Skin Reactions to Immune Checkpoint Inhibitors

11

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Abstract

Due to the novelty of immune checkpoint inhibitors, their cutaneous adverse events (AEs) have only been recently characterized. This, along with the substantial rate of cutaneous reactions, has left many clinicians without sufficient familiarity to diagnose and treat cutaneous AEs. Pruritus and rash are among the top five immune-related AEs reported in clinical trials for this class of therapy. Incidence varies between 35 and 50% for cutaneous AEs among the eight FDA-approved drugs. Although only 2% are reported as grade 3 or 4 events, the impact on quality of life can be significant for these patients and is best described and most severe in ipilimumab trials. Of ipilimumab patients, 43.5% have a cutaneous AE and, at our institution, 20% of them had a dose interruption as a result. This means potentially 9% of patients have dose interruption of ipilimumab because of their cutaneous AEs. In the following chapter, we review the categories of these drugs, common cutaneous effects, their grading, and management options.

Keywords

Immune checkpoint inhibitors · Dermatitis · Ipilimumab · Nivolumab Anti-PD-1 · Anti-CTLA-4 · Dermatitis · Rash · Immunotherapy · Pruritus

The novelty of immune checkpoint inhibitors has only recently led to the characterization of cutaneous adverse events (AEs). This, along with the substantial rate of cutaneous reactions, has left many clinicians insufficiently familiar with diagnosis and treatment. Pruritus and rash are among the top five immune-related AEs reported in clinical trials in this class of therapy. Incidence varies between 35 and 50% for cutaneous AEs among FDA-approved drugs. Although only 2% are reported as grade 3 or 4 events, the quality of life impact can be significant for these patients and is best described in ipilimumab trials. Of ipilimumab patients, 43.5% have a cutaneous AE and, at our institution, 20% of them had a dose interruption as a result. This means potentially 9% of patients have dose interruption of ipilimumab because of their cutaneous AEs [1]. In the following chapter, we review the categories of these drugs, common cutaneous effects, their grading, and management options.

In general, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade and the drugs that

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bind the programed death receptor-1 (PD-1) have similar reactions, although PD-1 receptor inhibitors are usually better tolerated than CTLA-4 inhibitors with fewer reported skin AEs (43.5% and 18%, respectively) [1]. Additionally, it appears that both the reactions tend to be delayed, with anti CTLA-4s causing a rash after about a month of therapy and anti PD-1s slightly later [1]. Programmed death-ligand 1 (PD-L1) inhibitors and a second-generation CTLA-4 inhibitors are now being used in clinical trials, and these drugs are increasingly being used in combination therapies; however, large population AE data is not yet available. Both of these drug classes appear to have the same milieu of cutaneous AEs as their first-generation counterparts, possibly with lower severity overall. Interestingly, skin toxicities have been associated with improved responses and paradoxically, if well managed, can be an indicator of a good prognosis [2–4].

Common Cutaneous Adverse Events Seen with Immune Checkpoint Inhibitors

This class of medication is not *immune* to the typical cutaneous drug reactions seen with other classes of medications. Histologically, these reactions present a spectrum with morbilliform drug eruptions on the mild end and Stevens Johnson's Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) on the severe end [5].

Morbilliform drug eruption (commonly identified as "maculopapular") clinically presents with erythematous macules and thin nonscaling papules coalescing into blanchable patches and thin plaques that start on the trunk and spread peripherally to the extremities. Histology shows a superficial perivascular infiltrate with variable vacuolar change, dyskeratosis, and eosinophils. Patients are usually asymptomatic and occasionally pruritic. If painful or if there is progression to vesicles, one should consider early erythema multiforme (EM) or SJS/TEN. EM presents with targetoid erythematous thin papules often involving the acral and mucosal skin. The papules can become centrally dusky and vesiculate. When the distribution is more diffuse and mucosal surfaces are involved, but body surface area (BSA) remains below 10%; this is SJS. When the BSA is greater than 30%, this is called TEN, which can rapidly progress. For morbilliform eruptions, topical steroids with drug continuation are often sufficient. For EM, depending on the severity, oral or IV steroids can be used with drug cessation. For SJS and TEN, drug cessation and supportive care are critical, possibly with the addition of intravenous steroids or intravenous immunoglobulin therapy.

Urticaria is also a common type I drug reaction that can be seen with immune checkpoint inhibitors. Histology demonstrates minimal epidermal change with an edematous papillary and superficial reticular dermis with an infiltrate of lymphocytes, eosinophils, and variable neutrophils. Onset is within days, and the erythematous pruritic wheals can usually be controlled with oral antihistamines and drug cessation. Biologic therapies, such as anti-IgE monoclonal antibodies, could also be considered.

Cutaneous Adverse Events Shared by Anti-CTLA-4 and Anti-PD-1 Therapies

"Rash" is one of the most commonly reported cutaneous AEs, second only to pruritus, and has an 11% incidence in trials for pembrolizumab and nivolumab and a 19% incidence in trials for ipilimumab. This nonspecific description encompasses a variety of inflammatory skin diseases, including psoriasiform, eczematous, lichenoid, and morbilliform drug eruptions. Compared to anti-CTLA-4 antibodies, the anti-PD-1 antibodies have a lower incidence of rash; however, the incidence of severe (grade 3 and 4) cutaneous AEs is the same (2.4% and 2.6%, respectively). Eczema, pruritus, and vitiligo are seen with both classes of immune checkpoint inhibitors [6–12].

It is important to distinguish between the inflammatory skin reactions as they have different treatment options for the more severe presentations. Although mild presentations may be treated with topical steroids, diffuse presentations

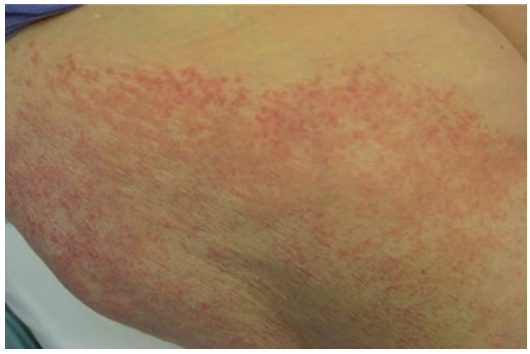

Fig. 11.1 Eczema, erythematous papules coalescing into plaques that are rough and have minimal scale

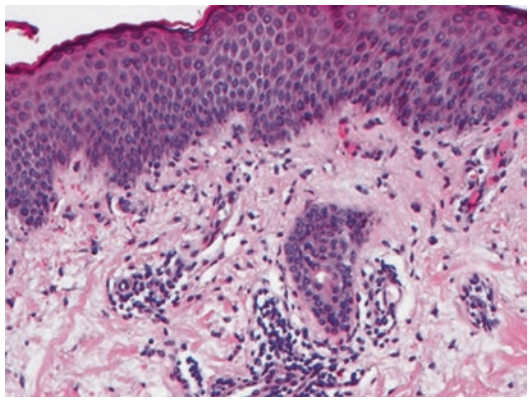

Fig. 11.2 Eczema, spongiotic dermatitis with dermal eosinophils

require systemic treatments, some of which are specific to the type of inflammatory reaction (Figs. 5.1 and 5.2).

Eczema appears as pruritic, ill-defined, edematous, and erythematous papules coalescing into plaques occasionally with vesicles in exuberant cases. As it evolves, the plaques are rough, erythematous, and have visible excoriation. Distribution is diffuse, affecting the trunk and extremities more than the face with a flexural predominance, as is typical with atopic dermatitis. Scalp and genital areas are often involved in diffuse presentations. Plaques are very pruritic with pain in areas of microfissures or superinfection. The histology shows prominent spongiosis and the variable presence of eosinophils [13]. Treatment consists of topical steroids, usually mid-strength creams, such as triamcinolone 0.1%, to begin with and graduating to super-potent formulations, such as clobetasol 0.05% cream. The face, axilla, and groin are usually treated with mild and low-potency steroids, such as hydrocortisone 2.5% or desonide 0.05% creams. Patients can be effectively controlled with a regimen of topical steroids involving twice daily application for flares and twice weekly application for maintenance. Supplementation with first-generation oral antihistamines, such as diphenhydr- amine or hydroxyzine, is a mainstay. In the author's experience, the addition of second-generation nonsedating antihistamines, such as cetirizine or loratadine, in the morning is also beneficial. In patients with grade 3 AEs, involving >30% of BSA, and refractory to topical therapies, the addition of oral steroids, such as prednisone at 1 mg/kg, is usually effective and can be slowly tapered. The slow taper is often effectively weaned with topical steroid maintenance.

Preliminary literature does not show a change in treatment efficacy with the use of oral steroids, making this the first choice systemic therapy in patients who are resistant to topical steroids [14, 15].

As the rash duration for severe grade cutaneous AEs can be prolonged, lasting months after therapy cessation, steroid-alternatives are needed. Biological therapy for atopic dermatitis targeting interleukin-4 receptor alpha subunit (IL-4Ra) is a potential treatment option for severe refractory eczema in patients requiring continuing therapy with immune checkpoint inhibitors.

For pruritus without rash, clinical presentation is variable. Most often patients have normal-appearing skin, although they can have skin changes secondary to manipulation masquerading as a primary rash. Geometric erosions and ulcerations, prurigo nodules, and linear erosions are secondary to pruritus. Prurigo nodules are ill-defined, discrete, erythematous, hyperpigmented acanthotic papules often with central erosion. Histology shows fibrosis and vertically oriented blood vessels in the superficial dermis with an overlying acanthotic epidermis. The first step in management is to eliminate a primary inflammatory condition. For primary pruritus, a stepwise approach depending on severity is best. For mild

cases, a first- generation antihistamine is oftentimes sufficient, with the added benefit of sedation that can help patients sleep when pruritus is usually most severe—right before bed. As the intensity increases, the addition of tricyclic antidepressant doxepin nightly and GABA agonists like gabapentin at increasing doses have been effectively used.

Vitiligo presents as depigmented well-demarcated macules coalescing into patches, occasionally preceded by erythema and pruritus, exclusively reported in melanoma patients (Fig. 11.3). Incidence is about 2% for anti-CTLA-4 and anti-PD-1 therapies [3]. Histology shows loss of melanocytes at the dermal–epidermal junction (Fig. 11.4). Patients are usually asymptomatic, but can have occasional preceding pruritus. Treatment for vitiligo includes a combination of topical steroids and ultraviolet (UV) light therapy; however, in melanoma patients with this drug-induced side effect, treatment is not usually undertaken because of the risk of further skin cancers with increased UV exposure.

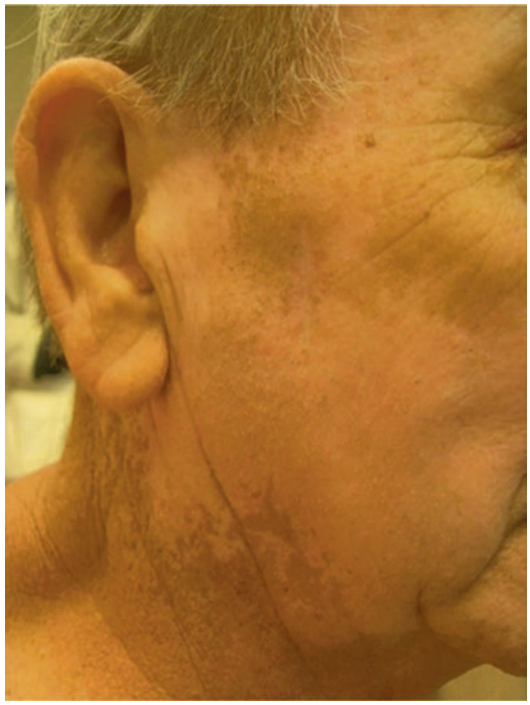

Fig. 11.3 Vitiligo, depigmented patches of head and neck

The unmasking of rheumatologic disease, with or without cutaneous involvement, can be seen as well. Although less common than inflammatory rashes, these AEs can be seen with both classes of checkpoint inhibitors and include large-vessel vasculitis, dermatomyositis (with or without muscle involvement), lupus erythematosus, and Sjogren's disease. [16, 17] It is unclear if these AEs are being unmasked or induced by the drug. In cases such as dermatomyositis, which is also a paraneoplastic disease, careful evaluation of the time course is necessary to determine the most likely correlation. [18]

Common Cutaneous Adverse Events for Anti-CTLA-4

The most commonly reported adverse events in patients receiving ipilimumab are "rash" from one quarter to more than one half of patients and

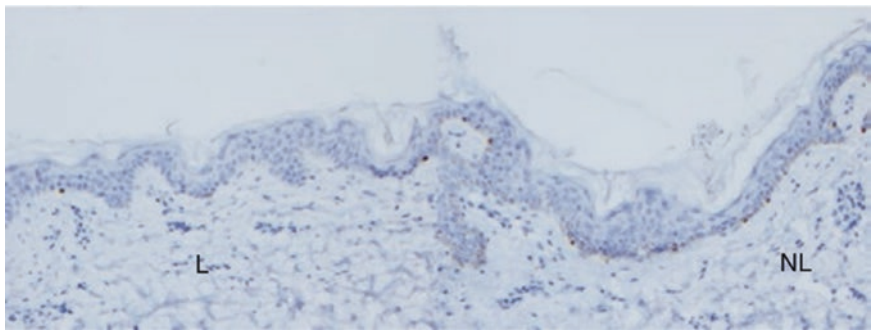

Fig. 11.4 Vitiligo-MART1 immunostain in lesional skin (L) showing decreased melanocytes at the dermal–epidermal junction compared to MART1 immunostain of nonlesional (NL) skin

pruritus from a quarter to one-third [19]. The type of rash varied from mild eczema to toxic epidermal necrolysis [20], with the majority experiencing a more traditional morbilliform drug eruption or an eczematous atopic dermatitis-like eruption [19]. The onset of rash has been reported to appear at about 3 weeks and then usually resolves around 2.5 months [19]. Although in our institutional review, complete resolution was usually not obtained for most patients until drug cessation (unpublished data Patel). The most common CAEs seen with this class of medication are discussed above. Less frequent eruptions include acneiform eruption [12] and granulomatous dermatitis [21].

Its mechanism of action through the activation of T cells by the prevention of T cell blockade leads to an upregulation of the body's immune system and therefore its antitumor activity as described elsewhere in this text. It appears that the cutaneous AE is independent of dosing with those on 10 mg/kg developing similar CAEs as those on 3 mg/kg. Fortunately, high-grade rash as defined by the common terminology criteria as grade 3 or higher was substantially lower at 2.4% [22].

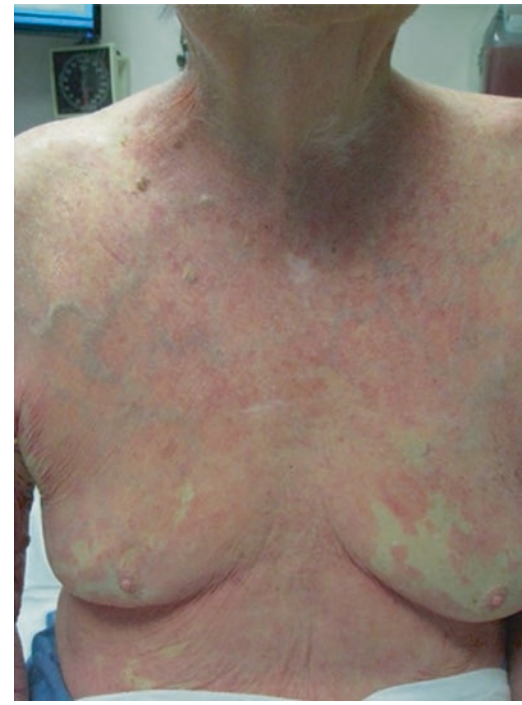

Fig. 11.5 Psoriasiform dermatitis, erythematous well-demarcated plaques with fine adherent scale

CAE in Anti-PD-1

In addition to the shared inflammatory skin reactions discussed earlier, psoriasis [23, 24], lichenoid dermatitis [25] and bullous pemphigoid have been induced by anti-PD-1 antibodies [26, 27]. More recently, eruptive keratoacanthomas has been reported in patients receiving anti-PD-1 therapy [28] (Figs. 5.5 and 5.6).

Psoriasiform dermatitis can appear clinically as classic psoriasis vulgaris with well-demarcated erythematous slightly indurated plaques with adherent fine scale and areas of sparing in a focal to diffuse distribution. It is often worse on extremities than trunk and has a predilection for the scalp. It can also present in inverse distribution with prominence in intertriginous areas [24] or in the pustular variant [29]. It can be pruritic or painful, induce microfissures, and contribute to edema of extremities. Histology shows a spongiotic psoriasiform dermatitis with subcorneal pustules with variable eosinophils. The authors have found psoriasis to be more resistant to treatment than eczema, making distinguishing between the two a prognostic indicator of rash outcome. Treatment should start with topical steroids with antihistamines, if indicated. Escalation of treatment includes oral acitretin, oral apremilast, ultraviolet-B (UV-B) therapy, or oral steroids. Biological medications such as interleukin-17 (IL-17) inhibitors are a potential therapy for refractory cases and have been used anecdotally with success [29].

Lichenoid dermatitis is a pruritic papular eruption mimicking lichen planus. Treatment should start with topical steroids, and can include oral acitretin, methotrexate, or steroids. Bullous pemphigoid is an antibody-mediated bullous disorder presenting with tense bullae. The bullae vary in size, are filled with serous fluid, and are extremely pruritic. Histology shows a subepidermal vesicular dermatitis with prominent eosinophils in the superficial dermis and within the

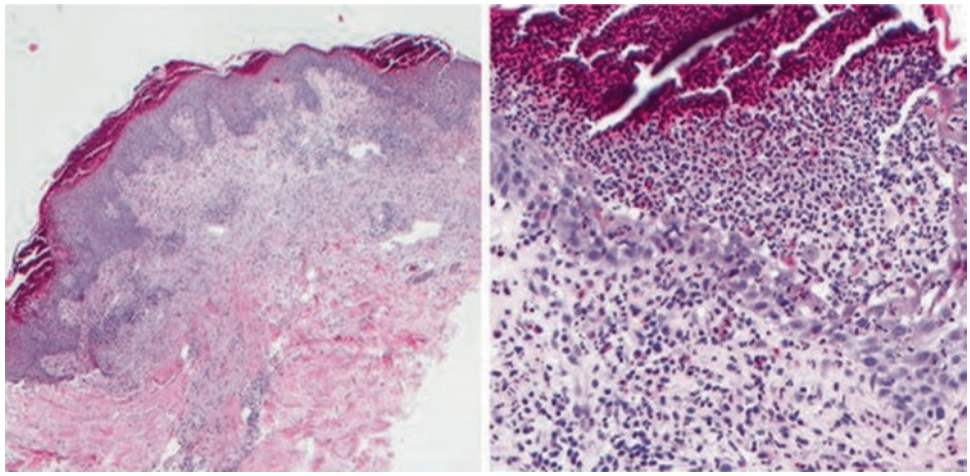

Fig. 11.6 Spongiotic psoriasiform dermatitis with subcorneal pustules, irregular acanthosis, and numerous eosinophils

bullae. The dermal–epidermal split is cleaved and the epidermal roof is intact. Dyskeratosis is not a feature. Direct immunofluorescence high- lights IgG deposition at the dermal–epidermal junction. Topical and oral steroids as well as rituximab have been used successfully in this slow-to-appear cutaneous AE [30].

Eruptive keratoacanthoma appears to be relatively well-demarcated and a low grade of squamous cell carcinoma. They were treated conservatively in this report without treatment interruption for the patients [28].

Combination Therapies

Combination checkpoint inhibitor therapies are being used more frequently with loading doses of anti-CTLA4 and antiPD-1/PD-L1 therapies, followed by maintenance anti-PD-1/anti-PD-L1. Although the cutaneous AEs are predominantly eczema, psoriasis, pruritus, and vitiligo, the incidence numbers are approximately 50% in our institutional database, which includes both clinical trials and standard-of-care patients. Dose impact appears to be less than with monotherapy as patients have systemic toxicities that are dose-limiting, minimizing the effects of the CAE.

Grading

Grading has nearly been universally based upon the Common Terminology Criteria for Adverse Events and more recently a modified version produced by the American Society of Clinical Oncology as their "Practice Guideline," which focuses on symptoms and quality of life rather than extent of involvement. This appears to be a more useful measure as relatively small body surface area involvement can still be dose limiting (Table 11.1 and Fig. 11.7).

CAE as Prognostic Indicators

Vitiligo is a relatively innocuous adverse event as it is largely asymptomatic and untreated. It is, however, associated with increased progression free survival and tumor response when occurring in patients on immune checkpoint inhibitors. Vitiligo is widely believed to be an underreported side effect as it can be easily missed if a full body skin exam is not performed. Vitiligo has only been reported in patients being treated with melanoma [2, 3, 33, 34]. Incidence of rash was also associated with increased survival and tumor response [2].

Table 11.1 Common terminology criteria for adverse events [31]

Grade	1	2	3	4	5
Rash	Macular or papular eruption covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macular or papular eruption covering 10–30% BSA with or without symptoms (e.g., pruritus, burning, tightness) and limiting of instrumental ADL	Macules/ papules covering >30% BSA with or without associated symptoms and limiting of self-care ADL	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
Alopecia	Hair loss of up to 50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hairstyle may be required to cover the hair loss, but it does not require a wig or hairpiece to camouflage	Hair loss of >50% of normal for that individual that is readily apparent to others; a wig or hairpiece is necessary if the patient desires to completely camouflage the hair loss or if loss is associated with psychosocial impact			
Hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA, with no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA or with associated psychosocial impact			
Pruritus	Mild or localized, relieved spontaneously or by local measures	Intense or widespread, relieved spontaneously or by systemic measures	Intense or widespread, and poorly controlled despite treatment		

1.0 Skin Toxicities	
1.1 Rash/inflammatory dermatitis	
Definition: Erythema multiforme minor (a targetoid reaction in the skin and mucous membranes usually triggered by infections, such as herpes simplex viruses, but can be associated with an immune-related drug eruption and if progresses to erythema multiforme major, it and can be a harbinger of SCAR, such as SJS), lichenoid (resembling the flat-topped, polygonal, and sometimes scaly or hypertrophic lesions of lichen-planus), eczematous (inflammatory dermatitis characterized by pruritic, erythematous, scaly, or crusted papules or plaques on the skin, which is vulnerable to superinfection, psoriasiform [resembling the well-demarcated, erythematous, and scaly papules and plaques of psoriasis], morbilliform [a nonpustular, nonbullous measles-like exanthematous rash of the skin often referred to as "maculopapular" and without systemic symptoms or laboratory abnormalities, excluding occasional isolated peripheral eosinophilia, palmoplantar erythrodysesthesia [hand-foot syndrome; redness, numbness, burning, itching, and superficial desquamation of the palms and soles], neutrophilic dermatoses [eg, Sweet syndrome], and others)	
Diagnostic work-up Pertinent history and physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease or unrelated primary skin disorder If needed, a biologic checkup, including a blood cell count and liver and kidney tests Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis: a screening antinuclear antibody test, SS-A/Anti-Ro, SS-B/Anti-La if predominantly photodistributed/photosensitivity, antihistone, double-stranded DNA, and other relevant serologies. Consider expanding serologic studies or diagnostic work-up if other autoimmune conditions are considered based on signs, symptoms Skin biopsy Consider clinical monitoring with use of serial clinical photography Review full list of patient medications to rule out other drug-induced cause for photosensitivity	
Grading	**Management**
Grading according to CTCAE is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.	
G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	Continue ICPi Treat with topical emollients and/or mild-moderate potency topical corticosteroids Counsel patients to avoid skin irritants and sun exposure
G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis	Consider holding ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1 Consider initiating prednisone (or equivalent) at dosing 1 mg/kg, tapering over at least 4 weeks In addition, treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids
G3: As G2 but with failure to respond to indicated interventions for a G 2 dermatitis	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks
G4: All severe rashes unmanageable with prior interventions and intolerable	Immediately hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) ≤ 10 mg Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to G1 or less; if ICPIs are the patient's only option, consider restarting once these adverse effects have resolved to a G1 level
1.2 Bullous dermatoses	
Definition: Including bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction	
Diagnostic work-up Physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease If needed, a biologic checkup, including a blood cell count, liver, and kidney tests; consider serum antibody tests to rule out bullous pemphigoid or, under the guidance of dermatology, sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering diseases Referral to dermatology for blisters that are not explained by infectious or transient other causes (eg, herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister) Consider skin biopsy (both hematoxylin and eosin evaluation of lesional skin and direct immunofluorescence evaluation of perilesional skin)	

Fig. 11.7 Management of skin irAEs in patients treated with ICPIs [32]

Grading	Management
G1: Asymptomatic, blisters covering < 10% BSA and no associated erythema	If blisters are < 10% BSA, asymptomatic, and noninflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary, and only observation and/or local wound care is warranted. When symptomatic bullae or erosions, which are deroofed vesicles or bullae, are observed on the skin or mucosal surfaces, the cutaneous irAE is by definition considered at least G2 See G2 management recommendations
G2: Blistering that affects quality of life and requires intervention based on diagnosis not meeting criteria for grade > 2 Blisters covering 10%-30% BSA	Hold ICPi therapy and consult with dermatology for work-up and to determine appropriateness of resuming Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left over on the skin after the blister has popped or if the roof of the blister easily sloughs off Counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, use sunscreens Work-up for autoimmune bullous disease as above Initiate class 1 high-potency topical corticosteroid (eg, clobetasol, betamethasone or equivalent) and reassess every 3 days for progression or improvement Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks Monitor patients with G2 irAEs closely for progression to involvement of greater BSA and/or mucous membrane involvement. Consider following patients closely using serial photography Primer on monitoring for complicated cutaneous adverse drug reactions: • Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements • Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN
G3: Skin sloughing covering > 30% BSA with associated pain and limiting self-care ADL	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.
G4: Blisters covering > 30% BSA with associated fluid or electrolyte abnormalities	Permanently discontinue ICPi Admit patient immediately and place under supervision of a dermatologist Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg with tapering over at least 4 weeks when the toxicity resolves If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc

Fig. 11.7 (continued)

1.3 SCARs, including SJS, TEN, acute generalized exanthematous pustulosis, and DRESS/DIHS

Definition: Severe changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug

Diagnostic work-up

- Total body skin examination with attention to examining all mucous membranes as well as complete review of systems
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease
- A biologic checkup, including a CBC with differential test, and liver and kidney function tests, including urinalysis, in addition to the blood work; if the patient is febrile, blood cultures should be considered as well
- Skin biopsies to assess for full-thickness epidermal necrosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as acute generalized exanthematous pusulosis
- Consider following patients closely using serial clinical photography
- If mucous membrane involvement or blistering is observed on the skin, consider early admission to a burn center for further monitoring and management
- Primer on monitoring for complicated cutaneous adverse drug reactions:
  - Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements
  - Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN

All grades	In cases of suspected SJS or any mucous membrane involvement, discontinue ICPi treatment and monitor closely for improvement, regardless of grade
G1: NA	For SCARs, there is no G1 category; if lower BSA is involved with bullae or erosions, there should remain a high concern that this reaction will progress to G3 or G4
G2: Morbilliform ("maculopapular") exanthem covering 10%-30% BSA with systemic symptoms, lymphadenopathy, or facial swelling	Hold ICPi and monitor patients closely every 3 days with G2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement Consider following patients closely using serial photography Initiate therapy with topical emollients, oral antihistamines, and medium- to high-strength topical corticosteroids Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks
G3: Skin sloughing covering < 10% BSA with mucosal involvement associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment)	Hold ICPi therapy and consult with dermatology Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (eg, ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate)
G4: Skin erythema and blistering/sloughing covering ≥ 10% BSA with associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (eg, liver function test elevations in the setting of DRESS/DIHS)	Permanently discontinue ICPi Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services Consider further consultations based on management of mucosal surfaces (eg, ophthalmology; urology; gynecology; ear, nose, and throat surgery; etc) Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal IVIG or cyclosporine may also be considered in severe or corticosteroid-unresponsive cases Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations

Additional considerations: The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immunodirected toxicity. Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/DIHS

All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate

Abbreviations: ADL, activities of daily living; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; G, grade; ICPi, immune checkpoint inhibitor; ICU, intensive care unit; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; NA, not applicable; SCAR, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TENS, toxic epidermal necrolysis.

Fig. 11.7 (continued)

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