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Case Report Open Access

Delayed Immune-Related Erythrodermia in a Squamous NSCLC Patient Treated with Nivolumab: A Case Report

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Abstract

Immunotherapy has been changing the scenario of the treatment of non-small cell lung cancer (NSCLC) and is leading to a dramatic improvement in the clinical outcome of patients suffering from this disease. Immunotherapy has a specific toxicity profile and many oncologists are facing a new challenge in the form of clinical management of immune-related adverse events (irAEs). Even though most irAEs remain mild in intensity, around 10% of patients treated with anti-PD1/anti-PDL1 drugs will develop severe, sometimes life-threatening, dysimmune toxicities. Skin toxicity is one of the most common irAEs. The irAEs related to skin toxicity can have many different presentations, which includes maculopapular or papulopustular rash, Sweet's syndrome, follicular or urticarial dermatitis. It typically occurs within 6 weeks from the beginning of the treatment but, due to the mechanism of action of immunotherapic drugs, delayed toxicities are reported. We present a case study of delayed grade 4 skin toxicity in a 75-year-old male patient with stage IV squamous NSCLC treated with Nivolumab.

Keywords: Immunotherapy; Drug toxicities; Neoplasms; Non-small cell lung cancer; Dermatitis; Erythrodermia

Introduction

Immunotherapy represents the new era in cancer treatment. Survival rates for metastatic lung cancer including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are very low. 5-year survival rate of NSCLC and SCLC are less than 5% [1]. However, immunotherapy in NSCLC is changing this scenario [2-7]. Immunotherapy has a specific toxicity profile and the clinical management of immune-related adverse events (irAEs) is a new issue to many oncologists. Most of the irAEs remain mild in intensity but around 10% of patients treated with anti-PD1/anti-PDL1 drugs will develop severe, sometimes life-threatening, dysimmune toxicities [8,9].

In a randomized phase III clinical trial CheckMate017, the effect of nivolumab, a fully human IgG4 PD1 immune-checkpoint-inhibitor antibody and docetaxel in previously treated patients with advanced squamous NSCLC was studied. Nivolumab showed significantly better overall survival (OS), response rate (RR) and progression free survival (PFS) with immunotherapy than chemotherapy, regardless of PDL1 expression level. Moreover, adverse events (AEs) of any grade were less frequent in the nivolumab group [5].

Skin toxicity is one of the most common irAEs, and typically occurs after about 6 weeks from the beginning of the treatment. A variety of clinical presentations of skin toxicity can manifest, including: maculopapular or papulopustular rash, Sweet's syndrome, follicular or urticarial dermatitis. In a pooled safety analysis of melanoma patients with dermatological AEs such as rash, pruritus, and vitiligo, toxicities were observed in 34% of patients receiving nivolumab [9], and 39% of patients receiving pembrolizumab [10].

We present a peculiar case of a delayed grade 4 skin toxicity in a 75-year-old male patient with a stage IV squamous NSCLC treated with Nivolumab, occurred after the suspension of the treatment in the form of erythrodermia involving the whole-body surface.

Written informed consent was obtained from the patient for publication of this case report.

Case Presentation

On May 2016 a 75-year-old male patient started a third line systemic therapy with Nivolumab for a Stage IV squamous NSCLC. In the patient's medical history, no autoimmune pathologies were present. We performed all the lab tests aimed to rule out any silent disease that could compromise the treatment with immune-checkpoint inhibitors, such as Hepatitis B and C sierological tests, thyroid hormones dosage, anti-nuclear antibodies (ANAs), anti-thyreoperoxidase antibodies, anti-thyroglobulin antibodies, cortisol hormone, adrenocorticotropic hormone (ACTH).

The baseline whole body CT scan performed on April 18th, 2016 showed a 7 cm lesion at the upper left lobe, multiple bilateral pulmonary centimetric lesions, lymphangitis and mediastinal lymph nodes.

The whole-body CT scan performed on July 05th 2016, after 4 administrations of Nivolumab, showed a partial response according to version 1.1 of RECIST criteria.

The patient received Nivolumab at the standard dosage of 3 mg/kg every 15 days and he didn't report any toxicity during the first five administrations of the drug. On the end of July 2016, the patient experienced a traumatic femoral fracture and discontinued the treatment with Nivolumab. On September 2016 the patient showed a progressive skin erythrodermia involving the whole-body surface (grade 4) (Figure 1).

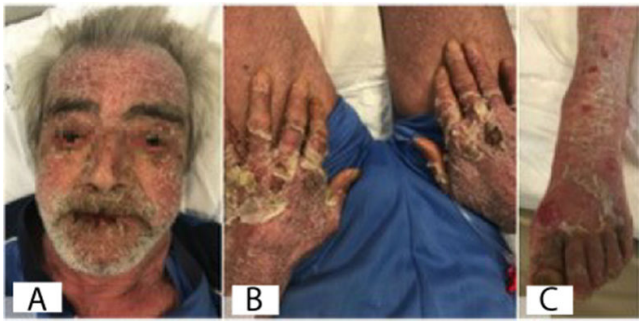

Figure 1: (A-C) Grade 4 immune-related skin toxicity characterized by severe erythrodermia involving the whole-body surface of the patient.

The patient needed to be hospitalized. We performed a skin biopsy and after that, we started a topical therapy with emollient moistures, steroids and antibiotics and high dose intravenous corticosteroid (the equivalent dose of prednisone 2 mg/kg). Nonetheless, the erythrodermia progressively got worse.

The skin biopsy showed orthokeratotic hyperkeratosis, hyperplasia of the epidermis, hypergranulosis, ectasia of the vessels of the papillary dermis, fibrosis of papillary dermis and perivascular infiltration of lymphocytes and macrophages with cytoplasmic hemosiderin.

After 40 days of high dose steroid therapy, as per label of Nivolumab, mild improvement of the skin toxicity was evident (grade 1) and we decided to reduce the dose of Intravenous methylprednisolone to the equivalent of prednisone 1 mg/kg, but the clinical situation got worse again so resuming the initial high dose of steroids was necessary.

Two months after the beginning of high dose steroid therapy, the skin toxicity improved, we decided to reduce the dose of steroid to prednisone 1 mg/kg orally and progressively tape it within 1 month till the complete suspension when the skin toxicity recovered (Figure 2).

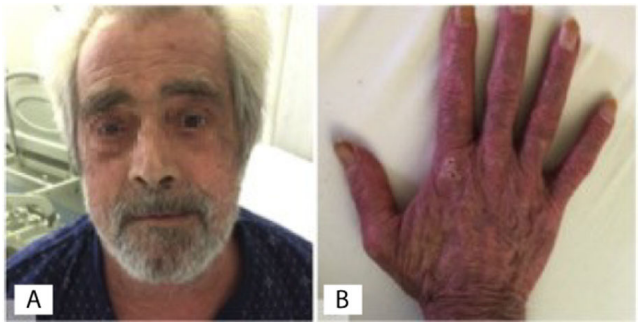

Figure 2: (A-B) Completely recovered skin toxicity after two months of high dose corticosteroid therapy.

The skin toxicity had a new mild exacerbation after 3 weeks of the suspension of the steroid therapy, but a low dose of oral prednisone was sufficient to treat it.

The patient underwent a new whole-body ct scan on December 1st, 2016, confirming the partial response already seen in the last evaluation, even if the patient didn't receive any anticancer therapy since July 19th, 2016.

We didn't resume the treatment with Nivolumab because of the grade 4 skin toxicity experienced by the patient. The patient underwent a clinical and radiological follow-up program. The radiological evaluation performed on February 2017 showed a progressive disease and the patient underwent a 4th line of chemotherapy.

Discussion

Skin rash is one of the most common irAEs associate with immune checkpoint monoclonal antibody(mAb) therapy. It typically occurs within six weeks from the onset of the oncological immunotherapy [11,12]. The clinical presentation can range from maculopapular or papulopustular eritemas, Sweet's syndrome, to follicular or urticarial dermatitis as well. Even if the maculopapular rash is most commonly observed, rarer rashes have been observed, including lichenoid (e.g., lichenoid dermatitis) [13], and bullous disorders including bullous pemphigoid [14], Stevens Johnson syndrome, and toxic epidermal necrolysis [11], which are of special interest due to their severity and potentially life-threatening consequences. It has been believed that in some cases the mechanism for developing the skin toxicity may be because of blockade of a common antigen, co-expressed on a patient's tumor cells, and those of the dermo-epidermal junction and/or other levels of the skin [15].

Our case report underlines that each irAEs, while being characterized by its own timing of onset, may occur anytime and even after the discontinuation of the immunotherapy. This is certainly associated with the mechanism of action of the immunotherapy drug: the activation of the host's immune system against the tumor is maintained for many weeks after the suspension of the treatment. This is the reason why we can observe delayed toxicity but also prolonged clinical and radiological benefit from the treatment.

Moreover, the use of corticosteroids for the management of irAEs doesn't compromise the outcome of the treatment.

The clinical case we observed underlines the importance of each step of the management of immune-related toxicities, the knowledge of the immune-toxicity spectrum, the identification of the risk factor. The correct information of the patients and caregivers are fundamental to promptly identify a potentially serious problem in order to implement the best treatment for each clinical situation [16].

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