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Management of dermatological adverse events during nivolumab treatment

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ABSTRACT

Programmed death 1 receptor (PD-1) inhibitors, such as nivolumab, are effective in the treatment of advanced and metastatic melanoma, as well as in kidney, bladder, and non-small cell lung carcinomas. Adverse events of PD-1 inhibitors result mostly from autoimmune mechanisms, include gastrointestinal inflammatory diseases, hepatotoxicity, neurotoxicity, endocrinopathies, and skin toxicities. In this article, we highlight the main cutaneous adverse events associated with PD-1 inhibitors and provide a set of practical guidelines about their management. Additionally, we report a case of nivolumab-induced bullous pemphigoid in a patient with metastatic melanoma.

Key words: nivolumab, PD-1 inhibitors, cutaneous adverse events

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Introduction

Nivolumab, a human monoclonal antibody, targets programmed cell death 1 receptor (PD-1), which is an essential negative regulator of the immune response. PD-1 plays a role in sustaining peripheral tolerance and preventing autoimmunological reactions, mostly via the inhibition of proliferation, activation, and functional effectiveness of T lymphocytes. Expression of PD-1, as well as its ligands, is present in several types of cancer and can modify tumour microenvironment, enabling cancer cells to evade immunosurveillance [1]. This mechanism is present in the development of melanoma, lung, and renal cancer. Role of PD-1 and its ligands in the expansion of other types of cancer (such as basal-cell and squamous-cell carcinoma or primary cutaneous T-cell lymphomas) are currently under investigation [2–4].

Induction of an anticancer immune response that arises from PD-1 inhibition can also lead to several immune-related adverse events, distinctive to the PD-1 blockade. Antigens targeted by T lymphocytes, and therefore responsible for autoimmunity induction, have not yet been identified. The most common adverse events related to nivolumab include: gastrointestinal disorders (diarrhoea, colitis, hepatitis), endocrinopathies (hypo- and hyperthyroidism, hypophysitis, diabetes, and ketoacidosis), nephritis, autoimmunological pneumonitis, and rheumatological disorders [5–7].

Nivolumab-associated dermatological adverse events

Immunotherapy-related cutaneous toxicities are common. Combined results from the two phase 3 trials in melanoma (CA209066 and CA209037) indicate that the most common adverse events (≥ 10%) are: fatigue (33%), rash (20%), pruritus (18%), diarrhoea (16%), and nausea (14%) [5]. Most of the adverse events reported in the studies were mild to moderate (grade 1 or 2). Belum et al. [8] presented results from a meta-analysis regarding the incidence of dermatological toxicities after PD-1 inhibitors. The incidence of nivolumab-associated cutaneous adverse events were as follows: 14.3% rash, 13.2% pruritus, 7.5% vitiligo, 5.3% xeroderma, 2% alopecia, 1.5% stomatitis, 1.4% urticarial, 1.4% photosensitivity reactions, 0.9% hyperhidrosis, and 0.7% skin exfoliation. In a single-centre study that included 82 patients treated with PD-1 inhibitors for metastatic melanoma, Hwang et al. [9] reported the following: 17.1% lichenoid reactions and similar rates of rash, 14.6% vitiligo, 13.4% actinic keratosis and similar rates of seborrheic keratosis, 11% pruritus, 8.5% skin infections (viral — zoster; tinea, infections of cutaneous and subcutaneous tissue — cellulitis), 6.1% new nevi and similar rates of squamous-cell carcinomas, 6%

folliculitis, 3.7% melanoma metastases, 2.4% bullous pemphigoid and similar rates of basal-cell carcinoma, and 1.2% primary melanoma and similar rates of hypopigmented nevus. Additionally, single cases of acute generalised exanthematous pustulosus (AGEP) reaction type, photosensitivity reaction, psoriasis, *livedo reticularis*, and rosacea were described. Presented reports of new non-melanocytic skin malignancies are unexpected because some previous data suggested beneficial effects of PD-1 inhibitors on the development of actinic keratosis, basal-cell, and squamous-cell carcinomas [2, 3, 10].

Nayar et al. [11] reported a case of toxic epidermal necrolysis after administration of two doses of nivolumab, and Cappelli et al. [12] reported a case of secondary sicca syndrome with concomitant arthritis. Recently, several studies have evaluated the safety of immunotherapy in patients with a previous history of autoimmunological diseases. Menzies et al. [13], based on multi-institutional data of metastatic melanoma patients treated with PD-1 inhibitors, described exacerbations of autoimmunological diseases in 38% of the patients, with a 33% incidence of grade 1 autoimmunological flair [according to Common Terminology Criteria for Adverse Events (CTCAE)] and a mean time to flair appearance of 38 days (8–161 days). Exacerbations occurred in 52% of the patients with a history of rheumatological diseases (rheumatoid arthritis, scleroderma, Sjögren's syndrome, and psoriatic arthritis) and in 38% of the patients with a history of dermatological diseases (e.g. psoriasis). Emphasis should be given to the fact that, prior to nivolumab therapy, most of the analysed patients had their autoimmunological diseases active (60% of patients) and nearly 50% of them received a immunosuppressive treatment. About 14% of patients with an autoimmunological flair needed oral or intravenous steroids. The character of immune-related adverse events was unconventional in nearly 70% of the patients. Interestingly, reappearance of previous immunological reactions induced by ipilimumab occurred only in 3% of the patients. Novel immune-related toxicities associated with PD-1 inhibitors appeared in 34% of the patients (grade 1 and 2 intensity in 13% and grade 3 intensity in 18% of the cases).

Table 1 shows the definitions and descriptions of chosen nivolumab-associated dermatological adverse events (according to 4.0 CTCAE) [14].

Management of the most common nivolumab-associated cutaneous adverse events

Measles-like maculopapular rash

The estimated rate of incidence is 9.3–14.7% [15, 16]. The rash usually appears soon after a therapy initiation. Histopathological examination of the skin biopsy specimen shows the presence of perivascular eosinophilic infiltrates, accompanied by an increased eosinophil count in the complete blood count [17]. Grade 1 (according to CTCAE) maculopapular rash requires topical administration of strong corticosteroids one or two times daily and oral antihistamines. In grade 2 reactions, it is advised to initiate systemic corticosteroids in a dose equivalent to 0.5 mg/kg of prednisone [18]. Grade 3 reactions require a pause in nivolumab therapy, and in grade 4 reactions nivolumab should be stopped indefinitely [5]. After a week without improvement in symptoms, systemic corticosteroids should be initiated in a dose equivalent to 0.5–1 mg/kg of prednisone. Systemic corticosteroids should be slowly tapered within a month. Topical corticosteroids and oral antihistamines (e.g. diphenhydramine or hydroxyzine) should be continued until the resolution of symptoms. Treatment inefficiency implies an increase in the systemic corticosteroid dose to 1–2 mg/kg of prednisone, continued until improvement.

In grade 3–4 skin adverse events, a dermatologist's consultation is indicated because hospitalisation and a skin biopsy might be required. Permanent withdrawal of the immunotherapy is advised [19].

Pruritus and dry skin

Pruritus is a common skin toxicity of nivolumab, with an incidence of about 11–18.8% [8, 9, 16]. Grade 1–2 pruritus is not a contraindication for nivolumab continuation. Skin care in grade 1 pruritus and dry skin includes: application of greasy emollients such as petroleum jelly or cholesterol based; protection from an UV radiation; administration of topical antipruritic medications containing polidocanol, menthol, camphor, or pramocaine (one or two times per day). Grade 2 pruritus and skin dryness are an indication for moderate or strong topical steroids, as well as the addition of systemic first-generation antihistamines that block H1 receptor. If the symptoms are unresponsive, proceed with grade 3 recommendations. Treatment of grade 3 pruritus include administration of drugs blocking H1 receptor and intermittent low to medium doses of systemic corticosteroids (e.g. equivalent to 0.5 mg/kg of prednisone). In the case of eczema, lichenification, fissures, and/or secondary infections, topical administration of moderately strong or strong steroids one or two times per day is advised. Alternatively, formulation combining corticosteroids and antibiotics might be utilised. Unresponsive or progressing adverse events require adjustment of corticosteroid dose and/or a pause in nivolumab treatment, according to the Summary of Product Characteristics [18].

Lichenoid reactions

Lichenoid lesions have a papular appearance, a tendency to merge in larger lesions, and are accompanied

Table 1. Chosen dermatological nivolumab-associated adverse events, according to Common Terminology Criteria for Adverse Events (4.0 CTCAE)

Grade	Adverse event			
	1	2	3	4
Bullous diseases Definition: a disorder characterised by an inflammation of skin with a presence of fluid-containing blisters	Asymptomatic; blisters covering < 10% BSA	Blisters covering 10–30% of BSA, limits instrumental activities of daily living	Blisters covering > 30% BSA, limits self-care activities of daily living	Blisters covering > 30% BSA, electrolytes and fluid imbalances; hospitalisation in an intensive care unit or a burn unit indicated
Pruritus	Mild intensity and limited outreach; requires local treatment	Intensive or widespread; intermittent; secondary skin changes due to scratching, limits instrumental activities of daily living; requires systemic treatment	Intensive or widespread; constant; limits self-care activities of daily living or sleep; oral corticosteroids or immunosuppressive treatment indicated	–
Rash maculopapular Definition: a disorder characterised by a presence of macules (flat) and papules (elevated) Known also as a measles-like rash One of the most common skin toxicities Often involves upper parts of the body and spreads centrically, accompanied by pruritus	Macules/papules covering < 10% BSA, may be associated with symptoms (e.g. pruritus, tingling, or tenderness)	Macules/papules covering 10–30% BSA, may be associated with symptoms (e.g. pruritus, tingling, or tenderness), limits instrumental activities of daily living	Macules/papules covering > 30% BSA with or without symptoms, limits self-care activities of daily living	–
Vitiligo Definition: patches of hypopigmented or depigmented skin or hair Toxicity limited only to the patients treated for melanoma	Hypopigmentation or depigmentation covering < 10% BSA, without negative impact on psycho-social wellbeing	Hypopigmentation or depigmentation covering > 10% BSA, with negative impact on psycho-social wellbeing	–	–
Erythema multiforme Definition: a disorder characterised by the presence of target lesions (macules pale in the middle surrounded by a rosy or red annulus)	Target lesions covering < 10% BSA, without accompanying skin tenderness	Target lesions covering 10–30% BSA, skin tenderness present; possibility of overlapping with Stevens-Johnson syndrome	Target lesions covering > 30% BSA with accompanying erosions on mucosa of oral cavity or mucosa of reproductive organs; possibility of Stevens-Johnson syndrome overlapping toxic epidermal necrolysis	Target lesions covering > 30% BSA, electrolytes and fluid imbalances, hospitalisation in an intensive care unit or a burn unit indicated, corresponds to a diagnosis of toxic epidermal necrolysis

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Table 1 cont. Chosen dermatological nivolumab-associated adverse events, according to Common Terminology Criteria for Adverse Events (4.0 CTCAE)

Grade	Adverse event			
	1	2	3	4
Stevens-Johnson syndrome Definition: a disorder characterised by a separation of dermis involving > 10% BSA Thought to be a hypersensitivity reaction affecting skin and mucous membranes	–	–	Separation of dermis involving > 10% BSA with accompanying erythematous and macular changes, as well as erosions on mucous membranes	Separation of dermis involving 10–30% BSA with accompanying erythematous and macular changes, as well as erosions on mucous membranes; electrolytes and fluid imbalances, hospitalisation in an intensive care unit or a burn unit indicated, possibility of Stevens-Johnson syndrome overlapping toxic epidermal necrolysis
Toxic epidermal necrolysis Definition: a disorder characterised by separation of dermis involving > 30% BSA The syndrome arises from a hypersensitivity reaction affecting skin and mucous membranes	–	–	–	Separation of dermis involving ≥ 30% BSA with accompanying erythematous and macular changes, as well as erosions on mucous membranes, electrolytes and fluid imbalances, hospitalisation in an intensive care unit or a burn unit indicated

BSA — body surface area

by pruritus [15, 20]. Biopsy examinations reveal the presence of PD-1–positive T lymphocytes and lack of C3+ lymphocytes. Lichenoid reactions usually develop a few months after nivolumab initiation. Typically, no modification of the treatment schedule is indicated [20]. Severe cases of a lichenoid reactions require systemic corticosteroids. Most of the moderate cases resolve after topical corticosteroids [15, 20].

Vitiligo

Vitiligo is usually generalised, but in some patients it is limited to the regions with metastatic involvement. It does not require interruption of nivolumab therapy. Recommendations include: sun protection; skincare with proper moisturisers; topical corticosteroids in grade 1 changes; and phototherapy in grade 2 changes (although this remains controversial in patients with advanced melanoma and should be limited to a specific region only, e.g. the face) [8, 15].

Severe drug reactions

Besides the nivolumab-associated dermatological adverse events described above, single cases of severe and life-threatening dermatological toxicities (grade 3–4 according to CTCAE) have been described. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reactions with eosinophilia and systemic symptoms (DRESS) syndrome, or AGEP reactions [8, 9, 11]. Some of them, despite being potentially fatal, can fully resolve with proper systemic management and nivolumab withdrawal [6–8, 15–17]. Severe grade 3 and 4 skin toxicities require: nivolumab interruption and

multidisciplinary management (including dermatological consultation); hospitalisation in an intensive care unit or in a burn unit; rapid treatment of secondary infections; proper provision of erosions and wounds; withdrawal of all drugs potentially exacerbating skin changes; management of fluid and electrolyte imbalances; and sufficient analgesia [18]. In patients with a previous history of serious or life-threatening dermatological reactions to other immunotherapeutic drugs, nivolumab usage should be considered with extreme caution [5].

In a contrast to the adverse events related to autoimmunological reactions, which occur from 3–20 weeks to even 1–2 years after immunotherapy initiation, toxic drug reactions arise sooner, from a period of a few hours (as in urticaria) to about three weeks. This phenomenon has an important role in the differential diagnosis of dermatological adverse events. Valuable clinical insights come from the mean period to toxicity occurrence: 7–21 days for toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme; 14–21 days for type I rash (viral-like; e.g. maculopapular rash); 1–4 days for AGEP reactions; 7–21 days for DRESS syndrome; up to few days for photosensitivity reactions.

Nivolumab-induced bullous pemphigoid — a case report

A 69-year-old female patient with a metastatic mucosal melanoma originating from anal canal was admitted to the Department of Dermatology of the Military Institute of Medicine due to a presence of diffuse skin changes: erythematous lesions, blisters with a tense-roof, and erosions partially encrusted with haemorrhagic eschars (Fig. 1). Changes show traits of photodistribution. Dermatological lesions appeared in the eighth month of nivolumab therapy. These were initially limited to the face and forearms but subsequently spread also to the neck, anterior side of the chest, and the crura. Intensive pruritus was also present. In the ambulatory setting, antibiotics (doxycycline 200 mg/day for 10 days), antihistamines, and topical corticosteroids were used without improvement. Medical history included asthma and arterial hypertension. The patient received perindopril, amlodipine, bisoprolol, acetylsalicylic acid, and pantoprazole on a daily basis. Diagnostics workup for skin changes included: complete blood count with a smear (normal results); blood biochemical panel (without significant abnormalities); erythrocyte sedimentation rate (elevated to 69 mm/h); coagulation testing (D-dimer 1.94 μg/mL, fibrinogen 746 mg/dL), urinalysis (proteinuria 50 mg/dL and elevated concentration of urobilinogen 2.0 mg/dL was detected), antinuclear antibodies panel (positive for anti-RO IgG antibody 130 U/mL); complement components C3 and C4 concentrations (within normal range); evaluation of hepatotropic viruses (negative); and proteinogram (elevated concentration of alpha-1 fraction — 0.3 g/dL). Phototesting results were also negative. Two biopsy specimens from changed skin were obtained for histological examination (microscopic evaluation suggested image of *interface dermatitis* — presence of lichenoid infiltrates and subepidermal blistering). An additional skin sample was examined under direct immunofluorescence microscopy; deposits of IgG immunoglobulin and complement component C3 immunoglobulin were discovered within the zone of basement membrane. Blood serum was positive for desmoglein 1 and 3 an-

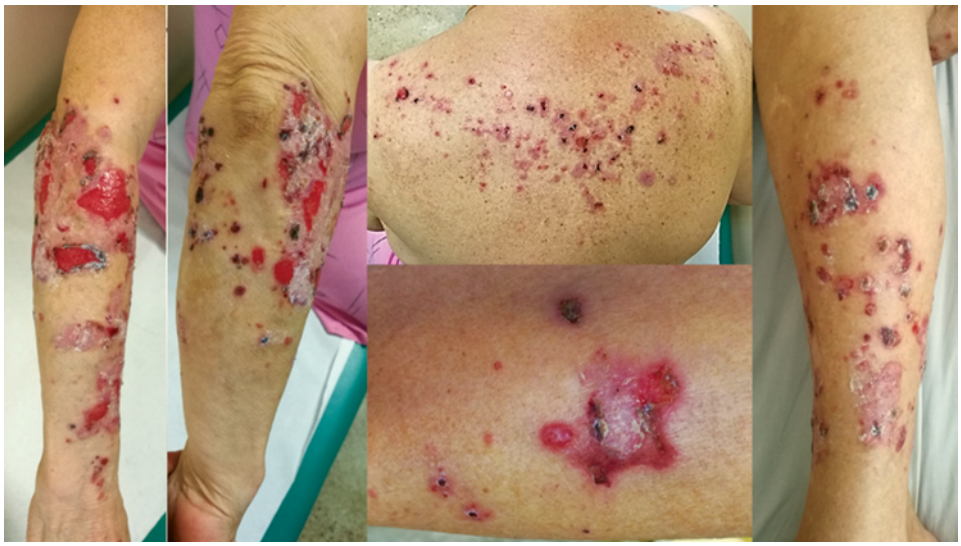

Figure 1. Dermatological changes in the reported case. Visible lesions include: erythematous indurations; singular vesicles on an erythematous foundation; numerous erosions and excoriations

tibodies, as well as for antibodies against antigens of epidermal basal membrane (IgG antibodies against basal membrane antigens in a titre of 40). Despite the pathologist's suggestion of *Interface dermatitis with bullous erythema multiforme anti-PD-1 therapy associated* (Am J Dermathopathol. 2017; 39, 2), due to the lack of clinical, histopathological, and laboratory workup correlation, nivolumab-induced bullous pemphigoid was diagnosed. For the last two months the patient has been treated with prednisone in slowly modified doses of 30–20 mg/day (0.375–0.25 mg/kg) and topical clobetasol propionate and silver sulfadiazine. As a result of prolonged treatment with corticosteroids and a simultaneous progression of melanoma, the therapy with nivolumab was withheld.

Commentary

Autoimmunological bullous diseases are rare adverse events of immunotherapy. Bullous pemphigoid is the most common example of autoimmunological bullous disease in the general population (80% of cases; incidence of 43/1 million in Great Britain) [21]. It usually develops in older patients and sometimes can be induced by the presence of a malignancy, although the evidence regarding correlation of pemphigoid and cancer remains equivocal [23]. Only a few cases of a bullous pemphigoid induced by nivolumab, pembrolizumab, or durvalumab have been reported so far [9, 17]. The pathomechanism behind immunotherapy-induced bullous pemphigoid remains unclear and no standard of care exists. A cautious approach to the evaluation of different erythematous skin changes is advised because pemphigoid lesions might be diverse: erythematous indurations; urticaria; target lesions; vesicles; and blisters. Lesions are often accompanied by pruritus and, in severe cases, by increased eosinophilic content in complete blood count. In some variants, pemphigoid may lack the visible bullous component and resemble urticaria. Close cooperation between the oncologist and dermatologist is required for appropriate diagnostic and therapeutic proceedings, especially in cases unresponsive to the standard therapy based on available guidelines. Diagnostic workup in bullous diseases includes histopathological examination and direct and indirect immunofluorescence to detect the localisation of immunological reactions in skin [17].

Common findings in bullous pemphigoid include IgG (less often IgE) and C3 deposits in the dermo-epidermal junction, detected in direct immunofluorescence, as well as serum antibodies against the antigens of basal membrane BP180(NCI6) and BP230 (occasionally also other antigens). Clinical findings in drug-induced pemphigoid are not different from "classic" pemphigoid, although signs and symptoms should resolve, or at least improve, after cessation of the responsible drug. However, some cases may persist for several months after drug withdrawal. Prolonged effects of anti-PD-1 therapy, arising from a chronic immune activation, might explain this phenomenon [23]. A predisposition of some patients treated with the anti-PD-1 antibodies to develop bullous pemphigoid might be due to the presence of BP180 antigen in both basal membrane of the epidermis and in cancer cells. A pathomechanism leading to the production of auto-antibodies, might also be responsible for other immunological adverse events in predisposed patients [17].

Summary

Growing access to novel oncological therapies is resulting in improved patient prognosis. However, the diverse and unexpected adverse events induced by the new oncological drugs require a multidisciplinary approach. The guidelines presented above are based on recommendations available in the current medical literature in English and include management of the most common nivolumab-associated skin adverse events. Cutaneous adverse events induced by a combination of anti-PD-1 and anti-CTLA-4 antibodies (such as ipilimumab) require additional attention because their spectrum is more diverse and requires intensified treatment. Appropriate management of the immunotherapy-induced dermatological adverse events have a profound impact on the treatment optimisation and on personalising patient care. We harbour a hope that the presented guidelines will be helpful in common daily practice, for both dermatologists and oncologists.

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