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Immune checkpoint inhibitor—related dermatologic adverse events

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Abstract

Immune checkpoint inhibitors have emerged as a pillar in the management of advanced malignancies. However, nonspecific immune activation may lead to immune-related adverse events, wherein the skin and its appendages are the most frequent targets. Cutaneous immune-related adverse events include a diverse group of inflammatory reactions, with maculopapular rash, pruritus, psoriasiform and lichenoid eruptions being the most prevalent subtypes. Cutaneous immune-related adverse events occur early, with maculopapular rash presenting within the first 6 weeks after the initial immune checkpoint inhibitor dose. Management involves the use of topical corticosteroids for mild to moderate (grades 1–2) rash, addition of systemic corticosteroids for severe (grade 3) rash, and discontinuation of immunotherapy with grade 4 rash. Bullous pemphigoid eruptions, vitiligo-like skin hypopigmentation/depigmentation, and psoriasiform rash are more often attributed to programmed cell death-1/programmed cell death ligand-1 inhibitors. The treatment of bullous pemphigoid eruptions is similar to the treatment of maculopapular rash and lichenoid eruptions, with the addition of rituximab in grade 3–4 rash. Skin hypopigmentation/depigmentation does not require specific dermatologic treatment aside from photoprotective measures. In addition to topical corticosteroids, psoriasiform rash may be managed with vitamin

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D₃ analogues, narrowband ultraviolet B light phototherapy, retinoids, or immunomodulatory biologic agents. Stevens-Johnson syndrome and other severe cutaneous immune-related adverse events, although rare, have also been associated with checkpoint blockade and require inpatient care as well as urgent dermatology consultation.

Keywords

checkpoint inhibitor; CTLA-4 inhibitor; dermatologic adverse event; immune-related cutaneous adverse event; lichenoid eruption; maculopapular rash; PD-1 inhibitor; PD-L1 inhibitor; pruritus; vitiligo

EPIDEMIOLOGY

Key points

- Immune-related adverse events are less frequent and less severe in patients treated with anti-programmed cell death-1/programmed cell death ligand-1 than with cytotoxic T-lymphocyte-associated protein-4 inhibitors
- Cutaneous immune-related adverse events are the most common and usually manifest first
- Multiple studies have suggested an association between cutaneous immune-related adverse events and tumor response

Immunotherapy has emerged as a dominant paradigm in the management of advanced malignancies. Checkpoint inhibitors (CPIs) have shown dramatic efficacy; however, their use can be accompanied by nonspecific immune activation leading to a myriad of autoimmune and autoinflammatory phenomena termed immune-related adverse events (irAEs). These irAEs profoundly impact patient quality of life and may impact CPI treatment efficacy through CPI dose-limiting effects. irCAEs are the most frequent and earliest irAEs to arise in patients receiving CPIs; thus, understanding their clinicopathologic features and crafting targeted and effective management strategies is paramount to a successful oncodermatologic practice.

irAEs affecting a variety of organ systems occur in 90% of patients treated with cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) inhibitors, 70% of patients treated with programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) inhibitors, and almost all patients receiving combined therapies.¹ irAEs are generally mild to moderate, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, with severe (grade 3–4) toxicity (Table I) observed in 25% of patients treated with CTLA-4 inhibitor monotherapy and <20% of patients treated with PD-1/PD-L1 inhibitor monotherapy.^{2,3} Severe irAEs may lead to death in <2% of cases.¹ Whereas colitis complicated by bowel perforation represents the majority of life-threatening events under CTLA-4 inhibition, pneumonitis represents the majority of life-threatening events under PD-1/PD-L1 blockade.^{2,4}

Typically, mild to moderate irAEs (CTCAE grades 1–2) are largely reversible within 2 weeks when adequately treated.^{2,5,6} With prompt recognition and management, <5% of irAEs require discontinuation of CPI therapy.^{7–10} For patients treated with CTLA-4 inhibitors, irAEs mostly involve the skin (44%), gastrointestinal tract (35%), endocrine system (6%), and liver (5%).^{2,11} Not only are irCAEs the most common, but they also occur earliest, at an average of 3.6 weeks after treatment initiation versus a 6- to 7-week latency for gastrointestinal toxicities and a 9-week latency for endocrine toxicity.^{2,5,7,8,12,13} irCAEs occur before systemic irAEs, and therefore it is important to identify them early in the course of treatment.^{2,5,7,8,12,13}

Combination therapy using the CPIs ipilimumab and nivolumab has been approved for the treatment of patients with advanced melanoma.^{14–16} Studies evaluating the concurrent use of a CTLA-4 inhibitor and PD-1 inhibitor versus CTLA-4 inhibition alone showed a superior response rate (>50%) and increased incidence of irAEs (>50%) in the combination.^{2,7,8,14,17–29} As early as 2015, an association between irAEs and tumor response to CPIs was observed.^{30,31} This association is supported by a meta-analysis demonstrating statistically significant overall survival benefit and longer progression-free survival.^{30,31}

The most common irCAEs include nonspecific maculopapular rash (MPR), pruritus, psoriasiform, eczematous, and lichenoid dermatoses.^{32,33} Other less frequent irCAEs include bullous pemphigoid, vitiligo-like skin hypopigmentation/depigmentation, and alopecia.^{7,8} Cutaneous complications are usually self-limiting, but severe irCAEs may also rarely occur, including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS).^{2,7,8} Treatment algorithms for irCAEs center around early recognition and the use of corticosteroids or anti-tumor necrosis factor- α agents.^{2,34} However, the early use of corticosteroids immediately before or after CPI initiation may lead to decreased tumor efficacy.^{28,35–40} It is thought that CTLA-4 downregulates T cell activation primarily in lymphoid tissue, whereas PD-1/PD-L1 inhibitors act primarily in the tumor microenvironment, resulting in distinct irAE spectra between CPI classes.^{2,7,8,18,41–46} Because of their differing mechanisms, it can be hypothesized that in the case of severe toxicity with a CPI, rechallenge with an agent of a different class may be a safe treatment strategy.⁴⁷ Given the diverse inflammatory eruptions observed in CPI recipients, tailored management strategies have been developed through expert consensus and retrospective analyses from supportive oncologic and dermatologic perspectives.

CUTANEOUS ERUPTIONS

Key points

- MPR, pruritus, psoriasiform rash, eczema, and lichenoid eruptions represent the most common irCAEs
- Less common irCAEs include bullous pemphigoid, skin hypopigmentation/depigmentation, alopecia, SJS, TEN, and DRESS

- Whereas high-potency topical corticosteroids are first-line treatment for mild to moderate irCAEs, systemic corticosteroids may be indicated for widespread or severe disease
- Although an area of ongoing investigation, consideration should be given to phenotype-directed therapies (ie, specific biologics in psoriasiform rash)

MPR

A pruritic MPR represents the most prevalent irCAE induced by CTLA-4 inhibition.^{7,8} There is a predilection for the MPR phenotype under CTLA-4 blockade compared with PD-1/PD-L1 monotherapy.⁴³ MPR of any grade is observed in 49% to 68% of patients treated with anti-CTLA-4 therapy versus 20% of patients treated with anti-PD-1/PD-L1 therapy.^{48–50} The rash occurs early in treatment, usually 3 to 6 weeks after the initial dose, and appears to be dose dependent (Fig 1).^{7,8,14,49,51} MPR most commonly affects the trunk and extensor surfaces of the extremities (Fig 2).^{2,7,8,14,50–52} A typical rash consists of faint erythematous macules and papules coalescing into plaques.^{2,7,8,14,50–52} The body surface area (BSA) involved varies, but MPR is usually self-limiting (grade 1–2), covering <30% BSA. In 4% of patients, rash is considered severe (grade 3–4).⁴⁹ External trauma (ie, excoriation) may lead to new lesion formation (ie, Koebner phenomenon).⁵²

Histopathologic features include a superficial, perivascular CD4-predominant T cell infiltrate with eosinophils^{2,5,7,8,43,49,52} with or without a mild epidermal spongiosis, papillary dermal edema, and rare dyskeratotic cells.^{5,7,8,43,52} Management of CPI-related MPR (grade 1–2) includes either superpotent or midpotent TCS because the former is not superior to the latter ($P = .07$),^{2,7,8,49–51,53} and continuation of immunotherapy.^{7,8,14} Grade 3 rash is treated with TCS plus a 4-week tapering course of systemic corticosteroids, starting with prednisone 1 mg/kg/day and increasing the dose up to 2 mg/kg/day if needed.^{2,14,49} In addition, immunotherapy should be withheld until rash is grade 1 or less.^{14,49,51} In grade 4 rash, immunotherapy should be discontinued and methylprednisolone 2 mg/kg/day should be administered (Table II).^{14,49}

Lichenoid/lichen planus–like eruption

The incidence of CPI-related lichenoid or lichen planus (LP)–like eruption is sporadically reported and probably underestimated.^{7,8,54} One study suggested that lichenoid eruptions occur more frequently than MPR, with an incidence of 26 in 103 patients as opposed to 18 in 103 patients.³³ Lichenoid eruption is associated with anti-PD-1/PD-L1 therapy.^{48,53} Clinically, lichenoid eruptions have been reported in 0.5% to 6% of patients.^{48,53,55} The onset of lichenoid eruptions is delayed compared with MPR, with a mean time to onset of 6 to 12 weeks (Fig 1).^{7,8,48,51,56} Lichenoid eruptions present as multiple, discrete, erythematous, violaceous papules and plaques on the chest and back, but may rarely involve the limbs, palmoplantar surfaces, and oral mucosa (Fig 3).^{7,8,14,56,57}

Histopathologic features include a dense superficial dermal bandlike lymphocytic infiltrate with vacuolar degeneration and scattered apoptotic keratinocytes in the basal layer of the epidermis; occasional eosinophils, parakeratosis, and slight spongiosis may be present.^{7,8,56} Compared with idiopathic LP, CPI-related lichenoid eruptions have an increased abundance

of CD163⁺ cells, indicating a macrophage–monocyte lineage.^{51,58,59} These lesions are managed with high-potency topical corticosteroids (TCS) without CPI dose interruption, but may require systemic corticosteroids and CPI treatment cessation in high-grade toxicity (Table II).^{7,8,51,56} Alternative treatment options for high-grade toxicity include phototherapy and acitretin.⁸

Bullous pemphigoid eruption

Both lichenoid and bullous pemphigoid (BP) eruptions are associated with PD-1/PD-L1 inhibitors and primary tumor types including melanoma, non-small cell lung carcinoma, urothelial carcinoma, and head and neck squamous cell carcinoma.^{48,53} More than twenty cases of BP eruptions with PD-1/PD-L1 inhibitor therapy have been reported.⁶⁰ Compared with other irCAEs, BP eruptions have a delayed mean onset of 14 weeks after treatment initiation (Fig 1)⁴⁸ and present with a prodromal nonbullous phase of pruritus followed by the development of generalized or localized tense blisters filled with serous or hemorrhagic fluid (Fig 4); the oral mucosa is involved in 10% to 30% of cases.^{61,62} A high suspicion for BP eruptions should be maintained when patients with pruritus or rash are refractory to TCS.⁶⁰ Distribution is mostly typified by involvement of the trunk and extremities.^{48,63}

Pathologic autoantibody production has been identified in patients with CPI-related BP eruptions, and therefore a humoral component to its development is hypothesized because of T cell activation. Serologic testing by enzyme-linked immunosorbent assay for circulating antibodies against the basement membrane components BP180 and BP230 (expressed in melanoma, basement membrane of the skin, and non-small cell lung carcinomas) is helpful in confirming the diagnosis, correlating with disease severity, and monitoring treatment response.⁶³ In addition to serologic testing, the standard diagnostic workup comprises obtaining biopsy specimens of lesional skin and normal-appearing perilesional tissue for routine dermatopathologic evaluation and direct immunofluorescence (DIF), respectively. Histopathologic features include a subepidermal cleft with eosinophilic infiltrate. The presence of linear deposits of immunoglobulin G and complement component C3 at the dermoepidermal junction on DIF is characteristic, although not entirely specific for BP because it is seen in cicatricial pemphigoid and epidermolysis bullosa acquisita; thus, DIF on salt-split skin can be performed to differentiate BP from these entities, showing immunoglobulin G deposition on the blister roof. Indirect immunofluorescence could be performed to test for circulating immunoglobulin G autoantibodies targeting the roof of the blister on salt-split skin.

Although grade 1 BP eruptions may respond to TCS, the addition of systemic corticosteroids in grade 2 and the addition of rituximab in grades 3–4 is often warranted (Table II).^{53,62,64} In contrast to traditional drug-induced BP, CPI-related BP may persist for several months after discontinuation of immunotherapy, consistent with an enduring state of immune activation that contributes to the maintenance of tumor response.⁶³

PRURITUS

Key points

- Pruritus is the second most common irCAE
- CPI-related pruritus may occur with and without cutaneous eruption
- Pruritus can be managed with TCS, oral antihistamines, and oral neuromodulators

Pruritus is second to MPR as the most common irCAE.^{7,8} However, the two often coexist.^{43,51} As with MPR, pruritus is most frequently encountered in patients receiving the antiCTLA-4 agent ipilimumab.^{7,8} Pruritus also occurs in 21% of patients treated with antiPD-1/PD-L1 therapy.^{7,8,44,65} Symptoms are usually grade 1–2 in severity, with high-grade pruritus occurring in <1% of cases.^{7,8} Pruritus is usually managed with emollients and oral antihistamines (ie, hydroxyzine), with or without the addition of TCS (Table II).^{7,8,18,44,53} Gamma-aminobutyric acid analogs (ie, pregabalin) have also been used, resulting in moderate to significant improvement in 17 of 17 patients (compared to oral antihistamines, which have demonstrated benefit in 13 of 16 patients).^{51,53} Based on its success in epidermal growth factor receptor inhibitor (EGFRi) and tyrosine kinase inhibitor (TKI) related pruritus and uremic pruritus, the neurokinin receptor inhibitor aprepitant could be considered for patients who are refractory to other treatments.⁶⁶ In a trial of 45 patients with EGFRi and TKI-related pruritus, every other day aprepitant dosing for a total of 3 doses yielded a >50% reduction in pruritus intensity, with pruritus recurring in only 13% of those treated.^{51,66}

VITILIGO-LIKE SKIN

HYPOPIGMENTATION/DEPIGMENTATION

Key points

- The risk of CPI-related skin hypopigmentation/depigmentation among patients with melanoma is 10-fold higher than in the general population
- Vitiligo has been shown to be a positive predictive factor for tumor response to CPIs
- The development of vitiligo-like skin hypopigmentation/depigmentation has been associated with greater anticancer benefit from CPIs in patients with melanoma

Vitiligo is an autoimmune disorder characterized by depigmented macules or patches originating from the loss of functional melanocytes in the epidermis, which can be delineated with a Wood's lamp (Fig 5).^{51,67,68} Vitiligo incidence reaches 11% in antiCTLA-4 therapy and 25% in antiPD-1 therapy.^{7,8,51} Vitiligo does not appear until months after CPI initiation and does not seem to be dose related (Fig 1).^{7,8,50} In antiPD-1 treatment, CD8⁺ cytotoxic T cells are activated against melanoma-associated antigens (MART-1/MelanA, gp100, and tyrosinase-related proteins 1 and 2) shared by normal melanocytes and melanomas.^{7,8,67,69} Immunohistochemical staining done after treatment

with antiCTLA-4 has shown CD4 and MelanA-specific CD8⁺ T cells in close proximity to apoptotic melanocytes, suggesting that antiCTLA-4 antibodies stimulate an immune response against melanocytes.⁴⁹

Although CPI-related skin hypopigmentation/depigmentation has been observed in 2.0% to 8.3% of melanoma patients by meta-analysis,^{2,7,67–74} its incidence in nonmelanoma patients is not known. Immune-related depigmentation has been reported in 8 patients with non-small cell lung cancer, 3 patients with renal cell carcinoma, 1 patient with hepatocellular carcinoma, 1 patient with cholangiocarcinoma, 1 patient with acute myelogenous leukemia, and 1 patient with soft tissue sarcoma.^{53,71–73,75–100} CPI-related vitiligo appears to have a distinct phenotype, characterized by multiple flecked macules of depigmentation evolving into large plaques on photoexposed skin.⁷¹ The development of CPI-related vitiligo in patients with melanoma portends a favorable response to therapy, demonstrating the correlation of irAEs with enhanced antitumor response.^{51,67,68} Those who develop vitiligo have 2 to 4 times prolonged progression-free survival and overall survival, respectively.⁶⁸ Vitiligo-like skin hypopigmentation/depigmentation does not resolve after immunotherapy cessation^{7,8,51} and does not require specific treatment aside from photoprotective measures and camouflaging to limit its psychosocial impact (Table II).^{7,8}

OTHER CUTANEOUS ERUPTIONS

Key points

- Psoriasiform rash has been reported after the use of PD-1/PD-L1 inhibitors
- Although severe cutaneous adverse reactions, such as SJS, TEN, and DRESS, have rarely been reported with the use of CPIs, these may be life threatening, and management includes discontinuation of immunotherapy and administration of systemic treatment

A broad spectrum of CPI-related cutaneous eruptions has been reported, representing the potential for varied autoinflammatory and autoimmune phenomena in the setting of nonspecific immune activation. Psoriasiform rash, either de novo or reactivated, has been reported after the use of a PD-1/PD-L1 inhibitor for melanoma and the eruption correlates strongly with tumor response.^{53,101–105} Lesions appear after about 3 weeks of treatment (Fig 1) and present as sharply bordered, scaly, erythematous plaques on the trunk and extremities (Fig 6).^{102,103} Skin biopsy specimens reveal parakeratosis, hypogranulosis, acanthosis with elongation of rete ridges, and a perivascular lymphocytic infiltration.^{102–104} CPIs augment helper T cell 1 as well as helper T cell 17 activity, which produces interleukin-17 and plays a pivotal role in the pathogenesis of psoriasis.^{7,8,101,103} Treatment for CPI-related psoriasiform rash includes high-potency TCS, vitamin D₃ analogues, narrowband ultraviolet B phototherapy; and if lesions persist, retinoids or biologics (Table II).^{7,8,53,102,104}

While severe cutaneous adverse reactions (SCARs) including SJS, TEN, and DRESS have rarely been reported (Fig 7),^{2,7,8,48,49,63,106–108} these reactions are potentially life threatening. However, they are usually reversible upon the discontinuation of immunotherapy and administration of systemic immunomodulatory treatment.^{49,60} The mortality rate is 10% for SJS, 30% for SJS-TEN overlapping, and 50% for TEN.¹⁰⁶ The

latency from the start of CPI treatment to the onset of SCAR varies from 1 to 20 weeks (Fig 1).¹⁰⁶ SCARs may manifest as MPR initially and develop clinical symptoms suggestive of a potentially life-threatening skin reaction (eg, blister formation, Nikolsky sign, mucosal ulcerations, fever, or skin pain).^{7,8} Biopsy specimens show full-thickness epidermal necrosis with minimal inflammatory infiltrate. Immunohistochemical studies show increased expression of PD-L1 on both lymphocytes and keratinocytes at the dermoepidermal junction. Although PD-L1 is not usually detectable in skin, the use of antiPD-1 therapy increases the expression of PD-L1 in keratinocytes, leading to the targeting and apoptosis of cells by activated cytotoxic CD8⁺ T cells.^{106–109} CPI-related skin eruptions share similar gene expression profiles with SCARs, such as the upregulation of major inflammatory chemokines (CXCL9, CXCL10, and CXCL11), cytotoxic mediators (PRF1 and GZMB), and proapoptotic molecules (FASLG).^{106,110} The management of SCARs includes immunotherapy discontinuation, hospitalization, intravenous corticosteroids, and cyclosporine (Table II).^{2,49,108,109}

HAIR AND MUCOSAL TOXICITIES

Key points

- The most common CPI-related hair toxicity is alopecia, with an incidence of 1% to 2%
- CPI-related alopecia has a phenotype similar to alopecia areata, although cases of telogen effluvium have also been reported
- Xerostomia and lichenoid reactions are the most common oral mucosal toxicities

Hair and mucosal irAEs represent a significant, albeit small, portion of CPI toxicity profiles. The most common hair toxicity of CPI is alopecia areata, with an incidence of 1% to 2%,^{52,111,112} and some cases of telogen effluvium (Fig 8). Evidence shows that PD-L1 is expressed on the hair follicle dermal sheath and PD-1 inhibitors directly induce alopecia areata or universalis through a CD4⁺ and CD8⁺ T cell–mediated immune response.⁵⁸ The onset is within 3 to 6 months (Fig 1) and histopathology is significant for perifollicular lymphocytic inflammation.¹¹¹ Diagnostic workup includes clinical evaluation of the scalp, a hair pull test, obtaining a biopsy specimen of the scalp, and laboratory testing for other causes of alopecia (thyroid dysfunction and deficiencies of zinc, vitamin D, or iron). Treatment includes intralesional triamcinolone and clobetasol foam (Table II). Hair regrowth in the alopecic areas manifesting with poliosis is a well-recognized feature.¹¹¹ Hair depigmentation may also be observed in the context of CPI-related skin hypopigmentation/depigmentation.^{7,8}

Although CPI-related mucosal toxicities have not emerged as treatment-limiting AEs in key clinical trials, they nevertheless impact patient quality of life.^{2,50,58,113,114} Nonspecific stomatitis, mucosal inflammation, periodontal disease, and lichenoid reactions have been described with both anti-PD-1 and antiPD-L1 therapy.^{2,7,8,58,113} The incidence of oral complications with antiCTLA-4 therapy is not well defined.^{2,113} Periodontal disease represents a chronic infectious/inflammatory condition modulated by T cell dysregulation, resulting in periodontal pocket formation, alveolar bone resorption, and tooth loss.¹¹³ Lichenoid reactions present as reticulated white streaks consistent with Wickham striae and

whitish confluent papules, sometimes with plaque-like, ulcerative, atrophic, erythematous lesions. The lesions may affect dorsal or lateral sides of the tongue, the lips, gingivae, hard palate, buccal mucosa, or perianal and vulvar areas. Patients may report pain or soreness, but the lesions can be asymptomatic.^{7,8,14,58} Histologic analysis shows a patchy or florid lichenoid interface lymphocytic infiltrate in the upper lamina propria, composed of an admixture of CD4⁺ and CD8⁺ T cells.⁵⁷ These lesions are reversible and can be treated with TCS and lidocaine in order to maintain immunotherapy dose intensity (Table II).⁵⁸ However, candidiasis should always be kept in the differential diagnosis for these patients who may be treated with corticosteroids for the management of other irAEs.^{2,50,113}

FUTURE DIRECTIONS AND CONCLUSIONS

Key points

- As CPIs become the mainstay of cancer treatment, a better understanding of their irAEs is warranted
- Management of corticosteroid-resistant CPI treatment-related irCAEs is being actively investigated

The advent of CPIs has challenged the medical community to redefine the fundamental aspects of melanoma and other solid tumor treatments, including prognostication, monitoring, and toxicity management.⁴² Clinicians and patients must be well-educated regarding irAEs; yet, in the published literature, there is substantial variability in the reporting of these toxicities.⁴² In addition, patients may develop distinct irAEs when transitioned between classes of CPIs.¹⁰⁴ As CPIs transition to the forefront of cancer treatment, standardization of irAE reporting will be vital in promoting safe clinical practice. Traditional cytotoxic chemotherapy toxicity is usually temporally related to drug administration and self-limited in duration. Conversely, CPI-related irAEs may have a delayed and refractory course.⁴² Therefore, consideration should be given to developing a unique toxicity monitoring, grading, and reporting framework specifically designed to tackle the dynamic challenges posed by irAEs.⁴²

A subset of irCAEs appear to be corticosteroid-refractory, persisting or worsening despite CPI discontinuation and systemic corticosteroids. These cases present a management challenge without clear therapeutic recourse. As immunotherapies become the mainstay of metastatic malignancy management, ongoing studies will be critical for understanding the incidence, phenotype, and management of irAEs.^{104,115,116}

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Abbreviations used:

AE	adverse event
BP	bullous pemphigoid

BSA	body surface area
CPI	checkpoint inhibitor
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
DIF	direct immunofluorescence
DRESS	drug reaction with eosinophilia and systemic symptoms
irAE	immune-related adverse event
irCAE	immune-related cutaneous adverse event
LP	lichen planus
MPR	maculopapular rash
PD-1	programmed cell death protein-1 receptor
PD-L1	programmed cell death protein-1 ligand
SCAR	severe cutaneous adverse reaction
SJS	Stevens–Johnson syndrome
TCS	topical corticosteroids
TEN	toxic epidermal necrolysis

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Learning objectives

After completing this learning activity, participants should be able to identify the significance of dermatologic reactions to immune checkpoint inhibitors to cancer outcomes; recognize the clinical and histological features of dermatologic reactions to immune checkpoint inhibitors; distinguish primary autoimmune/autoinflammatory conditions from immune-related dermatologic adverse events; describe appropriate management of immune-related dermatologic adverse events to immune checkpoint inhibitors; and identify novel or emerging strategies of managing immune checkpoint inhibitor-related dermatologic adverse events.

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irCAE Time to Onset (weeks)					
0-3	4-6	7-9	10-12	13-15	16+
Psoriasiform rash	Maculopapular rash	Lichenoid eruption		Bullous pemphigoid	
	Pruritus				
SJS					
TEN					
DRESS					
		Vitiligo-like skin hypopigmentation or depigmentation			
				Alopecia	

Fig 1.

Time to onset of immune-related cutaneous adverse events. *DRESS*, Drug reaction with eosinophilia and systemic symptoms; *irCAE*, immune-related cutaneous adverse event; *SJS*, Stevens–Johnson syndrome; *TEN*, toxic epidermal necrolysis.

Fig 2.

Maculopapular rash, grade 2. Patient receiving pembrolizumab for stage IV lung adenocarcinoma. Histopathology reveals interface dermatitis with increased dermal mucin. There are many features, including interface changes, mucin and increased basement membrane suggestive of connective tissue disease, and also the possibility of a drug reaction resembling connective tissue disease.

Fig 3. Lichenoid eruption, grade 2. Patient receiving atezolizumab for multifocal muscle invasive bladder carcinoma. Histopathology reveals interface and perivascular lymphocytic dermatitis with rare eosinophils and evidence of minor vascular damage, consistent with a reaction to treatment.

Fig 4. Bullous pemphigoid eruption, grade 3. Patient receiving pembrolizumab for stage IV sarcomatoid lung carcinoma. Histopathology shows a subepidermal blister with a superficial dermal lymphocytic infiltrate and scattered eosinophils.

Fig 5.
Skin hypopigmentation/depigmentation, grade 2. Patient receiving pembrolizumab for metastatic melanoma.

Fig 6.

Psoriasiform rash, grade 3. Patient receiving pembrolizumab for metastatic non-small cell lung cancer. Histopathology reveals epidermal hyperplasia with elongation of rete ridges, overlying parakeratosis and hypogranulosis, and a superficial perivascular lymphocytic infiltrate.

Fig 7.
Stevens–Johnson syndrome, grade 4. Patient receiving combination therapy with ipilimumab plus nivolumab for melanoma.

Fig 8.
Alopecia and telogen effluvium. Patient receiving combination therapy with ipilimumab plus nivolumab for metastatic melanoma.

Table I.

Common Terminology Criteria for Adverse Events Version 5.0

CTCAE grade	Description
1	Lesions covering <10% BSA with or without symptoms (ie, pruritus, burning, or tightness)
2	Lesions covering 10–30% BSA with or without symptoms (ie, pruritus, burning, or tightness); OR limiting instrumental ADL; OR lesions covering >30% BSA with or without mild symptoms, without limiting self-care ADL
3	Lesions covering >30% BSA with moderate or severe symptoms; limiting self-care ADL
4+	Life-threatening consequences, urgent intervention needed

ADL, Activities of daily living; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events.

Table II.

Immune-related cutaneous adverse events: Management and recommendations

CTCAE grade	MPR*	Lichenoid eruption*	Bullous pemphigoid eruption	Psoriasisiform rash	SJS/TEN/DRESS	Pruritus	Vitiligo-like skin hypopigmentation/depigmentation	Alopecia	Mucosal toxicity
1	High-potency TCS twice a day	High-potency TCS twice a day	High-potency TCS twice a day	High-potency TCS twice a day	N/A	High-potency TCS twice a day	Photoprotection	Moderate- to high-potency TCS	TCS, lidocaine
2	High-potency TCS twice a day or systemic corticosteroids (prednisone 0.5–1 mg/kg/day)	High-potency TCS twice a day or systemic corticosteroids (prednisone 0.5–1 mg/kg/day)	Hold CPI until grade 0–1; high-potency TCS twice a day and systemic corticosteroids (prednisone 0.5–1 mg/kg/day)	High-potency TCS twice a day and NBUVB phototherapy or apremilast	N/A	High-potency TCS twice a day and GABA analogs	Photoprotection	Moderate- to high-potency TCS	TCS, lidocaine
3+	Hold CPI until grade 0–1; systemic corticosteroid (prednisone 0.5–1 mg/kg/day with dose increase up to 2 mg/kg/day if no improvement) or biologics (infliximab or tocilizumab)	Hold CPI until grade 0–1; systemic corticosteroid (prednisone 0.5–1 mg/kg/day with dose increase up to 2 mg/kg/day if no improvement) or biologics (infliximab or tocilizumab)	Hold CPI until grade 0–1; systemic corticosteroid (prednisone 0.5–1 mg/kg/day with dose increase up to 2 mg/kg/day if no improvement) and rituximab	Hold CPI until grade 0–1; biologics (ustekinumab, guselkumab, infliximab, adalimumab, or apremilast) or retinoids	Discontinue CPI, hospitalization, intravenous corticosteroid, cyclosporine, and close monitoring	Hold CPI until grade 0–1; oral antihistamines and GABA analogs; and omalizumab or dupilumab	N/A	N/A	Hold CPI until grade 0–1; TCS, lidocaine

The level of evidence for all management recommendations is III–IV. Level IA evidence includes evidence from meta-analysis of randomized controlled trials. Level IB evidence includes evidence from 1 randomized controlled trial. Level IIA evidence includes evidence from 1 controlled study without randomization. Level IIB evidence includes evidence from 1 other type of experimental study. Level III evidence includes evidence from nonexperimental descriptive studies (ie, comparative, correlation, or case-control). Level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

CPI, Checkpoint inhibitor; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *GABA*, gamma-aminobutyric acid; *ixCAE*, immune-related cutaneous adverse event; *IV*, intravenous; *MPR*, maculopapular rash; *NBUVB*, narrow band ultraviolet B light; *SJS*, Stevens–Johnson syndrome; *TCS*, topical corticosteroids; *TEN*, toxic epidermal necrolysis.

* For corticosteroid-resistant MPR or lichenoid eruption, preliminary success has been shown with targeted biologic monoclonal antibody therapy (infliximab or omalizumab).