Cutaneous adverse reactions to anti–PD-1 treatment—A systematic review

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The use of the humanized monoclonal anti–programmed cell death 1 antibodies pembrolizumab and nivolumab as potent anticancer therapies is rapidly increasing. However, since their approval, numerous cases of cutaneous reactions have been reported. Cutaneous adverse reactions to these agents have yet to be fully characterized and range from nonspecific eruptions to recognizable skin manifestations, which may be localized and vary from mild to life threatening. This systematic review article provides an overview of the various adverse cutaneous reactions to pembrolizumab and nivolumab therapy and offers suggestions for their management. (J Am Acad Dermatol 2020;83:1415-24.)

Key words: anti–PD-1; cutaneous adverse reaction; dermatology; immunotherapy; oncology.

The humanized monoclonal anti–programmed cell death-1 (anti–PD-1) antibodies pembrolizumab and nivolumab have entered the standard of care for several cancers[1-4] and have substantially changed the life expectancy of patients with metastatic disease.[5] Although their clinical benefits are unquestionable, immune-mediated adverse events are apparent, perhaps predictably given their mode of action.[6] Since their approval by the US Food and Drug and Administration (2014) and European Medicines Agency (2015), numerous cases of cutaneous reactions have been reported. It has been estimated that 49% of patients treated with anti–PD-1 will develop skin toxicity.[2] The breadth of cutaneous adverse reactions to anti–PD-1 treatment have yet to be fully characterized. With this review article, we provide an overview of the various adverse cutaneous reactions to pembrolizumab and nivolumab therapy as well as suggestions for management.

METHODS

The medical databases PubMed and Embase were searched systematically by 2 authors (ABS and JK) in July 2019 using the search terms ((“SKIN” OR “CUTANEOUS” OR “DERMATOLOGIC”) AND (“REACTION” OR “ADVERSE” OR “COMPLICATIONS”) AND (“ANTI-PD1” OR “PD1” OR “PEMBROLIZUMAB” OR “NIVOLUMAB”)). The same 2 authors independently reviewed the titles and abstracts of studies that described cases of cutaneous adverse reactions to treatment with either pembrolizumab or nivolumab. Additional studies were identified by screening reference lists of key articles and review articles. The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[7]

Inclusion and exclusion criteria

We included articles describing cutaneous reactions to nivolumab or pembrolizumab given as monotherapy and providing detailed information on numbers of patients, cutaneous reaction, and primary cancer, thus excluding all articles in which patients were given combination therapy.

Data extraction

Two authors (ABS and JK) performed data extraction individually. Titles and abstracts were screened for relevance. Relevant abstracts or articles without abstracts were selected for full-text review. Duplicates were removed, along with studies presenting the identical population in different articles.

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The time from initiation of anti–PD-1 treatment to onset of adverse cutaneous reaction was heterogeneously reported as "cycles," "days," "weeks," or "months." To obtain uniformity in the explanatory table (Supplemental Table I; available via Mendeley at https://doi.org/10.17632/8j6bjfc2m5.1), this was converted to weeks for all cases.

RESULTS

A total of 114 unique articles were identified, describing specific cutaneous adverse reactions in 253 patients. Six patients experienced 2 different specific cutaneous adverse reactions.[8-12] One patient developed bullous pemphigoid during nivolumab treatment that later flared during subsequent treatment with pembrolizumab.[1] Table I shows the most common cutaneous adverse reactions. Supplemental Table I provides a comprehensive list of all reported cutaneous adverse reactions. The most frequently reported specific cutaneous reactions to anti–PD-1 treatment are described in detail in the following sections. Table I provides an overview. Fig 1 shows examples of 3 common cutaneous adverse reactions.

CAPSULE SUMMARY

- Numerous adverse events from treatment with anti–programmed cell death 1 (anti–PD-1) have been reported, but the breadth of cutaneous reactions has not previously been fully characterized.
- Early referral for dermatologic evaluation is recommended to target the treatment of adverse cutaneous reactions, thus reducing morbidity and increasing the chance of continuing anti–PD-1 treatment.

Vitiligo/depigmentation

Fifty-six cases of vitiligo, hypopigmentation, or loss of pigment occurring after anti–PD-1 treatment have been reported.[9,11-24] The majority of patients received immunotherapy for metastatic melanoma.[11,14-17,19-21,25,26]

Clinical presentation. The time from treatment to the appearance of depigmentation or vitiligo ranged from 6 days to 36 weeks. The vitiligo/vitiligo-like skin changes after immune therapy were symmetric, depigmented macules and patches located in sun-exposed areas.[20,23,27] One patient experienced generalized loss of pigment including whitening of skin, scalp hair, eyelashes, and eyebrows. Furthermore, nevi, solar lentigines, and seborrheic keratosis disappeared.[19]

Pathogenesis. Vitiligo may occur spontaneously in patients with melanoma. T cells target common antigens shared by normal melanocytes and melanoma cells, and this cross-reactive immune response may result in vitiligo.[25] The exact mechanism of immune therapy–induced vitiligo is not clear, but it is thought to be similar to the destruction of melanocytes after anti–PD-1 activation of T cells.[14]

Management. Most patients continued anti–PD-1 therapy despite the appearance of vitiligo. In 2 cases, treatment was stopped because of progression of the cancer.[12,23] Two patients were treated with topical corticosteroids and 1 additionally with topical tacrolimus, but with limited effect.[9,14] Interestingly, Hua et al[15] found an association between occurrence of vitiligo and response to pembrolizumab treatment. Nardin et al[26] reported a case in which vitiligo repigmentation was associated with the progression of metastatic melanoma.

In general, vitiligo or depigmentation occurring after anti–PD-1 treatment does not require treatment unless indicated for cosmetic reasons. Treatment recommendations are the same as for classic vitiligo and include potent topical corticosteroids, calcineurin inhibitors, phototherapy,[28,29] and sun protection to keep the vitiliginous areas from burning.[30]

Psoriasis

Thirty-three cases of psoriasis have been reported: 17 were de novo psoriasis,[11,31-40] and 16 were exacerbation of pre-existing disease.[40-44]

Clinical presentation. The time from initiation of anti–PD-1 treatment to development of psoriasis ranges from 2 to 22 weeks. The clinical type of psoriasis reported as adverse reactions spans from guttate psoriasis[35,42] to plaque psoriasis,[34,35,40] inverse psoriasis,[32] and palmoplantar psoriasis.[35,36] Three patients had concurrent psoriatic arthritis of several joints.[33,35,36] The patient reported by De Bock et al[41] had no other complaints aside from cutaneous psoriasis vulgaris. In the remaining reports, information regarding joint symptoms is missing.

Pathogenesis. T-cell activation induced by the blockade of PD-1 promotes an inflammatory state and likely triggers the development of psoriasiform lesions.[34]

Management. In the majority of the described cases, skin involvement was mild. Patients were able to continue anti–PD-1 treatment,[11,31,32,34,35,37,38,41-44] and psoriasis could be controlled with topical corticosteroids and/or topical vitamin D analogues.

Abbreviations used:

anti–PD-1: anti–programmed cell death 1
PD-L1: programmed death ligand 1
TEN: toxic epidermal necrolysis

Two cases of psoriasis exacerbation were treated successfully with systemic retinoids and the anti–PD-1 was continued.[43,44] Three patients were treated with methotrexate[33,35,36]; 1 of these continued anti–PD-1 therapy.[35] A patient with widespread psoriasis lesions that were refractory to acitretin treatment responded well to anti–interleukin 17A treatment.[39]

Both personal and family history of psoriasis seem to be significant risk factors for the development or exacerbation of psoriasis during anti–PD-1 treatment[35] and should be recognized before the initiation of treatment.

Bullous pemphigoid

Whereas classic bullous pemphigoid is idiopathic, several medications are associated with drug-induced bullous pemphigoid.[45,46] Thirty-one cases of bullous pemphigoid during treatment with either nivolumab or pembrolizumab have been reported.[1,10,47-62]

Clinical presentation. The latency of bullous disorders due to immunotherapy is generally longer than that of other cutaneous toxicities. Most patients will have clinical, histologic, and immunologic features of classic bullous pemphigoid.[1,60] Bullous lesions may develop or persist even after cessation of immunotherapy because of prolonged immune activation associated with anti–PD-1 therapy.[47,59] The average time of onset for bullous eruptions associated with anti–PD-1 therapy has been reported to be approximately 12 weeks.[49] In the reviewed cases, the time to onset ranged from 3 to 84 weeks.

Pathogenesis. No specific features differentiate classic bullous pemphigoid from drug-induced bullous pemphigoid,[63] and the exact pathomechanism of immunotherapy-related bullous pemphigoid is not yet established. BP180 has been shown to be expressed in melanoma[64] and non–small cell lung cancer,[65] which raises the possibility of the production of antibodies against tumor cell antigens that also target the skin.

Management. Bullous pemphigoid may result in extensive skin blistering, warranting interruption of the immunotherapy and treatment with systemic agents. Systemic prednisolone was effective in the vast majority of reported cases. Doxycycline was the most commonly used steroid-sparing treatment,[1,49,57] but treatment with niacinamide,[49,60] nicotinamide,[1] methotrexate,[56] rituximab,[55] and omalizumab[1,62] has also been reported. In all but 3 cases,[48] patients required either temporary or permanent interruption of immunotherapy.

Lichenoid reactions

Twenty-nine cases of lichenoid reactions to anti–PD-1 treatment have been reported.[1,9,12,66-81]

Clinical presentation. The diagnosis is usually based on the typical clinical appearance, characterized by lichenoid papules on the trunk and/or extremities, as well as on the histologic finding of interface dermatitis with a lichenoid lymphocytic infiltrate and epidermal necrosis. The clinical presentations range from typical lichen planus with flat-topped polygonal papules/plaques and visible Whickham striae to hypertrophic vesiculobullous lesions.[1,9,12,66-80] The lesions may progress to the more severe bullous form.[66,77] Pruritus can be severe and debilitating.

The latency interval between the first dose and the onset of the rash can range from a few days to several months.[9,67,75]

Pathogenesis. The immunologic mechanism of lichenoid drug reactions is thought to be a T-cell–mediated response. Blocking programmed death ligand 1 (PD-L1) causes not only an increase in the immune function of tumor-specific T cells but also an accentuating effect of self-immunity or antigenic immune response, which leads to widespread nonspecific T-cell activation, resulting in adverse reactions in multiple organ systems, including the skin.[81] Expression of PD-L1 on keratinocytes has been found in lichen planus lesions,[80] and it has been suggested that anti–PD-1 may cause lichenoid reactions by blocking the interaction between PD-L1 on keratinocytes and PD-1 on T cells.[72]

Management. The lichenoid reactions generally respond well to topical steroids.[73,74,80] Twelve patients required systemic therapy.[12,66,67,70,71,75-79,81] Systemic prednisolone was the first choice of systemic treatment in 11 patients and was effective in the majority of cases. One patient was treated with a short course of cyclosporine,[79] and 3 patients responded well to acitretin.[66,76] Anti–PD-1 treatment could often be continued along with systemic treatment.[9,12,66,70,71,75,77]

Granulomatous skin reactions

Ten cases of granulomatous reactions have been reported as adverse reactions to either nivolumab or pembrolizumab.[10,82-88]

Table I. Most frequently reported cutaneous adverse reactions

Cutaneous adverse reaction	Patients, n	Clinical presentation	Time to onset, weeks	Treatment
Pigmentary changes/vitiligo	58	Symmetric, depigmented macules and patches located in sun-exposed areas	1-36	Potent topical corticosteroids, calcineurin inhibitors, phototherapy, sun protection
Psoriasis	33	Guttate psoriasis, plaque psoriasis, inverse psoriasis, and palmoplantar psoriasis	2-22	First line: topical corticosteroids/vitamin D analogue 2 patients successfully treated with systemic retinoids, 3 with methotrexate, and 1 with anti−IL-17A
Bullous pemphigoid	31	Pruritus, tense bullae, with or without erythematous, urticarial plaques Most patients have clinical, histologic, and immunologic features of classic bullous pemphigoid	3-84 Bullous lesions may develop or persist even after cessation of immunotherapy.	First line: potent topical corticosteroids or systemic prednisolone Second line: doxycycline. Other treatments reported: niacinamide, nicotinamide, methotrexate, rituximab, and omalizumab
Lichenoid reaction	30	Ranges from typical lichen planus to hypertrophic vesiculobullous lesions May progress into a more severe bullous form	<1-92	First line: potent topical steroids or systemic prednisolone Second line: 3 patients were successfully treated with acitretin and 1 with cyclosporine
Granulomatous reaction	10	Subcutaneous nodules, indurated papules, and plaques Systemic granulomatous disease found in 8 of 10 patients	4-40	First line: prednisolone One case treated with prednisolone + hydroxychloroquine
Erythema multiforme/ SJS/TEN	10	1 patient erythema multiforme, 2 patients toxic epidermal necrolysis, 6 patients SJS	<1-20	Prednisolone, cyclosporine, immunoglobulins 1 patient treated with plasmapheresis and infliximab
Lupus erythematosus	8	Ranges from erythematous papules and plaques to annular scaling plaques, bullous lesions, and reactivation of discoid lupus erythematosus	4-34	Topical corticosteroids, prednisolone, hydroxychloroquine

IL, Interleukin; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

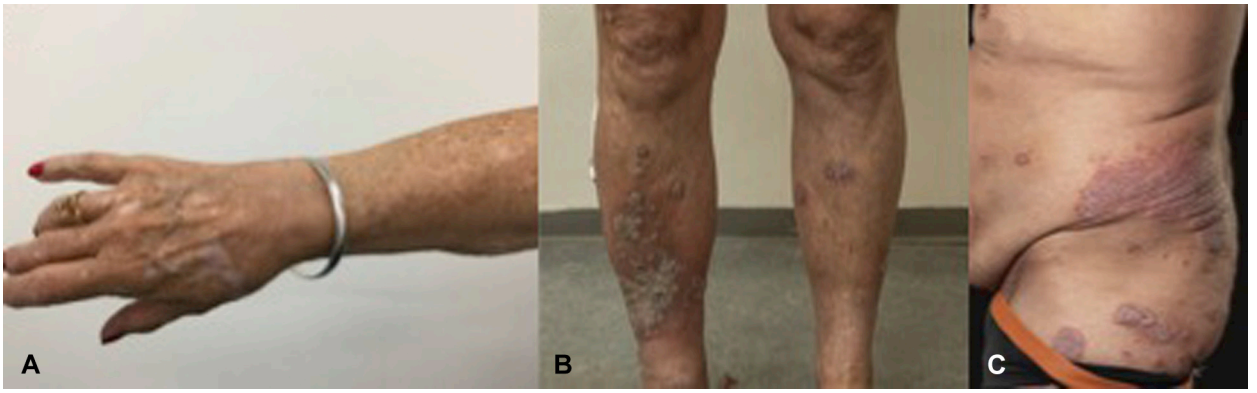

Fig 1. Examples of specific cutaneous adverse reactions from anti–PD-1 treatment: **(A)** vitiligo, **(B)** lichen planus, and **(C)** psoriasis.

Clinical presentation. In 4 cases, the patient presented with cutaneous sarcoidosis,[10,83,84,87] and in 5 cases, the cutaneous reaction was classified as a sarcoid-like granulomatous reaction.[82,84-86,88] The clinical presentation was subcutaneous nodules[84,87,89] or indurated papules and plaques.[10,83] In 2 patients, the granulomas appeared in quiescent scars.[82,86] Burillo-Martinez et al[8] reported a case of granulomatous panniculitis. All but 2 patients had systemic granulomatous disease, and the dermatologic symptoms preceded the detection of mediastinal/hilar lymphadenopathy and pulmonal nodules in the majority of cases.[8,10,84-86]

Pathogenesis. Immunotherapy-related granulomatous reactions may be triggered by a checkpoint inhibitor–mediated T helper type 17 immune response. Blockade of PD-1 has been associated with T helper type 17 cell hyperactivity and increased interleukin 17 expression.[90]

Management. In all but 1 case, the granulomatous adverse reaction appeared within 12 weeks of initiation of anti–PD-1 treatment.[82] The authors of 5 articles provide information on treatment of the cutaneous granulomatous reaction.[8,10,83,84,87] All responded well to systemic prednisolone. One case was treated with prednisolone and hydroxychloroquine in combination.[10]

In 4 of 10 cases, anti–PD-1 treatment was continued despite the adverse cutaneous reactions.[10,82,86,87]

Toxic epidermal necrolysis/Stevens-Johnson syndrome/erythema multiforme

Ten cases of severe cutaneous adverse reactions to pembrolizumab or nivolumab have been reported.[91-99]

Clinical presentation. The time from anti–PD-1 treatment to onset of skin symptoms ranged from a few days[91] to 20 weeks.[93] The majority were diagnosed within the first 4 weeks after initiation of immunotherapy.[91,92,94-99]

One patient was diagnosed with erythema multiforme major.[94] The remaining patients presented with bullae and erosions of the mucosa and skin and were classified as having either Stevens-Johnson syndrome[91,93,95,97,98] or toxic epidermal necrolysis (TEN)[92,96,99] according to body surface area involvement.

Pathogenesis. It is believed that the antagonism of PD-1 results in loss of T-cell homeostasis within the skin or mucosa of the eyes or oral cavity, leading to the failure of immune tolerance and self-directed cytotoxic reactions.[91,93,95]

Management. In all cases, anti–PD-1 treatment was stopped immediately. All but 1 patient received systemic prednisolone as first-line treatment. Three patients were given prednisolone as monotherapy,[91,94,97] 1 patient with Stevens-Johnson syndrome was treated with cyclosporine alone,[93] and 2 patients were treated with prednisolone and cyclosporine in combination.[92,93] Two patients with TEN received immunoglobulin treatment,[92,96] and 1 patient was treated with infliximab and plasmapheresis.[99] In 2 of the 3 reported cases of TEN, the outcome was fatal.[96,99]

Lupus erythematosus

Eight cases of lupus erythematosus caused or exacerbated by pembrolizumab or nivolumab have been reported.[6,100-103]

Clinical presentation. The time to onset of lupus erythematosus ranged from 4 to 34 weeks. In the reported cases, the cutaneous lesions were erythematous papules and plaques,[101,102] annular papulosquamous plaques,[6,100,102] bullous eruption,[103] and reactivation of discoid lupus erythematosus.[6] Clinically and histologically, lupus erythematosus and lichenoid reactions may, in some

cases, be difficult to distinguish.[104] Thus, it is recommended that both histopathology and immunofluorescence be performed. Measurement of antinuclear antibodies may be useful in establishing the diagnosis, although they may be absent. One patient presented with fever, arthralgia, asthenia, and bullous lupus erythematosus.[103] In the case reported by Liu et al,[100] there was no evidence of systemic lupus erythematosus. The remaining case reports provide no information regarding extracutaneous symptoms.[6,101,102]

Pathogenesis. The existing literature suggests a specific link between PD-1 and lupus, because PD-1—knockout mice develop lupus-like autoimmune symptoms. Furthermore, lower PD-1 expression on T cells and a higher frequency of PD-L1—expressing neutrophils have been reported in patients with systemic lupus erythematosus.[105,106]

Management. In 1 patient, the rash resolved without treatment within 1 month after cessation of pembrolizumab.[101] In 2 patients, the skin symptoms were controlled with topical corticosteroid treatment.[6] The remaining patients required systemic treatment with prednisolone[6,103] and/or hydroxychloroquine.[100,102] In 3 patients, anti—PD-1 treatment was withheld but later reinitiated,[6,100] and in another 3 cases, anti—PD-1 treatment was stopped permanently.[101-103]

Nonspecific cutaneous reactions

Nonspecific pruritic maculopapular rash and pruritus are frequent adverse reactions to drugs, including anti—PD-1.[13,107] The symptoms respond well to topical corticosteroids,[13,107] and modifications of immunotherapy are usually not required.[108] However, such nonspecific eruptions may worsen and may represent the early manifestation of a more characteristic skin disorder. It is, therefore, recommended that an exhaustive dermatologic evaluation be performed for any atypical, severe, persistent, recurrent, or poorly tolerated rash.

Sporadic cutaneous adverse reactions

A wide range of miscellaneous dermatologic reactions are listed in Supplemental Table II (available via Mendeley at https://doi.org/10.17632/8j6bjfc2m5.1). Four cases of alopecia areata were reported.[109,110] In 1 patient, the alopecia progressed to alopecia universalis.[110] Regrowth of hair occurred in 3 patients treated with topical corticosteroids, and immunotherapy could be continued.[109,110] Bousquet et al[111] described 6 cases of papulopustular rosacea. In all cases, topical metronidazole led to significant improvement. Three patients developed leukocytoclastic vasculitis after treatment with anti—PD-1. All were treated with a combination of prednisolone and hydroxychloroquine with complete clinical remission in a few days.[112] Dermatomyositis occurred in 2 patients treated with nivolumab, which was subsequently discontinued. Both patients were treated with systemic prednisolone,[113,114] and 1 of them was further treated with intravenous immunoglobulins.[114] Three patients developed scleroderma after anti—PD-1 treatment, which was discontinued in all cases.[115,116] The patients were treated with systemic prednisolone combined with either hydroxychloroquine,[115] mycophenolate mofetil,[116] or intravenous immunoglobulin.[115] Finally, single cases of eosinophilic fasciitis,[117] palmoplantar pustulosis,[118] intracorneal pustular drug eruption,[119] erythema nodosum-like panniculitis,[120] immune reaction in melanocytic nevi,[121] nevus regression,[8] eruptive keratoachantomas,[27] radiation recall dermatitis,[122] plantar erythema, skin flushing,[123] erythema nodosum,[89] oral erosions, urticarial plaques, 10-finger paronychia,[21] Merkel cell carcinoma,[124] mucositis,[125] inflamed seborrheic keratoses,[126] paraneoplastic pemphigus-like reaction, Grover-like rash,[127] sarcoidal form of tumoral melanosis,[128] mucous membrane pemphigoid,[129] lipodystrophy,[130] and squamous cell carcinoma[131] were reported.

CONCLUSION

Cutaneous adverse reactions to anti—PD-1 treatment are common and range from mild to life threatening. They may present as nonspecific rashes to life-threatening dermatoses and may result in significant morbidity, sometimes requiring cessation of therapy. Time to onset of adverse cutaneous reactions varies from days to several months and may even occur long after cessation of immunotherapy. Existing management recommendations for skin toxicity from anti—PD-1 treatment involves topical emollients, antihistamines, and topical and systemic corticosteroids.[132,133] Early referral for dermatologic evaluation is recommended to target the treatment of adverse cutaneous reactions as early as possible, thus reducing morbidity and increasing the chance of continuing anti—PD-1 treatment without disruption. Importantly, treatment of cutaneous adverse reactions does not interfere with the antitumor effect of PD-1.

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