Oncology

Immune-related lichenoid mucocutaneous erosions during anti-PD-1 immunotherapy in metastatic renal cell carcinoma - A case report

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Introduction

The field of immuno-oncology has dramatically changed the landscape of malignant diseases, becoming a mainstay of cancer therapy in solid tumours. Current guidelines recommend nivolumab, an Ig4 PD-1 antibody, for mRCC patients who received previous treatment with one or two regimens of antiangiogenic therapy. Despite long-lasting and deep response rates in some patients, physicians are confronted with a new spectrum of “immune-mediated” adverse effects, including various autoimmune disorders caused by chronic stimulation of the immune system. The most common cutaneous adverse effects during treatment with anti-PD-1 antibodies are rash (4–27%), pruritus (2–23%) and vitiligo (5–11%). Nevertheless, as yet only few cases of immune-related adverse cutaneous reactions have been described, and data regarding their clinical management is limited.1

This report describes the case of a patient who developed immune-associated lichen ruber during nivolumab therapy and whose oncological disease remained now stable for more than 14 months despite discontinuation of treatment.

Case presentation

A 74-year-old white male with type 2 diabetes and atrial fibrillation was diagnosed with primary mRCC of the left kidney with metastatic spread to multiple pulmonary sites with mediastinal lymphadenopathy. Neither he nor his family had a history of dermatological illness. After cytoreductive laparoscopic nephrectomy in May 2013, histological examination showed a clear cell renal carcinoma with areas of eosinophilic cytoplasm, stage pT3a, Fuhrman grade 3, R0. Systemic therapy with pazopanib (800 mg daily) was started in July 2013. Seven months later, in January 2014, the pulmonary metastases progressed. Treatment was then changed to everolimus (5 mg daily). CT scans over the following 29 months showed durable stable disease. In June 2016, disease progression was confirmed again showing progressive pulmonary metastases. Sorafenib (200 mg daily) was started in the third-line setting, which had to be stopped 2 months later because of treatment-related side effects such as therapy-resistant diarrhoea and fatigue. Nivolumab (3 mg/kg every 2 weeks) was then initiated in October 2016 and partial remission was already achieved after 7 cycles on the first restaging CT scan. After 12 cycles had been given, painful lesions on the torso and oral mucosa appeared, which were histologically confirmed as a lichen ruber. The patient had to be admitted to hospital for seven days for treatment with methylprednisolone (0.5 mg/kg). Because he had begun to take allopurinol (300 mg daily) due to hyperuricemia two weeks before the appearance of the first skin lesions, lichen ruber was assumed to be caused by this medication which was stopped, while nivolumab therapy was still continued. In August 2017, after a total 18 completed cycles, he developed extensive oral and
Discussion

There is growing evidence that immunotherapy can achieve remarkable response rates in mRCC. Nivolumab was approved for second-line treatment of mRCC according to the results of the phase III Checkmate 025 study. The substance facilitates T-cell activation by inhibiting the suppressive effect of PD-1 signalling on T-cells and by this mechanism exerts an antitumor effect. The T-cell activation which this substance induces occasionally causes T-cell-mediated conditions including also lichenoid cutaneous manifestations. Schaberg et al. published a detailed clinical and histological description of lichenoid mucocutaneous lesions associated with immunotherapy in 2016. Although skin involvement varies from mild rash to bullous eruptions, gene expression profiling defined all lesions as toxic epidermal necrolysis-like reactions. This fact suggests that PD-1/PD-L1 interactions are involved in the preservation of epidermal integrity during inflammatory skin reactions. Increased risk of cutaneous toxicity has also been reported to depend on the duration of treatment. Interestingly, the time of onset to cutaneous eruption is variable, ranging from 3 days to 13 months, respectively. In our case, the initial presentation of symptoms related to nivolumab were consistent with previously described features. The first lesions developed after 6 months of nivolumab therapy and it is known that autoimmune-related disease can start with subtle and masked symptoms. There is weak evidence about the management of these dermatological immune-mediated side effects in patients such as ours, which makes the diagnostic algorithm much more difficult resulting in therapeutic challenges in the daily clinical practice.

Conclusion

We present the case of a mRCC patient who developed “immune-mediated” lichen ruber 6 months after starting nivolumab therapy. Due to a variable onset of cutaneous adverse effects, patients have to be closely monitored for specific “immune-related” side-effects during and after immunotherapy. Early recognition and adequate treatment are essential in mitigating the severity of immune-mediated adverse events. The long duration of stable disease despite treatment discontinuation raises further ambiguity and questions if a durable continuation of immunotherapy is really necessary in patients with response to checkpoint inhibitors. Considering this, it is essential to discuss such cases and spread experience regarding early recognition, disease management and further research in the era of immuno-oncology.

Conflicts of interest

None.

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