IMMUNE-RELATED SKIN TOXICITIES TO CHECKPOINT INHIBITORS THERAPY

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Abstract: **Increasing use of new biologic therapies targeting immune checkpoints such as the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and the programmed cell death 1 (PD-1) or its ligand (PD-L1) leads to development of a range of immune-related adverse events (irAEs), and the skin is one of the most commonly involved organ. Severity of cutaneous irAEs varies from mild dermatitis to severe toxic epidermal necrolysis. The most common cutaneous irAEs are nonspecific maculopapular rash and pruritus whereas other skin manifestations are less frequent. Here we report a case of a patient with mRCC undergoing immune checkpoint inhibitors (ICPIs) therapy that developed a psoriasiform skin lesion.**

Keywords: **immune checkpoint inhibitors, PD-1, PD-L1, CTLA-4, pembrolizumab, nivolumab, immune-related adverse events, psoriasiform skin lesions.**

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Introduction. The most common approach in immunotherapy is suppressing some specific immune checkpoints to activate tumor-specific T cells, that is, use of immune checkpoint inhibitors (ICPIs). ICPIs comprise a relatively new class of drugs that have changed the landscape of advanced cancer treatment during the last few years and improved overall survival (OS) of patients suffering from many different cancer subtypes including renal cell carcinoma (RCC), hepatocellular carcinoma (HCC) and urothelial cancer (UC).

At present, there are two types of ICPIs: the anti-CTLA-4 (i.e. ipilimumab) and anti-PD-1 (i.e. pembrolizumab, nivolumab, cemiplimab) or anti-PD-L1 (i.e. atezolizumab, avelumab, durvalumab) agents. The main mechanism of their action is cytotoxic T-cell activation and subsequent elimination of cancer cells. However, alteration of the immune response can lead to irAEs that are new and specific to these therapies [1,2].

Cutaneous irAEs are diverse. According to morphological studies, they include inflammatory eruptions (pruritus, maculopapular, psoriasiform, eczematous rashes, lichenoid reactions and etc.), alteration of melanocytes (vitiligo-like depigmentation and etc.) and keratinocytes (Grover's disease, actinic keratosis and etc.), immunobullous eruptions (bullous pemphigoid). Hair follicles and mucosa also can be involved in the pathological process, what leads to development of alopecia areata, stomatitis, mucositis and etc. Remarkably that some irAEs (e.g. granulomatous, lichenoid reactions) require more time for their development than other such as maculopapular rash. Most skin reactions are not severe, although some of them, i.e. toxic epidermal necrolysis or bullous pemphigoid, is life-threatening conditions [3,4].

Establish the correct diagnosis and treatment plan are crucial to improve patient safety and to avoid unnecessary cessation of anti-cancer therapies [1].

Methods. A 55-year-old man was referred to dermatovenereology department diagnosed with mRCC with lung metastasis. Skin eruptions have been localized on both upper and lower limbs and trunk ongoing 2 weeks. Physical examination showed erythemato-squamous plaques that were located on skin of elbows, feet and back. Full-body inspection revealed no other skin lesions. He had 4 cycles of nivolumab plus ipilimumab therapy (at the dose of 3 and 1 mg/kg respectively every 3 weeks), and then he received only nivolumab (at the dose of 3 mg/kg every 2 weeks). Rashes appeared at 7 weeks after last infusion, developed well-demarcated erythema, isolated sharply bordered, scaly erythematous plaques on the trunk and extremities (Fig. 1 (a,b,c)). Grading according to CTCEA criteria (version 5) is grade 1, but it criteria of grading are challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration [5]. The patient had not a known history of psoriasis. A skin biopsy from the back was performed. It showed bandlike, predominantly lymphocytic infiltrate at the dermoepidermal junction, hyperkeratosis without

parakeratosis, and wedge-shaped hypergranulosis of the epidermis, consistent like picture with lichen planus (Fig.2).

It was recommended to continue therapy by nivolumab, topical steroids with emollients twice a day until the skin process resolves [6]. The follow-up period for the patient was 18 months. The condition of the skin remains stable, which allows the patient to continue immunotherapy without compromising the patient's quality of life.

Results. Pathogenesis of irAEs, in particularly cutaneous irAEs, is not fully understood. CTLA-4 and PD-1 signaling pathways play a key role in inhibition of mainly T-cell response. In some situations, for example, in cancers, these pathways are being up-regulated, so activity of immune system decreases. CTLA-4 and PD-1 blockage with monoclonal antibody leads to increase of immune system activity and changes in immune homeostasis. It induces immune-related damage of as tumor as healthy organs and tissues [5, 6].

Anti-CTLA-4 and anti-PD-1/PD-L1 agents can inhibit regulatory T-cells (T-reg) and activate effector T-cells. It contributes to proinflammatory cytokine releases (TNF, INF-γ, IL-2, IL-6 and etc.) promoting the inflammation development and the increase of immune response. This mechanism is the basis of many cutaneous irAEs development [7, 8].

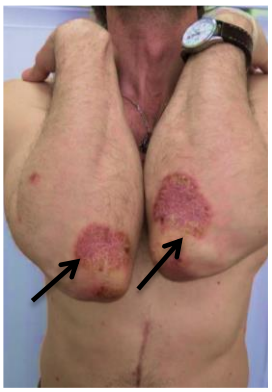

Fig. 1. Arrows indicate the rashes are red, well-demarcated, symmetric, and erythematous plaques with overlying silvery scale.

Moreover, activity of Th17 also increases due to suppressing T-reg. Th17 play dual role in cancers: they can both stimulate and suppress anti-tumor immune response; it depends on the type of tumor, tumor microenvironment and the severity of the disease. Th17 are also involved in irAEs development. These cells and cytokines producing by them (IL-17, IL-21, IL-22) are the key elements of the psoriasis pathogenesis. IL-17, the principal effector cytokine of Th17 cells plays a key role in the pathogenesis of both psoriasis and psoriatic arthritis [8]. Thus, a psoriatic eruption in patients receiving nivolumab treatment may be a consequence of the PD-1 blockade.

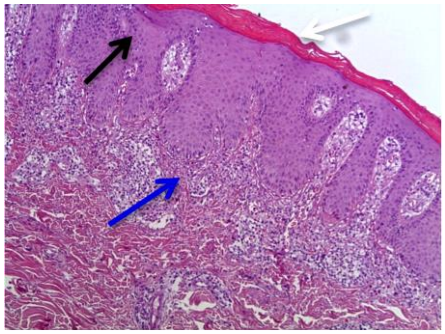

Fig. 2. Hematoxylin-eosin staining of biopsy x200. Histology demonstrates bandlike, predominantly lymphocytic infiltrate at the dermoepidermal junction (blue arrow), hyperkeratosis (white arrow) without parakeratosis, and wedge-shaped hypergranulosis of the epidermis (black arrow).

Discussion. Cutaneous irAEs are reported to appear within 21–42 days after commencement of therapy, may prompt clinicians to reduce drug doses, add systemic steroids to the regiment, and/or discontinue lifesaving immunotherapy. Extreme variability and unpredictability of cutaneous irAEs to confound clinicians. Therefore, it is necessary to develop guidelines for the treatment of cutaneous irAEs, depending on their variety and severity [5, 6, 9]. There is a grading system, which guides management of cutaneous manifestations based on the percent of BSA involvement and additional symptoms, because grading according to CTCEA criteria is challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration [6, 10].

Treatment for irAE is based on the use of corticosteroids and other immunomodulatory agents, which should be used judiciously. Immunotherapy is generally well tolerated. However, there is a possibility of development cutaneous irAEs that are immune-based and mostly reversible. The occurrence of irAEs often correlates with tumor regression, which may represent a positive prognostic factor for progression-free and overall survival**.** IrAEs are likely to increase in frequency and severity with increasing use and development of more effective immunotherapies.

Cutaneous irAEs may prompt clinicians to reduce drug doses or discontinue lifesaving immunotherapy so formulating an accurate diagnosis and treatment plan are crucial to improve patient safety. The main objective is an early recognition of the various cutaneous reactions and histopathology findings associated with them. It is imperative for accurate diagnosis and clear patient treatment.

Moreover, the histopathology may differ from the clinical picture. This will help physicians broaden their horizons and always be aware of the variety of clinical manifestations of skin toxicity such as irAEs [7].

To assess the long-term prospects of immunotherapy without loss of quality of life from skin toxicity, it is important to differentiate psoriasiform reactions from psoriasis. The main diagnosis is the discrepancy between the clinical picture and the histological picture with the development of skin toxicity.

Conclusion. Immune checkpoint inhibitors can lead to a variety of cutaneous toxicities that may influence decisions to continue therapy. The main part of irAEs treatment should consist of immunosuppression with corticosteroids or other immunosuppressant agents.

Overall, cutaneous irAEs are adequately and successfully treated with topical drugs. In our article, we have described clinical case of cutaneous irAEs associated with ICPIs therapy. We avoided discontinue lifesaving immunotherapy due to accurate diagnosis and treatment plan.

Thus, early referral to a dermatologist is warranted. It should be noted, clinicians and researchers will require a greater studying of the intersection between autoimmunity and effects of immunotherapy, both beneficial and harmful. Basic, preclinical, and clinical researches are critical in understanding irAEs development pathway. The insights gained from such studies will allow us to predict possible cutaneous irAEs and apply on time optimal clinical management on time.

An interdisciplinary approach to providing maintenance immunotherapy to cancer patients reduces the number of discontinue and interruptions of immunotherapy due to the development of cutaneous irAEs.

Conflicts of interest. The authors have no conflicts of interest to declare.

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