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HOSPITAL- BASED DERMATOLOGY (D KROSHINSKY, SECTION EDITOR)

Dermatologic Reactions to Novel Immune Checkpoint Inhibitors

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Abstract

Purpose of Review Dermatologic toxicities secondary to immune checkpoint inhibitors are prevalent and can be difficult to manage in the setting of underlying malignancy. This review summarizes the mucocutaneous adverse events associated with these agents and provides management options for varying degrees of presentation.

Recent Findings Pruritus and rash are the most common dermatologic findings, but other manifestations such as vitiligo, lichenoid reactions, bullous pemphigoid, alopecia, and mucosal lesions have been observed. More recently, novel cases of rarer side effects, such as immunotherapy-induced scleroderma, fasciitis, and dermatomyositis, have been reported. Management often involves topical corticosteroids while more severe reactions require systemic treatment or discontinuation of immunotherapy.

Summary Immune checkpoint inhibitors comprise a newer class of agents used in the treatment of various cancers. There is an increasing number and variety of cutaneous toxicities being reported as more of these immunotherapies are being used. Early diagnosis and treatment are crucial in effective management of these skin toxicities.

Keywords Immune checkpoint inhibitors · Immunotherapy · Cutaneous toxicities · Management

Introduction

Immune checkpoint inhibitors are currently being used in the treatment of various types of cancer and can be considered one of the greatest advances in oncologic care in recent years. These agents include monoclonal antibodies that target cytotoxic T lymphocyte–associated antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed death ligand 1 (PD-L1). They interrupt the negative regulation of T cell responses by interacting with receptors on T cells (CTLA-4 receptors), lymphocytes (PD-1 receptors), antigen-presenting cells (anti-PD-L1), or tumor cells (anti-PD-L1) which allows for the activation of antitumor T cells and subsequent destruction of tumor cells [1•]. Ipilimumab is the only CTLA-4 inhibitor approved by the US Food and Drug Administration for the treatment of unresectable or metastatic melanoma [2]. The PD-1 inhibitors include nivolumab and pembrolizumab. In addition to treatment of metastatic melanoma, PD-1 inhibition has been recently approved for the treatment of non-small cell lung cancer (NSCLC), renal cell carcinoma, squamous cell carcinoma of the head and neck, classic Hodgkin lymphoma, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma (nivolumab), and gastric cancer (pembrolizumab) [3, 4]. The PD-L1 inhibitors include atezolizumab, avelumab, and durvalumab. These three agents have been approved for the treatment of locally advanced or metastatic urothelial carcinoma. Atezolizumab and durvalumab are also used for treatment of NSCLC and avelumab is also used for merkel cell carcinoma [5–7].

Dermatologic toxicity is the most common immune-related adverse event (irAE) associated with the immune checkpoint inhibitors. These reactions commonly include pruritus, rash/dermatitis, vitiligo, photosensitivity, urticaria, and bullous pemphigoid. The incidence of more common cutaneous adverse events varies depending on the inhibitor used (Table 1). Overall, the incidence of dermatologic toxicity (all grades) is 47–68% and 30–40% with CTLA-4 inhibitor monotherapy and PD-1/PD-L1 inhibitor monotherapy, respectively [10••, 15••]. According to a recent review, incidence of cutaneous toxicity increases to 62% with combination anti-CTLA-4/anti-PD-1

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Table 1 Management of common cutaneous adverse events with immune checkpoint inhibitors

Cutaneous adverse event	Incidence [1•, 8, 9••]	Management [10••, 11–13]
Rash	Nivolumab	Grade 1
	All grades: 14.3% (range, 3.8–41.5%)	- Continue immunotherapy
		- Moderate-potency topical steroids
	High grade: 1.2% (range, 0–10%)	- Oral antihistamine*
		- Topical emollient
	Pembrolizumab	Grade 2
	All grades: 16.7% (range, 0–18%)	- Consider holding immunotherapy
	High grade: 1.7% (range, 0–4.5%)	- High-potency topical steroids and/or prednisone 0.5–1 mg/kg/day with slow taper (typically 4–6 weeks)
	Ipilimumab [14]	- Oral antihistamine*
	All grades: 24.3%** (range, 21.4–27.6%)	- Topical emollient
		Grades 3 and 4
	High grade: 2.4% (range, 1.1–5.1%)	- Hold immunotherapy
		- High-potency topical steroids
	Atezolizumab [15••]	- Prednisone 0.5–1 mg/kg/day (increase dose if no improvement) with slow taper (typically 4–6 weeks)
	All grades: 15%	
	High grade: < 1%	
	**Ipilimumab-induced rash observed in up to 50% of patients with melanoma [16]	- Urgent dermatology consultation
Pruritus	Nivolumab	Grade 1
	All grades: 13.2% (range, 2.3–31.7%)	- Continue immunotherapy
	Pembrolizumab	- Moderate-potency topical steroids
	All grades: 20.2% (range, 10–25.8%)	- Cream/ointment-based emollients
		- Topical anti-pruritic agents, such as pramoxine
	Ipilimumab [17]	Grade 2
	All grades: 30.7% (range, 15.9–51.0%)	- Consider holding immunotherapy until grade 1 or less
	High grade: 1.0% (range, 0.3–3.9%)	- High-potency topical steroids
	Atezolizumab [15••]	- Oral antihistamines*
	All grades: 12–14%	- Dermatology consultation
	High grade: < 1%	Grades 3 and 4
	Durvalumab [15••]	- Hold immunotherapy
	All grades: 3–4%	- Prednisone/methylprednisolone 0.5–1 mg/kg/day with slow taper (typically 4–6 weeks)
		- GABA agonists+
		- Consider aprepitant++
		- Consider omalizumab
		- Urgent dermatology consultation
Vitiligo	Nivolumab	- Strict sun protection (broad spectrum, SPF 30+)
	All grades: 7.5% (range, 2.4–10.7%)	- Can consider topical corticosteroids
	High grade: 0.4%	- Consider phototherapy
	Pembrolizumab	
	All grades: 8.3% (range, 4.5–9%)	
	High grade: 1.1%	
	Ipilimumab [18]	
	All grades: 4–11%	

* Cetirizine/loratadine 10 mg daily (non-sedating); hydroxyzine 10–25 mg QID, or at bedtime

+ Gabapentin or pregabalin 100–300 mg TID

++ Aprepitant 80 mg QD × 3–5 days or 120 mg/80 mg/80 mg

inhibitor therapy [19••]. In addition to skin, irAEs may involve multiple other organ systems as well, namely the endocrine (hypothyroidism, hyperthyroidism, hypophysitis, thyroiditis, adrenal insufficiency), gastrointestinal (diarrhea, colitis, pancreatitis, increased AST/ALT/bilirubin), respiratory (pneumonitis, lung infiltration, interstitial lung disease), and urinary systems (increased creatinine, nephritis, renal failure) [20].

The present review describes the cutaneous adverse events associated with these agents, highlighting recent interesting new reports, and management options for varying degrees of presentation.

Rash

A rash is the most common cutaneous adverse event seen with immune checkpoint inhibitors. These reactions can range from a mild morbilliform or maculopapular eruption which is often self-limited and manageable to the most severe reactions of Stevens-Johnson syndrome or toxic epidermal necrolysis requiring treatment with intravenous corticosteroids or immunoglobulin therapy. Various clinical and histologic types of rash have been described, including maculopapular eruptions, eczematous dermatitis, acneiform eruptions, and other forms of dermatitis (i.e., lichenoid, psoriasiform, granulomatous) [8].

Maculopapular Rash

The non-specific morbilliform rash presents with erythematous macules and papules coalescing into blanchable patches and thin plaques that occur on the upper trunk and spread peripherally to the extremities [14]. The head, palms, and soles are often spared. Lesions can be pruritic, but patients are often asymptomatic. The appearance of a rash occurs early during treatment, typically in the first 3–6 weeks. Onset can occur sooner at 2 weeks with anti-CTLA-4/anti-PD-1 combination therapy [8, 21]. In the setting of monotherapy, this type of morbilliform eruption occurs more commonly with anti-CTLA-4 therapy than with anti-PD-1 or anti-PD-L1 therapy.

Management of a maculopapular rash depends on severity of symptoms and the total body surface area (BSA) affected. The severity is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0) published by the National Cancer Institute. According to the most recently published criteria, grade I eruptions include macules/papules covering < 10% BSA which may or may not be associated with pruritus or tenderness. Grade II eruptions include macules/papules covering 10–30% BSA with or without symptoms, limiting instrumental ADLs or rash covering > 30% BSA with or without mild symptoms. Grade III eruptions include macules/papules covering > 30% BSA with moderate or severe symptoms that limit self-care ADLs [22].

There have been several organizations, including the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the Society for Immunotherapy of Cancer (SITC), which have recently published new sets of comprehensive guidelines for the management of immunotherapy-related toxicities. To summarize, patients undergo an initial assessment with their provider which includes a history and physical, total body skin exam, and skin biopsy when warranted. After initial grading, grades I and II eruptions typically involve combination therapy with moderate- to high-potency topical corticosteroids, oral antihistamines, and topical emollients. Immunotherapy can be continued in most patients. Grades III and IV eruptions involve holding immunotherapy and initiation of high-potency topical corticosteroids [15••]. Additionally, initiation of systemic steroids at the equivalent of prednisone 0.5–1 mg/kg/day is warranted and used until rash is improved to grade $\leq$ I. It is recommended that systemic steroids are slowly tapered over 4–6 weeks to ensure resolution and to prevent rebound flare of rash [15••]. Resumption of immunotherapy can be considered upon resolution to grade I or less with careful monitoring. If symptoms recur, permanent discontinuation of immunotherapy is recommended [11]. In general, grade IV toxicities warrant permanent discontinuation of immunotherapy.

Eczematous Eruption

Eczematous eruptions are seen with both CTLA-4 and PD-1 inhibitors and clinically present with pruritic, ill-defined, erythematous, and scaly papules and plaques, often with visible excoriations (Fig. 1a). One review noted onset of eczema within 10.3 months of anti-PD-1 therapy [18]. Histology reveals spongiosis with varying degrees of infiltration with lymphocytes, neutrophils, and eosinophils. Lesions are often distributed along the trunk and extremities. Diffuse presentation can include the face, scalp, axilla, and genital areas. Grade I includes asymptomatic or mild symptoms (i.e., pruritus), grade II includes moderate symptoms often requiring topical or oral treatment, and grade III includes severe symptoms but not immediately life-threatening [22]. Like the maculopapular rash, management is dictated by grade. Treatment consists of mild- to high-potency topical corticosteroids with low- to mild-potency topical steroids recommended for use on the face, axilla, and groin. Oral antihistamines are used as supplemental therapy and escalation to oral corticosteroids may be warranted if symptoms persist with topical therapy [21, 23•].

Lichenoid Dermatitis

Lichenoid reactions are often seen with PD-1 and PD-L1 inhibition. According to a recent review, median time to onset is 88 days (range, 1–266 days) [24]. Lesions appear as flat-

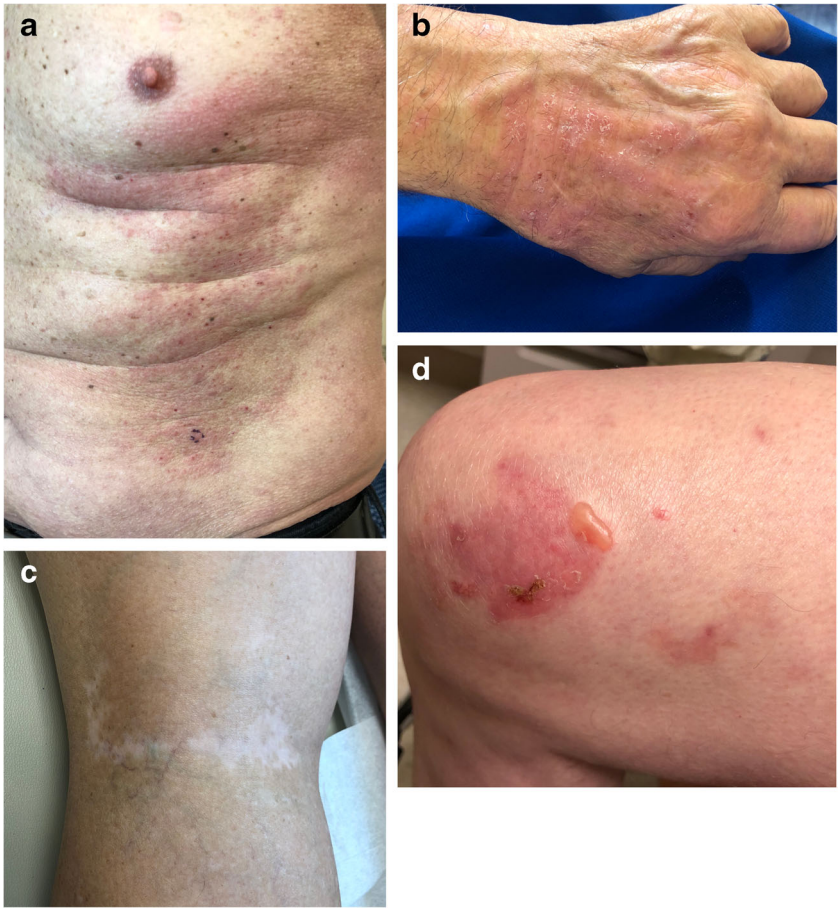

Fig. 1 **a** Eczematous pink scaly papules coalescent into ill-defined plaques in a patient with metastatic basal cell carcinoma on treatment with pembrolizumab. **b** Lichenoid pink scaly papules forming a plaque on the dorsal hand in a patient with metastatic renal cell carcinoma on treatment with combination ipilimumab and nivolumab. **c** Depigmented patches consistent with vitiligo koebnerizing in the crease of the popliteal fossa in a patient with metastatic melanoma on treatment with nivolumab. **d** Tense bulla overlying a pink erythematous patch with skin biopsy and serologies confirming bullous pemphigoid in a patient with metastatic urothelial cell bladder carcinoma on treatment with atezolizumab

topped, erythematous or violaceous, and pruritic papules and plaques that may coalesce over the trunk and extremities. Histology reveals a dense, band-like lymphocytic infiltrate along the dermal-epidermal junction, a vacuolar interface, and coexisting spongiosis. These eruptions may present as multiple, discrete or confluent lesions in a localized, generalized, inverse, palmoplantar, or mucosal (i.e., oral or genital) distribution (Fig. 1b). The number of lesions can range from tens to hundreds. Lichenoid oral lesions can involve the tongue, buccal mucosa, lips, and gingivae [21] and can occur in the absence of cutaneous lesions. One analysis of 20 patients who developed lichenoid dermatitis secondary to PD-1 or PD-L1 inhibitors revealed that 80% of the patients were concurrently taking medications that have been previously reported to cause lichenoid drug eruptions, raising the question of whether the lichenoid eruption was due specifically to the PD-1 or PD-L1 inhibitors versus being an unmasked immune response to a medication that was previously tolerated [25]. The mainstay of treatment for lichenoid dermatitis is topical corticosteroids, usually with good response. Withholding immunotherapy or initiation of systemic steroids may be considered in cases where symptoms are associated with severe pruritus or pain, or if symptoms persist despite potent topical corticosteroids. In cases where tapering systemic steroids lead to recurrence of dermatitis and/or pruritus, other treatment modalities can be considered. The author (JNC) has successfully treated a patient with pembrolizumab-induced lichenoid dermatitis and pruritus with thrice weekly narrowband ultraviolet B (NBUVB) phototherapy for 5–6 months. The patient initially had a widespread dermatitis, requiring high-dose oral prednisone, and upon two attempts of prednisone discontinuation, the dermatitis and pruritus became recurrent. With the use of NBUVB, the prednisone was successfully tapered to 5 mg daily and after 4 months, the prednisone was discontinued completely with no recurrence of dermatitis or pruritus. The patient has continued treatment with pembrolizumab for 12 more months with no recurrence yet of symptoms (case report submitted).

In a recent case series of 20 patients on treatment with PD-1 or PD-L1 inhibitors, lichenoid dermatitis or spongiotic dermatitis was associated with significantly longer progression-free survival and overall survival compared to controls [26].

Life-Threatening Skin Reactions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe and potentially fatal cutaneous adverse events that are characterized by tissue necrosis and epidermal detachment. Thought to be a hypersensitivity

reaction affecting the skin and mucosal surfaces, initial management involves permanent cessation of the offending agent. In cases of TEN, subsequent inpatient evaluation and management are indicated, with possible administration of intravenous corticosteroids, cyclosporine, other agents, close monitoring, and supportive care [23•].

Although rare, cases of SJS/TEN have been reported with both CTLA-4 and PD-1/PD-L1 inhibitors [24], some resulting in death [27, 28]. Interestingly, a report of two cases of pembrolizumab-induced SJS described two patients who achieved resolution of skin and mucosal lesions with cyclosporine [29]. A case of TEN in a patient with stage IV melanoma initially treated with ipilimumab and nivolumab has been reported [27]. In this case, a morbilliform eruption occurred after the first cycle of ipilimumab and nivolumab and slowly progressed for 3 months prior to admission. Ipilimumab was discontinued, but nivolumab was continued for two more cycles with a short course of systemic steroids after each infusion with some improvement. After the third cycle of nivolumab, treatment was held due to worsening of the eruption, and prednisone 1 mg/kg daily was initiated. A skin biopsy showed mild-interface dermatitis with rare necrotic keratinocytes and PD-L1 staining was positive in a few scattered keratinocytes with weak expression along the epidermis. The eruption continued to progress, and the patient was hospitalized with desquamating erythematous plaques involving 90% of her BSA including her buccal mucosa and erosions of her labia. A repeat skin biopsy showed markedly increased PD-L1 expression in the epidermis. Despite treatment with infliximab, high-dose steroids, and three doses of intravenous immunoglobulin, the patient expired on hospital day 6 [27]. The case ultimately highlights the ability of PD-1 antibodies to induce TEN without the classic clinical morphology or time course of the disease, as the eruption slowly progressed to TEN after 3 months. Morbilliform eruptions should be improved to grade I or less before immunotherapy is restarted, and any clinical suspicion for SJS/TEN should warrant immediate and permanent cessation of potential offending agents.

Pruritus

Pruritus is one of the most common cutaneous adverse events experienced by patients treated with immune checkpoint inhibitors. For ipilimumab, all grade incidence is 30.7% [17]. For the PD-1 inhibitors, nivolumab and pembrolizumab, all grade incidence is 13.2% and 20.2%, respectively [1•]. Pruritus can present with or without a rash and patients may have normal-appearing skin or skin changes (i.e., erosions, ulcerations, nodules) secondary to pruritus [23•].

Management begins with a total body skin exam and assessment of personal history of inflammatory dermatologic diseases. Grade I includes mild symptoms with localized distribution. Grade II includes intermittent, intense symptoms with skin changes or widespread distribution that limits instrumental ADLs. Grades III and IV are considered the most severe with constant, intense symptoms with skin changes or widespread distribution that limits self-care ADLs or interferes with sleep [11]. The cornerstone of treatment for grades I and II pruritus is high-potency topical corticosteroids with oral antihistamines and consideration of holding immunotherapy until pruritus is improved to grade $\leq$ I. For grades III and IV pruritus, immunotherapy should be held and treatment with systemic steroids (prednisone or methylprednisolone 0.5–1 mg/kg/day) can be initiated. Other agents can also be used, including oral doxepin and GABA agonists (gabapentin, pregabalin). Omalizumab may be considered in patients with increased serum IgE levels. Aprepitant, an oral neurokinin-1 receptor (NK-1R) antagonist, may also be considered as reported in a case for refractory nivolumab-induced pruritus [30]. Dosing for aprepitant that has been described includes 80 mg daily for 3–5 days or a 3-day course of 120 mg, 80 mg, and 80 mg. Our patients have also benefitted from general dry skin care recommendations, including use of alcohol-free emollients, moisturizing cleansers, cool compresses, oatmeal baths, and avoidance of fragrances.

Vitiligo

Vitiligo presents as depigmented well-demarcated macules coalescing into patches that often develop after several months of treatment (Fig. 1c). It is often seen in patients treated with anti-PD-1 agents for metastatic melanoma [31, 32]. Interestingly, vitiligo has also been reported in patients with a nonmelanoma malignancy such as NSCLC [33] and acute myeloid leukemia [34] while on treatment with nivolumab. Histology shows loss of melanocytes at the dermal-epidermal junction. Patients are often asymptomatic, but presentation may be preceded by erythema or pruritus. It has been proposed by recent studies that treatment with PD-1 inhibitors may be associated with clinical benefit and a more favorable prognosis [35, 36].

A case series of eight patients who presented with vitiligo-like lesions while on anti-PD-1 therapy were compared to 30 vitiligo controls [37]. These lesions were characterized by flecked depigmented macules occurring in photoexposed areas without Koebner phenomenon. Furthermore, these patients did not report a personal or family history of autoimmune disease. Analysis of blood and skin samples revealed increased CXC motif ligand 10 levels in the serum, skin infiltration of CD8+ T cells expressing CXC motif receptor 3, and elevated levels of interferon gamma and tumor necrosis factor alpha. Microphthalmia-associated transcription factor (MITF), which is involved in the survival of melanocytes after

exposure to ultraviolet light, may be associated with the development of vitiligo-like lesions. PD-1 inhibition may activate T cells that target MITF-associated antigens resulting in the destruction of normal melanocytes and subsequent development of vitiligo-like lesions [38].

In addition to vitiligo, cases of hypopigmentation have been reported. One case reported the fading or disappearance of solar lentigines, seborrheic keratoses, melanocytic nevi, and poliosis of the eyebrows, eyelashes, scalp, and body hair of a patient with metastatic melanoma treated with pembrolizumab [39]. Interestingly, a recent case of immunotherapy-induced leukoderma presenting as halo nevi was observed in a patient with stage IV NSCLC treated with carboplatin and paclitaxel therapy with the PD-L1 inhibitor, atezolizumab [40]. Treatment of spontaneously occurring vitiligo often involves high-potency topical corticosteroids and light therapy to affected areas. One case of nivolumab-induced vitiligo in a patient with metastatic melanoma was treated successfully with NBUVB light therapy [41]. Although a personal history of melanoma confers an increased risk of recurrence, there is a paucity of data to suggest NBUVB light therapy is associated with an increased risk of melanoma or would increase the risk of recurrence in patients with prior melanoma treated with immune checkpoint inhibitors. With the variability seen in patients and their corresponding risk factors for melanoma or nonmelanoma skin cancers, it may fall on clinical judgment and patient preference to determine whether UV light is a viable option for repigmentation specifically in these patients. Furthermore, because repigmentation often takes 12 to 24 months or longer, monitoring with skin exams every 3 to 6 months may be warranted.

Autoimmune Disorders

Psoriasis

In addition to a skin rash or pruritus, psoriasis and psoriasiform eruptions have been induced by anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibodies. Lesions can appear de novo or occur as an exacerbation in patients with a personal history or significant family history of psoriasis. Often characterized as well-demarcated, erythematous, and pruritic plaques with fine scale in a focal or diffuse distribution, patients can present with other variants including guttate, pustular, inverse, scalp, palmoplantar, and nail psoriasis [8, 23•, 42]. One study of 21 patients noted a mean time to onset between anti-PD-1 initiation and psoriasis flare of 50 days with onset occurring on average within 90 days for de novo psoriasis and 33 days in patients with pre-existing psoriasis [43]. In this study, 95% of patients developed plaque psoriasis and 91% were adequately controlled with treatment, which consisted mostly of topical corticosteroids. Common histologic findings include epidermal acanthosis, hyperkeratosis with parakeratosis, and variable presence of T lymphocytes, neutrophils, and eosinophils.

A recent report by Voudouri et al. [42] highlighted five patients who presented with psoriasis exacerbations while being treated with anti-PD-1 (pembrolizumab, nivolumab) or anti-PD-L1 (durvalumab) immunotherapy. Interestingly, the most severe flares were seen in the two patients on durvalumab. Topical steroids and NBUVB phototherapy were used as treatment with significant improvement of skin lesions, although one patient on durvalumab was refractory to NBUVB phototherapy and achieved psoriasis remission after withdrawal of anti-PD-L1 immunotherapy.

Psoriasis and psoriasiform eruptions can be successfully managed with topical corticosteroids. However, the second-line treatment may include NBUVB phototherapy, oral acitretin, oral apremilast, or systemic steroids [8, 23•].

Bullous Pemphigoid

Bullous pemphigoid (BP) is an antibody-mediated disorder that can present in patients treated with immune checkpoint inhibitors, especially PD-1 inhibitors and to lesser extent PD-L1 inhibitors [44–47]. Patients develop pruritic, tense bullae mainly over the trunk and extremities (Fig. 1d). The mean onset has been reported to be 190 days (range, 21–630 days) [24]. Histology shows subepidermal vesicular dermatitis with eosinophils and the classic linear IgG deposition at the dermal-epidermal junction on direct immunofluorescence [18•, 23•].

To date, at least 21 cases of BP induced by anti-PD-1 or anti-PD-L1 therapy, including pembrolizumab, nivolumab, durvalumab, and atezolizumab, have been reported [48]. Pruritus is a prominent feature, either preceding or concurrent with the onset of skin lesions. The mean time to development of pruritus is 17 weeks, and the median time to development of bullae is 24 weeks, although a small subset of patients does not develop bullae until 1–1.5 years after initiation of immunotherapy. The mean age of patients is 71 years. Oral mucosa can be involved in approximately 30% of patients [48]. Development of BP required discontinuation of immunotherapy in 76% of cases, and 37% of patients had cancer progression or death shortly after BP diagnosis and checkpoint inhibitor discontinuation.

Initial management of checkpoint inhibitor-induced BP involves withholding immunotherapy and initiation of high-potency topical corticosteroids. Escalation to systemic steroids is warranted with higher grade presentations. Other reported successful treatments include a combination of doxycycline and niacinamide, with or without oral and topical corticosteroids, rituximab, and omalizumab [48]. If bullae cover > 30% BSA, systemic steroids can be initiated until symptoms improve to grade I or less with a gradual taper of 4–6 weeks [11]. Permanent discontinuation of immunotherapy is advised

if symptoms persist after a trial of systemic steroids or other systemic treatment, symptoms limit self-care ADLs, or if severe grade lesions recur after immunotherapy is resumed [11]. It may take months for symptoms to resolve even after cessation of immunotherapy. The etiology of checkpoint inhibitor-induced BP is unknown, but it is possible that PD-1 or PD-L1 blockade may lead to an increase in autoantibody production against the hemidesmosomal protein BP180 through both a T cell and B cell mediated process. To date, there have been no reports of BP induced by CTLA-4 inhibitors, thus BP may be a class effect of PD-1/PD-L1 inhibitor therapy.

Alopecia

Variants of alopecia (areata and universalis) have been reported in patients receiving anti-CTLA-4 and anti-PD-1 inhibitors with an incidence of 1–2%. A case series noted alopecia in a patient with metastatic renal cell carcinoma treated with a PD-L1 inhibitor and a VEGF inhibitor. Alopecia developed after ten cycles and regrowth with poliosis was observed after treatment with intralesional triamcinolone and clobetasol spray. Notably, patients developed alopecia after several cycles of immunotherapy and poliosis was often seen in previous alopecic areas [49]. Treatment with steroids may be beneficial and providers must be aware of the impact alopecia may have on patients' quality of life.

Oral Mucosa

In a recent review, use of anti-PD-1/PD-L1 agents has been associated with non-specific stomatitis and oral mucosal inflammation in some cases. Grades I and II xerostomia was reported in 6% and 4–7.2% of patients with melanoma treated with nivolumab and pembrolizumab, respectively [50•, 51]. A case of sialadenitis was seen in a patient after 4 months of nivolumab therapy for lung adenocarcinoma. A course of corticosteroids and cessation of nivolumab led to complete resolution [52]. Cases of oral lichenoid reactions with nivolumab and pembrolizumab have also been reported [25, 53]. Lesions often appear as reticulated or linear white streaks or as papules with ulcerative, atrophic, or erythematous features. Treatment involves ongoing oral care with topical steroids and/or lidocaine for pain relief. In severe cases, tapered courses of systemic corticosteroids and temporary cessation of immunotherapy may be necessary.

Other Reported Cutaneous Reactions

Table 2 highlights reported cutaneous toxicities due to CTLA-4 and PD-1/PD-L1 inhibitors. Here, we summarize several interesting findings that have been reported within the last year.

Table 2 Other reported cutaneous reactions of immune checkpoint inhibitors

- Acneiform eruption
- Actinic keratosis
- Acute generalized exanthematous pustulosis (AGEP)
- Annular granuloma
- Alopecia areata, universalis
- Basal cell carcinoma
- Dermal hypersensitivity reaction (DHR)
- Dermatitis herpetiformis
- Dermatomyositis
- Drug rash with eosinophilia and systemic symptoms (DRESS)
- Eruptive keratoacanthoma
- Erythema
- Erythema nodosum–like panniculitis
- Exfoliative reaction
- Grover's disease
- Hair pigmentation changes
- Hyperhidrosis
- Hypopigmentation
- Nail changes
- Necrotizing vasculitis
- Palmar-plantar erythrodysesthesia
- Papulopustular rosacea
- Peritumoral inflammatory cellulitis
- Photosensitivity reaction
- Pityriasis lichenoides-like reaction
- Prurigo nodularis
- Pyoderma gangrenosum-like ulcerations
- Radiation-associated dermatitis
- Regression of melanocytic nevi
- Sarcoidosis
- Sclerodermoid reaction
- Seborrheic keratosis
- Sjögren's syndrome
- Squamous cell carcinoma
- Sweet's syndrome
- Tumoral melanosis
- Urticaria
- Xerosis

Adapted from Sibaud [8] and Curry et al. [24]

Erythema Multiforme

Utsunomiya et al. [54] reported a case of erythema multiforme (EM) major after sequential use of an anti-PD-1 inhibitor (nivolumab) and an anti-CTLA-4 inhibitor (ipilimumab) for treatment of melanoma. The patient underwent 12 cycles of

nivolumab due to multiple organ metastases, switched to ipilimumab after 42 days off nivolumab, and a week later experienced low-grade fevers and pancytopenia for which she was treated with an oral steroid taper, blood transfusion, G-CSF, and broad-spectrum antibiotics. After 2 days of the steroid taper, she experienced an eruption of erythematous papules and nodules over the trunk which spread to involve majority of her body. Pathology of biopsied lesions was consistent with EM major. Withdrawal of ipilimumab and broad-spectrum antibiotics and the addition of IV methylprednisolone led to resolution of the eruption. It is well known that treatment with two immunotherapeutic agents increases the risk of cutaneous toxicity compared to either used as monotherapy. Interestingly, this case highlights the notion that the effects of one agent—in this case, nivolumab—even with a significant wash-out period may increase the risk of cutaneous toxicity when a second agent is added given the onset of the eruption occurred only 7 days after ipilimumab was initiated.

Sarcoidosis

Sarcoidosis or sarcoid-like granulomatous reactions [55] induced by immune checkpoint inhibitors such as ipilimumab have been previously reported especially in the treatment of melanoma. Cases of nivolumab-induced sarcoidosis with erythema nodosum as the presenting feature [56] and a recurrent cutaneous sarcoid-like reaction at prior pembrolizumab infusion sites [57] have been reported. Recent reports of patients with melanoma have posited that development of sarcoid-like lesions while on targeted immunotherapy may indicate therapeutic response [58]. Yatim et al. [59] describe a case of cutaneous and pulmonary sarcoidosis following pembrolizumab therapy for stage IV melanoma. Like metastatic melanoma, sarcoidosis can present with pulmonary lesions, hilar lymphadenopathy, and skin nodules. However, in this case, the additional finding of bilateral anterior uveitis responsive to local corticosteroids increased serum ACE level, and pathology revealing non-caseating granulomas clinched the diagnosis. Altogether, it is important to be aware that sarcoidosis is not uncommon in the context of anti-PD-1/PD-L1 or anti-CTLA-4 therapy, but careful attention must be paid to avoid misdiagnosis of malignant lesions given how similarly sarcoidosis and metastatic melanoma can present.

Hair Repigmentation

Curiously, in contrast to hypopigmentation, dark hair repigmentation has been observed as a side effect of anti-PD-1 and anti-PD-L1 therapy [60, 61]. In a series of 14 patients being treated for NSCLC, 13 patients developed a diffuse darkening of the hair and one patient developed black patches between white hairs while on treatment with nivolumab, pembrolizumab, or atezolizumab [60]. Repigmentation beginning at the occipital and temporal areas and progression to the frontal and parietal regions was observed. Thirteen of the 14 patients had a good clinical response to treatment, with at least stable disease, with an average of 20.5 treatment sessions. In an additional case report, a patient being treated for concurrent relapsed Hodgkin lymphoma and metastatic colorectal cancer with microsatellite instability with nivolumab developed hair repigmentation of his whole body although he had harbored white hair for the past 25 years [61]. It is hypothesized that PD-1/PD-L1 blockade and cytotoxic tumor destruction likely lead to a systemic pro-inflammatory state. Inflammatory mediators such as interferon gamma and the neuropeptide substance P are known to collapse MHC class I-related immune privilege, which could result in inflammation of the hair follicle, and thus induce pigmentation [62].

Scleroderma and Dermatomyositis

Recently, there have been reports of patients developing new-onset autoimmune conditions, including scleroderma and dermatomyositis (DM). Three male patients with metastatic melanoma being treated with pembrolizumab developed fatigue, edema of joints, and stiffness and skin thickening over the extremities [63, 64]. Two patients developed symptoms after 5 cycles and one patient developed symptoms after 13 cycles. Skin biopsies confirmed dermal sclerosis with a lymphocytic infiltrate.

There have been three cases of checkpoint inhibitor-induced DM, one case secondary to ipilimumab in a patient with metastatic melanoma, one case secondary to ipilimumab in a patient with metastatic small cell lung cancer, and another secondary to nivolumab in a patient with metastatic lung adenocarcinoma [65–67]. All three patients developed classic cutaneous hallmarks of DM, including heliotrope erythema and V-neck distribution of chest erythema. Two patients developed muscle weakness, while one patient did not. In one patient, symptoms resolved with systemic corticosteroids and then recurred only after re-administration of ipilimumab, confirming the etiology of the DM as drug-induced and not paraneoplastic [65].

Majority of patients with DM have elevated muscle enzymes (e.g., creatine kinase, aldolase) and inflammatory markers (e.g., C-reactive protein) but these levels can also be normal. Several autoantibodies have been associated with primary DM including anti-synthetase (e.g., anti-Jo-1), anti-Mi-2, anti-transcription intermediary factor-1-gamma (TIF1γ), and anti-nuclear matrix protein 2 (NXP2) antibodies [68]. However, these tests are not specific for DM as they may also be positive in patients with other inflammatory myopathies. In two of the previously mentioned cases where serologies were obtained, both patients were negative for anti-Jo-1 antibody [65, 67]. Antibody positivity with anti-TIF1-gamma or anti-NXP2 has been associated with an increased risk of malignancy in patients with DM [68], but

this was not tested in the reported cases associated with immunotherapy. Currently, distinguishing between primary or malignancy-induced DM and immune checkpoint inhibitor-induced DM is difficult. Aside from patient history and exam findings, further workup may include serologies, electromyography (EMG), skin/muscle biopsy, and imaging. With only a few cases of immune checkpoint inhibitor-induced DM reported, the role of serologies remains unclear and both EMG and pathologic results may be variable.

Squamous Neoplasms

Squamous cell carcinomas (SCCs) and eruptive keratoacanthomas (KAs) have been reported to arise secondary to anti-PD-1 therapy. In one study of 82 patients, 6% of patients developed cutaneous SCCs, occurring on the face, chest, and arms [69]. In a recent report of three patients, multiple eruptive KAs on the sun-exposed areas of extremities occurred at a median time of 13 months after pembrolizumab initiation [70]. On histologic examination, the lesions appeared consistent with KAs, showing multiloculated, crateriform, and keratin-filled lesions; however, there was also a lichenoid infiltrate in the underlying dermis of the KA lesions, composed of CD3+ T cells with scattered CD20+ B cells. Instead of excision, all the lesions were successfully treated with topical clobetasol ointment and intralesional triamcinolone with or without cryotherapy. This series emphasizes the likelihood that such KA-like squamous proliferations in the setting of checkpoint inhibitor therapy may be treated non-surgically and in a manner to target the associated inflammation rather than being aggressive with surgical therapy. Such treatments can include topical, intralesional, oral corticosteroids, cryotherapy, oral retinoids, and topical 5-fluorouracil. The occurrence of these SCC/KA-like growths in the setting of lichenoid toxicity may be analogous to reports of keratoacanthomatous proliferations arising in other forms of lichenoid dermatitis, such as verrucous lupus erythematosus or hypertrophic lichen planus. The pathogenesis may be closer related to a reactive proliferation similar to exuberant squamous metaplasia in the setting of a pro-inflammatory cytokine milieu (Tables 1 and 2) [12].

Conclusion

Immune checkpoint inhibitors represent a newer class of anticancer agents that show promising results in the treatment of various cancers. Dermatologic toxicities secondary to CTLA-4 and PD-1/PD-L1 inhibitors remain the most common immune-related adverse events among all organ systems. Rash, pruritus, and vitiligo are frequently observed. These cutaneous manifestations are often low grade and can be managed with topical therapy. Higher grade presentations require escalation to systemic therapy and possible discontinuation of immunotherapy. Rarer side effects have been reported and new reports continue to emerge daily. Clinicians must understand that maintaining the balance between continuing immunotherapy and managing these adverse effects is critical. Involvement of a multidisciplinary team including oncologists and dermatologists is essential for early diagnosis and management of these cutaneous toxicities.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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