Nivolumab-associated Stevens-Johnson syndrome in a patient with lung cancer

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Abstract

Nivolumab is a fully human immunoglobulin G4 immune checkpoint inhibitor antibody approved for use in the treatment of several malignancies such as lung cancer. Cutaneous reactions to checkpoint inhibitors are frequent, appearing in approximately 40% of patients. Although most of the reactions are well tolerated, these drugs can lead to severe cutaneous adverse reactions, but a quick recognition of the symptoms can significantly decrease their mortality. In this case report, we describe a patient with metastatic squamous lung cell carcinoma suffering from nivolumab-induced Stevens-Johnson syndrome with severe skin denudation and mucosal involvement.

Keywords: nivolumab, Stevens-Johnson syndrome, erythema multiforme

Introduction

Checkpoint inhibitor immunotherapy has been revolutionary in the treatment of many tumors. Within this group are programmed cell death receptor one inhibitors (PD1 inhibitors) and inhibitors of its ligand (PDL1 inhibitors), [1]. Immunological self-tolerance is disfavored by the inhibition of the PD1 receptor, which results in a higher frequency of immune-related adverse events. This is because PD1 has a role in regulating the immunological tolerance to self-antigens, preventing autoimmune disorders [2,3].

Cutaneous reactions to checkpoint inhibitors are frequent and are seen in approximately 40% of patients; these include: morbilliform, lichenoid, granulomatous, and psoriasiform reactions, as well as, vitiligo-like lesions, eczema, lupus erythematosus, blistering diseases, and non-specific cutaneous reactions [4].

Most reactions are well tolerated and don´t place the patient's life at risk. However, they can lead to life-threatening severe cutaneous adverse reactions (SCARs) such as: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Fortunately, these severe cutaneous reactions are infrequent but a quick recognition of them can significantly decrease their mortality [5].

Case Synopsis

A 78-year-old man with no known allergies, on regular treatment with omeprazole, orfidal, and tiotropium bromide monohydrate inhaler, was receiving nivolumab, 240mg every two weeks for metastatic squamous cell carcinoma of the lung (T4N4M0). He was admitted to the hospital with fever and a week-long cutaneous eruption associated with painful mucosal lesions. Nivolumab treatment was started in November 2019 and after two cycles of treatment in December 2019, the skin examination revealed erosions on the upper and lower lips with hemorrhagic and yellow crust (**Figure 1A)**.

Violaceus macules, papules, and vesicles with positive Nikolsky sign were located over the face and

trunk with predominance on the upper body and less involvement of the extremities. Twelve percent of the total body surface area (BSA) was affected by epidermal loss. Erythematous macules with purpuric center were observed on both palms and soles (**Figure 1B)**. In addition, the ophthalmological examination revealed a corneal epithelial defect and diffuse conjunctival injection.

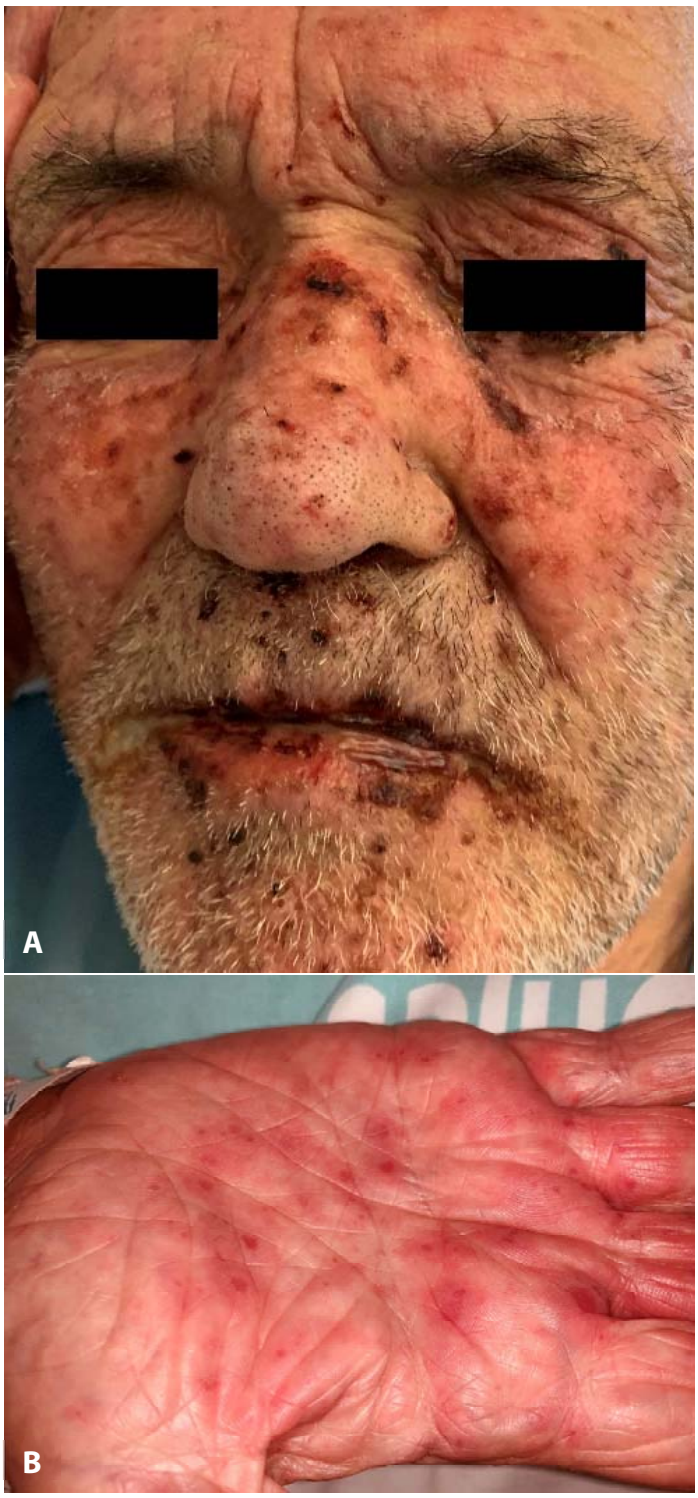

Figure 1. ***A)*** *Maculopapular rash over the face, ulcerations and bloody crusting lesions of vermilion surfaces of lips and ocular inflammation and involvement of eyelid skin.* ***B)*** *Atypical targets on the palm of the patient.*

The histology of skin lesions showed epidermal necrosis with numerous apoptotic keratinocytes and lymphocytic inflammation (**Figure 2**). The correlation of the clinical features and the pathologic changes established the diagnosis of SJS.

The patient was treated with methylprednisolone 50mg IV every 12h for 7 days following by prednisone 0.5mg/kg daily for two weeks (gradually reduced until it was withdrawn), dexamethasone/tobramycin eye drops, and mixed medication mouthwash for his stomatitis containing oral topical lidocaine 2% and nystatin in addition to supportive care. At the 1-month follow-up appointment, his initial eruptions had improved and immunosuppressive treatment was suspended. However, topical treatment with betnovate 0.1% ointment twice daily was prolonged for two more weeks until the lesions completely resolved.

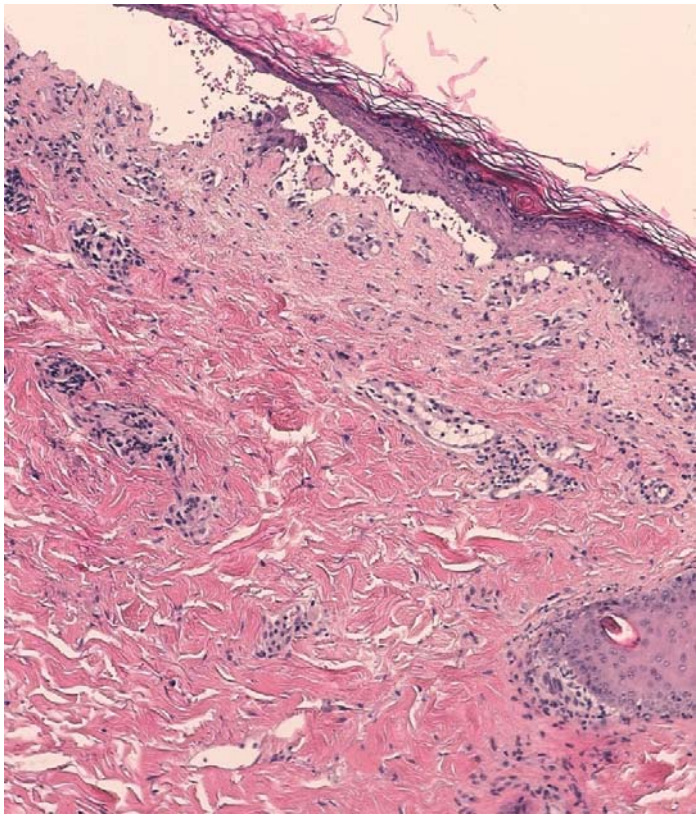

Figure 2. *Multiple apoptotic keratinocytes throughout the epidermis, and a subepidermal split forming a bulla; perivascular lymphocytic infiltrate within the dermis.*

Unfortunately, the patient died 16 weeks after being discharged from the hospital because of the progression of his metastatic disease,

Case Discussion

Monoclonal antibodies that are anti-PD1 include nivolumab, pembrolizumab, and cemiplimab. PD1 and its ligand, PDL1, are targets that tumor cells can hijack in an attempt to escape immune control [6].

The mechanisms by which checkpoints inhibitors produce SSJ and TEN are unclear. Studies suggest that the PD1/PDL1 axis plays a role in maintaining epidermal integrity. In addition there is a loss of T cell homeostasis causing self-directed cytotoxic reactions [2]. Most of the reactions are mild and resolve with topical treatments. However, occasional serious cutaneous adverse reactions occur; SJS/TEN is a grade 4 reaction of CTCAE (Common Terminology Criteria for Adverse Events), which fortunately only occur in less than 1% of patients during anti-PD1 therapy [7].

Recently, Maloney et al. [5] conducted a review of SJS- and TEN-like reactions to checkpoint inhibitors in which they collected 18 cases caused by nivolumab, pembrolizumab, atezolizumab, and ipilimumab, in which they estimated mortality at 60%. Also an extensive review of skin reactions caused by anti PD1 (pembrolizumab and nivolumab) consisted of 10 cases published in the literature and included SSJ, TEN, and erythema multiforme [8]. All these reactions generally occur a few days after starting treatment with a range that reaches up to 16 weeks [8].

Most cases improved with prednisolone or methylprednisolone (1mg/kg) treatment and the immediate interruption of the drug. In the most severe cases it was necessary to add immunoglobulins (IVIg), infliximab, and plasmapheresis.

There is limited literature available on the management of the severe cutaneous adverse reactions related to anti PD1. As an example, in the latest review on its therapeutic management, maculopapular eruptions rarely affect more than 30% BSA and can often be treated with skin-directed therapies, whereas SJS and TEN affecting even 5% BSA should be managed aggressively and the immunotherapy should be discontinued at once [9].

Conclusion

PD1 inhibitors and PDL1 inhibitors make up a group of drugs that has revolutionized the field of oncology. However, early diagnosis and management of associated skin toxicities are essential for optimal patient care to reduce mortality and long-term sequelae [10]. The study of more cases will help to elucidate the immunological pathogenesis and optimal treatment strategies.

Potential conflicts of interest

The authors declare no conflicts of interests.

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