



Case Report

Skin and Hypersensitivity reaction induced by Immune-Checkpoint Inhibitors: a case of two anti-PD1-induced toxicities

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Abstract

Immune checkpoint inhibitors are associated with a specific spectrum of toxicities defined as “immune-related adverse events”. Cutaneous toxicities represent the most frequent immune-related adverse events with a broad range of clinical presentations and histological different patterns, including interface dermatitis and lichenoid dermatitis. In literature there is no evidence of acute drug hypersensitivity reactions induced by immune checkpoint inhibitors. We report the case of a metastatic prostate cancer patient who experienced two different cutaneous toxicities induced by an anti-PDL1 agent. Early recognition and appropriate management of skin toxicities are mandatory to avoid unnecessary discontinuation of a potentially life-saving therapy and to prevent a negative impact on patients’ quality of life.

Keywords

Immune checkpoint inhibitors; immunotherapy; immune-related adverse event; dermatologic toxicity; lichenoid dermatitis; interface dermatitis; drug hypersensitivity reaction

Introduction

Immune checkpoint inhibitors (ICIs) have emerged as the major oncologic breakthroughs in the treatment of different types of advanced solid tumors. Given their mechanism of action as activators of the immune system against tumor cells, they are associated with a specific spectrum of toxicities defined as “immune-relat-

ed adverse events" (irAEs). More than 60% of treated patients develop irAEs, including hypophysitis, thyroiditis, dermatitis, pneumonitis, colitis, and more [1]. Cutaneous toxicities represent the most frequent irAEs and show a broad range of clinical presentations [2,3]. Histologically, ICI-induced skin lesions show various patterns, including perivascular and vacuolar interface dermatitis and lichenoid dermatitis [4]. To date, there is no evidence of acute drug hypersensitivity reactions to ICIs.

We present the case of a metastatic prostate cancer patient who experienced two different cutaneous toxicities associated with the administration of an anti-PDL1 agent.

Case presentation

Our patient was a 62-year-old male Caucasian with prostate adenocarcinoma (Gleason score 7 - 3+4) IV stage at diagnosis for multiple nodal and bone metastases. Medical history was positive for autoimmune-related hypothyroidism on thyroid hormone replacement therapy. Starting right after diagnosis, the patient was treated with complete androgen blockade (LHRHa and Bicalutamide) from March 2015 to July 2016. Then, due to rapid biochemical and bone progression, he underwent a first-line chemotherapy with Docetaxel for 8 cycles with initial biochemical and radiological response.

From January 2017, after the completion of chemotherapy, the patient continued LHRHa and PSA assessments every 3 months.

From August to December 2017 the patient was treated with Abiraterone Acetate for a new biochemical and radiological progression of the disease.

In January 2018 further disease progression was observed and the patient was included in a phase III multicenter trial comparing Atezolizumab, an anti-PDL1 antibody, in combination with Enzalutamide versus Enzalutamide alone (NCT03016312). Patients with autoimmune-related hypothyroidism were eligible for the study. The patient was randomized in the Atezolizumab and Enzalutamide arm and started therapy on the 12th of February 2018 (Atezolizumab 1200 mg IV every 3 weeks plus Enzalutamide 160 mg/die).

Eight days after the first cycle of therapy, the patient

experienced deep asthenia, fever, stomatitis, pharyngodynia, vomiting, watery diarrhea and diffuse itchy maculopapular rash with papules and macules that became confluent in a few days. For these symptoms, treatment with Enzalutamide was interrupted.

Four days after the onset of the symptoms, the patient presented to the Emergency room and was admitted to the Infectious Diseases ward. Chest CT scan, blood cultures and pharyngeal swab were performed. The CT scan revealed a small interstitial consolidation in the medium lobe of the right lung. Therefore, antibiotic therapy was started leading to rapid and complete remission of symptoms, except for the rash. In consideration of the persistence of the diffuse rash (Figure 1) after 7 days of antibiotic therapy, an immune-induced rash in a septic patient was suspected and a skin biopsy was performed. The histological examination revealed a lichenoid interface dermatitis. Blood cultures and pharyngeal swab being negative, oral steroid therapy was started (Prednisone 50 mg/die).

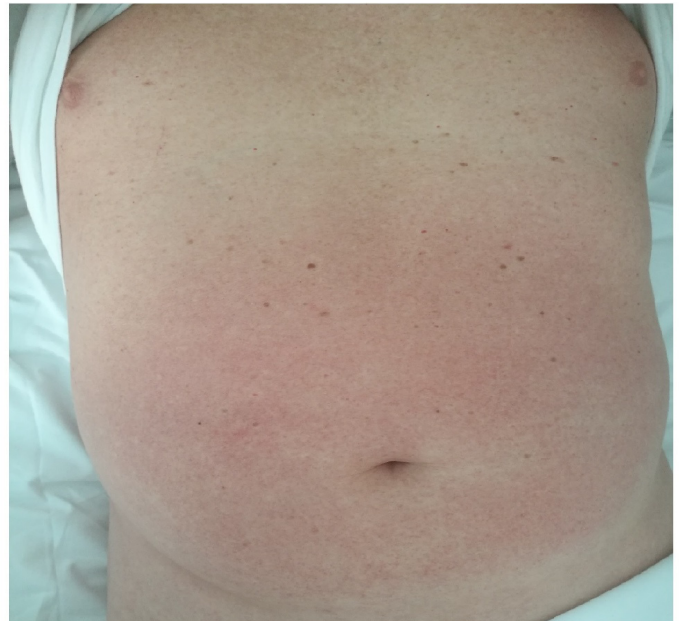


Figure 1: Diffuse itchy maculopapular rash. After one week of steroid therapy, the maculopapular rash was resolved and just a desquamative rash persisted. Therefore, steroid therapy was progressively tapered. The histologic examination revealed a vacuolar degeneration of the basal layer, spongiosis of the suprabasal epidermal layers, Civatte bodies and lymphocyte exocytosis. The papillary dermis presented

capillary endothelial swelling and perivascular lymphocytic inflammatory infiltrate. These histological findings were diagnostic of interface dermatitis with spongiotic and vacu-

olar alterations (Figure 2 A, B, C).

In April 2018, the patient started treatment with Enzalutamide again, without any adverse events. At the

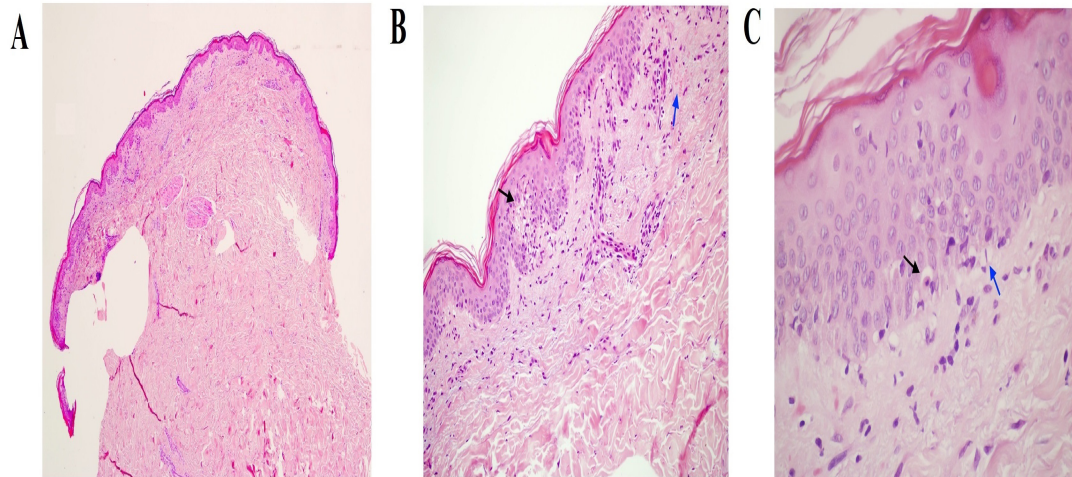


Figure 2: Histological examination of the maculopapular rash. A: 40x EE: Perivascular superficial dermatitis with subtle interface involvement. B: 200x EE: Vacuolar alteration of the epidermal basal layer (black arrow) with

erythrocytes extravasated in the papillary dermis (blue arrow). C: 400x EE: Necrotic keratinocyte in the basal layer (black arrow) and associated vacuolar damage (blue arrow).

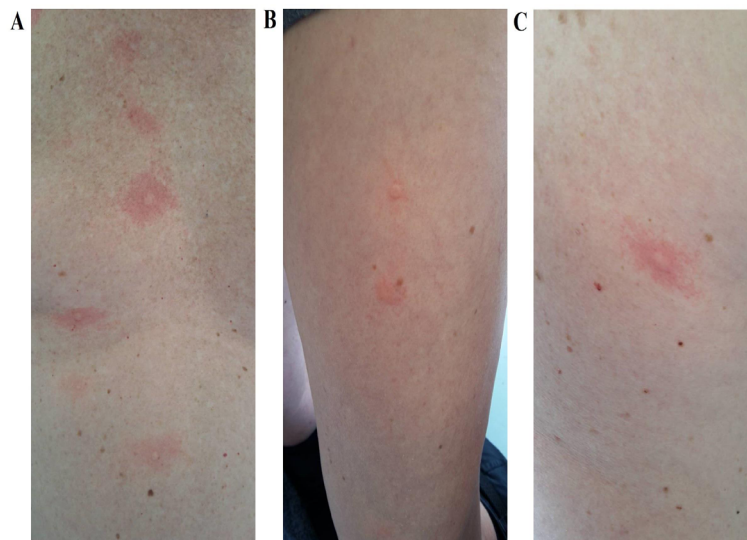


Figure 3: Diffuse nettle rash after the infusion of anti-PDL1 therapy which consisted on itchy, raised, reddish bumps on the skin of the chest (A) and the leg (B). A detail of nettle rash (C).

end of April 2018, the patient received the second cycle of Atezolizumab. In consideration of the previous skin toxicity, an antihistamine premedication (Chlorpheniramine maleate 10 mg iv) was given before infusion. Thirty minutes after the start of infusion of Atezolizumab, the patient presented with nettle rash all over the body (Figure 3 A, B, C). The infusion was stopped and an anti-allergic premedication with corticosteroids (Desametasone 8 mg iv) was prescribed with rapid resolution of the symptoms.

In consideration of the two skin toxicities, Atezolizumab treatment was definitively interrupted and the patient continued treatment with the Enzalutamide alone until August 2018 when it was stopped for progressive disease. No more skin reactions developed. The patient is currently alive.

Discussion

ICIs (anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and anti-programmed cell death 1 (PD-1) or anti-programmed death ligand 1 (PD-L1) inhibitors), have been shown to induce significant and prolonged clinical benefit in patients with multiple tumor types. ICIs enhance the antitumor immunity by interrupting the inhibitory and immune evasion mechanisms of cancer cells. The nonspecific enhanced immune system response promoted by ICIs can also lead to a peculiar pattern of adverse events, whose nature is similar to autoimmune diseases (irAEs). Cutaneous adverse events are some of the most common irAEs associated with ICIs. They usually occur early in the course of treatment and are often low-grade and dose-dependent [5]. However, they can be severe or life-threatening and are an emerging cause for interruption or discontinuation of therapy in clinical trials on ICIs [3]. They occur in more than one-third of the patients treated with ICIs. They develop more often and are usually more severe with anti-CTLA-4 than with anti-PD-1/PD-L1 [1, 4, 6]. The most common cutaneous adverse events include skin rash (especially morbilliform maculopapular eruption), vitiligo and pruritus. A wide range of other dermatologic manifestations can also occur, including lichenoid reactions, psoriasis and autoimmune skin diseases. More severe skin reactions, such as Steven Johnson syndrome or toxic epidermal necrolysis, have also been described [3,7,8]. Cutaneous irAEs have not

only a broad range of clinical presentations but also variable histologic patterns including epidermal spongiosis or perivascular CD4+/CD8+ lymphocytic infiltrates, with some eosinophils in the areas of rash. Dermatologic irAEs present as lichenoid or non-lichenoid patterns [4]. Lichenoid interface dermatitis is the most common histological pattern observed in maculopapular rashes induced by ICIs, especially anti-PD-1/PD-L1 agents [1,2,4,9,10,11,12,13,14,15,16]. Histologically, it is characterized by a superficial band-like lymphohistiocytic infiltrate (mixed CD4+/CD8+ or predominantly CD4+ T-cell infiltrate) along the dermal-epidermal junction, with vacuolar interface dermatitis and basilar/suprabasilar apoptotic keratinocytes. It is also associated with variable degrees of hypergranulosis, acanthosis, spongiosis, basal vacuolar changes and eosinophils [1,14]. This reaction pattern may be due to the nonspecific activation of T-cells against antigen (drug)-presenting keratinocytes [11]. Non-lichenoid pattern includes immunobullous eruptions, vitiligo, granulomatous dermatitis and urticarial-type reaction [1,2,4,13,17].

The first skin toxicity experienced by our patient was diagnosed as a maculopapular rash with lichenoid interface dermatitis. The clinical presentation was relatively nonspecific, characterized by a morbilliform, maculopapular rash of low grade (grades 1 and 2), but histologically it was confirmed as a lichenoid interface dermatitis. The co-presence of pneumonia in our patient could have misled to a different cause of maculopapular rash other than ICIs, since skin rashes are often associated with infectious conditions. We excluded the infectious hypothesis due to (1) antibiotic therapy rapidly and completely resolving all infection-related symptoms, except for the rash and (2) skin biopsy being suggestive for lichenoid reaction, typically associated with drug-related cutaneous toxicity. The second cutaneous adverse reaction described in our case had different onset and history. The urticarial-type reaction can be a rare dermatological irAE associated with ICIs [1,2,4,13,17] and it should be considered in the differential diagnosis. It was not possible to collect a blood sample to test IgE levels and skin tests and in vitro assays are not currently available, therefore we could not prove our hypothesis of an allergic reaction.

Nonetheless, the rapid onset (30 minutes after the start of the infusion), the clinical presentation and the rap-

id resolution of symptoms after the infusion of IV steroids were highly suggestive of an acute drug hypersensitivity reaction, possibly type I hypersensitivity [18]. Improving in vivo and in vitro assays for allergic reactions to ICIs and elaborating standardized premedication protocols in order to manage ICIs-related drug hypersensitivity reactions are currently unmet needs. To date, there are few dermatological toxicities induced by Atezolizumab and no type I hypersensitivity reaction induced by ICIs reported in the literature. We hope our case could make oncologists more aware of the various morphologic types of cutaneous toxicities induced by ICIs and of their diagnostic-therapeutic management. In order to recognize and effectively manage the whole spectrum of dermatologic toxicities induced by ICIs, it is of the utmost importance that oncologists work in collaboration with dermatologists. In fact, although dermatologic irAEs induced by anti- PD-1/PD-L1 and anti-CTLA-4 are usually low grade, self-limiting and readily manageable, early recognition and appropriate management are mandatory to avoid unnecessary discontinuation of a potentially life-saving therapy and to prevent a negative impact on patients' quality of life.

Conclusions

Our case report describes the occurrence of two different adverse cutaneous effects associated with the administration of Atezolizumab, one maculopapular rash with lichenoid interface dermatitis and one acute drug hypersensitivity reaction. Oncologists should be more aware of the broad range of clinical presentations of cutaneous toxicities induced by ICIs. Multidisciplinary collaborations should be an integral part of clinical practice for the best diagnostic-therapeutic management of ICIs-induced irAEs.

Ethical conduct of research

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Declaration of interest

The authors declare no conflicts of interest.

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Informed consent disclosure

A written informed consent was obtained from the patient for the inclusion of his medical and treatment history within this case report.

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