year-old HIV positive patient on highlyactive antiretroviral therapy and with a stage IVA hepatoma developed severe psoriasiform dermatitis after ten doses of nivolumab. The dermatitis rapidly progressed from isolated hyperkeratotic lesions to large coalescent plaques covering the scalp, arms, legs and trunk anteriorly and posteriorly (80% of the skin surface area). There was no mucosal involvement or evidence of other irAEs. Weight loss increased with the worsening of the dermatitis. Nivolumab was discontinued. A skin biopsy confirmed the diagnosis of nivolumab-associated psoriasiform dermatitis, and therapy with immunosuppressive doses of glucocorticoids was initiated. There was continued progression of the skin lesions and significant debilitation of his general condition. We elected to treat him with etoposide, known to effectively inhibit activated T-cells [6]. After only seven days of 50 mg of oral etoposide twice a day, there was a dramatic response with universal flattening of the thick psoriatic plaques and complete histological resolution of the dermatitis (Fig. 1). There were no side-effects associated with the administration of the etoposide. He took additional seven days of etoposide and then stopped it with no recurrence of the skin lesions. He has gained weight and was able to start a new treatment for his hepatoma.

To our knowledge, this is the first report of the successful use of oral etoposide in the management and

treatment of a serious irAE associated to the use of an ICPi. It is known that in human cases of primary hemophagocytic lymphohistiocytosis (HLH) and in its experimental models, the absolute deficiency of perforin production by T-cells can result in pathological immune activation caused by a prolonged antigen presentation by dendritic cells [7]. Presumably, this activation is due to the absence of a negative feedback loop because of the lack of perforin production, responsible under normal physiological conditions for this immunoregulation [8,9]. Based on the known commonality of activation of T-cells in HLH and by ICPis, we postulated that etoposide, a topoisomerase II inhibitor, active against HLH and one of the most effective and potent inhibitors of activated T-cells [6,10] could be a viable option to control this severe manifestation of an ICPi toxicity with the results seen here. Several important considerations can be inferred from this dramatic clinical response. First, regardless of the type of side-effects caused by ICPis, etoposide can be a universal expedient form of controlling these reactions without the drawback associated with the prolonged use of glucocorticoids or other immune suppressive measures. This is of particular relevance in the case of grade III–V ICPis irAEs such as pneumonitis, colitis or myocarditis [11–13]. Second is the potential for the prospective use of etoposide to modulate the immune response to ICPis, particularly when used in combination (CTLA-4 inhibitors combined with PD-1 or programmed death-ligand 1 (PDL-1) inhibitors) [14]. This observation has prompted us to plan further studies to better understand this dramatic clinical response. Finally, this case illustrates the importance of clinical observations in fostering fundamental basic science research.

Conflict of interest statement

None declared.

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