American Journal of Clinical Dermatology (2022) 23:707–717
https://doi.org/10.1007/s40257-022-00706-y

REVIEW ARTICLE

Challenging Dermatologic Considerations Associated with Immune Checkpoint Inhibitors

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Accepted: 16 May 2022 / Published online: 16 June 2022

Abstract

Immune checkpoint inhibitors have emerged as a new paradigm in oncologic care for many malignancies. However, non-specific immune activation has led to "collateral damage" in the form of immune-related adverse events, with skin being a commonly affected organ. Cutaneous immune-related adverse events include a wide spectrum of clinical presentations and challenging considerations, often necessitating dermatology referral to support diagnosis and management, particularly for atypical presentations or more severe, cutaneous immune-related adverse events that may require specialized dermatologic evaluations including biopsy and histopathology. Close collaborations between oncologists and dermatologists may optimize clinical decision making in the following challenging management settings: non-steroidal therapies for corticosteroid-refractory, cutaneous immune-related adverse events, immune checkpoint inhibitor rechallenge, balancing cutaneous immune-related adverse events and treatments, and immune checkpoint inhibitors in patients with pre-existing autoimmune disease, skin conditions, and organ transplants. These complex clinical decisions that often lack rigorous data should be made in close collaboration with dermatologists to minimize unnecessary morbidity and mortality. This article provides a review of approaches to challenging dermatologic considerations associated with immune checkpoint inhibitor therapies.

Key Points

Cutaneous immune-related adverse events are common side effects of immune checkpoint inhibitor therapy.

Collaborations between dermatologists and oncologists are necessary to optimize diagnosis and management in challenging clinical scenarios involving cutaneous immune-related adverse events.

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1 Introduction

Immune checkpoint inhibitors (ICIs) continue to progress as favorable treatment options with efficacy across multiple malignancies including metastatic melanoma, non-small cell lung cancer, renal cell carcinoma, head and neck cancer, urothelial carcinoma, Merkel cell carcinoma, cutaneous squamous cell carcinomas, and microsatellite instability-high tumors [1–6]. Immune checkpoint inhibitors are monoclonal antibodies that increase immune activation and promote a host-mediated antitumor response by blocking cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death 1 receptor, and its ligand (PD-1/PD-L1). The clinical benefit demonstrated by ICIs has led to an increasing number of clinical trials evaluating various checkpoint inhibitors, and the US Food and Drug Administration approval of eight different agents in at least 17 different tumor types.

Despite their effectiveness, ICIs are also associated with overactivation of the immune system that can lead to a host of unique immune-related adverse events (irAEs) that present similarly to autoimmune diseases (ADs) and can affect any organ system. Cutaneous irAEs (cirAEs) are among the most common irAEs and occur in > 30% of patients treated with ICIs [7]. Maculopapular eruptions, pruritus, and

lichenoid reactions are among the most common cirAEs, while more severe cirAES such as drug reaction with eosinophilia and systemic symptoms and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) are rare [8]. The diagnosis and management of cirAEs can be complex owing to the wide spectrum of clinical presentations and morphologies. Although the most frequent cirAEs such as rash and/or pruritus are relatively benign, there are also less common but potentially life-threatening toxicities that require prompt recognition and treatment [9]. These severe cirAEs can lead to severe morbidity and permanent discontinuation of immunotherapy. Optimizing the management of challenging cirAEs demands a multidisciplinary approach, involving collaborative approaches between oncologists and dermatologists.

2 Pathophysiology

Several hypotheses have been proposed to explain the occurrence of irAEs. Immune checkpoint inhibitors disrupt the balance between immune activation and quiescence by blocking checkpoints in the immune system. Cytotoxic T-lymphocyte-associated protein 4 is involved early in T-cell responses in thymic T-cell maturation and peripheral inhibition of T-cell activation, whereas PD-1/PD-L1 are involved at the later stages of the immune response by maintaining peripheral tolerance of self-reactive T cells [10]. Blocking these checkpoints leads to the release of key immune "brakes" that ultimately gives rise to the antitumor response; however, it may also promote autoreactivity through the proliferation of self-reactive T cells. Of note, the mechanistic differences of anti-CTLA-4 and anti-PD-1 underlie the distinct irAE profiles observed in preclinical models and patients [10–13]. Mouse models with deletions of the gene encoding CTLA-4 result in multiorgan inflammation and early death, whereas mice with deletions of the PD-1 encoding gene have a later onset of arthritis, lupus-like features, and/or cardiomyopathy (depending on the genetic background of the mice) [12, 14].

While this off-target immune activation seems to explain the general mechanism of irAEs, we still have little insight into specific explanations for individual toxicities and patients (e.g., why one patient experiences a cirAE and another does not). One interesting case study involves the association between vitiligo and melanoma [15]. Cross-reactivity between antigens present on melanocytes and melanoma cells is thought to result in the increased incidence of vitiligo-like rash in patients with melanoma [16]. Notably, the occurrence of vitiligo-like depigmentation has been demonstrated as a predictive marker of response to anti-PD-1 therapy [15]. Somewhat analogously, one study showed that patients with an ICI skin rash and lung cancer had T cells with identical T-cell receptor sequences in both the skin and tumor, suggesting cross-reactivity [17]. There may also be non-tumor-related explanations. As an epithelial surface with extensive environmental exposure, the skin has substantial immune surveillance and infiltration. Thus, removal of immune checkpoints may simply activate these tissue-resident immune cells, leading to autoinflammation. Ultraviolet exposure leading to skin damage (and resultant exposure of self-antigens) has also been associated with autoreactive T-cell generation [18, 19]. Ultimately, the exact pathophysiology remains unknown, and it is likely that multiple mechanisms are at play depending on both tumor and host factors.

3 General Management of cirAEs

The management of cirAEs depends on the severity of the symptoms. Adverse events are graded by the Common Terminology Criteria for Adverse Events (version 5.0) [20]. Along with the Common Terminology Criteria for Adverse Events, several consensus guidelines have been developed by professional societies to guide the management of cirAEs [21–24]. For grade 1 cirAEs (< 10% body surface area [BSA] in the case of rash), immunotherapy can be continued, and management is primarily symptomatic with over-the-counter emollients, antipruritic agents, and/or topical corticosteroids. Grade 2 cirAEs (10–30% BSA) generally have similar recommendations as for grade 1; however, corticosteroids may be escalated to higher potency topicals or occasionally oral regimens, and a consult to a dermatologist is recommended to exclude other dermatologic conditions, as well as more severe cirAES including SJS/TEN and bullous pemphigoid. Of note, there are certain cirAEs (i.e., immunobullous, granulomatous, connective tissue disease, hair changes, and oral involvement) where grade 2 symptoms necessitate cessation of immunotherapy until improvement to grade 1 [25]. For grade 3 cirAEs (> 30% BSA), immunotherapy discontinuation is recommended, usually along with oral corticosteroids, and a dermatologist should be consulted. Systemic corticosteroids are often the mainstay of treatment, but other agents may be considered if refractory to treatment or contraindications are present, and aggressive topical agents may prevent the need for systemic agents. Immunotherapy can be reconsidered once the cirAE is reduced to grade 1 (although this is a complex decision, as discussed in Sect. 4.5). As flares or recurrences are common with repeat ICI exposure, these patients may require long-term corticosteroid-sparing agents for prevention and symptom management. Grade 4 cirAEs usually necessitate permanent discontinuation of immunotherapy. Other commonly used systemic agents to treat cirAEs include antimetabolite agents, calcineurin inhibitors, and tumor necrosis factor-α inhibitors.

While current published guidelines and several review articles provide general recommendations for management, there are several cirAEs and clinical situations that demand a more individualized therapeutic approach where dermatologist involvement may be necessary to optimize patient outcomes. Here, we discuss these challenging and often "data-sparse" clinical situations for treating dermatologists and oncologists.

4 Challenging Dermatologic Management/ Topics

4.1 Need for Dermatology Referral/Consult

Dermatologists play key roles in evaluating and managing cutaneous toxicities. Although more common, mild cirAEs such as low-grade pruritus and non-specific rashes are often managed by oncologists, a dermatology consult is beneficial for challenging, severe, or refractory cases. Here, we propose settings in which dermatology consults are indicated for the diagnosis and management of cirAEs: (1) patients with known histories of immune-related skin conditions; (2) unclear or atypical presentations that may require a skin biopsy; (3) ICI rechallenge after a severe cirAE; (4) grade 3/4 cirAEs (including rash covering > 30% BSA); (5) patients with blisters; (6) rash with mucosal involvement; (7) rash with skin pain; and (8) scars [23, 26].

Clinical diagnoses made by dermatologists can differ from non-specialists in up to 50% of cases, meaning that severe or life-threatening cirAEs may be misdiagnosed by non-dermatologists [27]. Delays in accurate diagnosis may lead to delays in appropriate management or conversely, the unnecessary interruption of treatment [27]. Dermatologist involvement has been shown to reduce the use of systemic immunosuppressive drugs or treatment discontinuation, optimizing anti-tumor outcomes and minimizing long-term consequences of high-dose corticosteroids [28]. Ultimately, these differences improve the likelihood of appropriate treatment for cirAEs, as well as progression-free survival and overall survival [29].

Last, existing grading systems are valuable but do not capture the full spectrum or nature of cirAEs. Oncologists grade cirAES according to the Common Terminology Criteria for Adverse Events, which is based on BSA involvement; however, dermatologists often use different grading tools that focus on disease pathology [30]. This may contribute to disparities in accurate diagnosis and appropriate management. As most cirAEs are treated based on their idiopathic counterparts, they should be graded similarly with dermatologist involvement.

4.2 Need for Biopsy and Other Diagnostic Methods

Some diagnoses require skin biopsies to support accurate diagnosis, minimizing unnecessary morbidity in patients receiving ICIs. Although many diagnoses can be made clinically, biopsy and other methods can play a supportive role or help rule out more serious conditions. This is becoming increasingly important as we move to personalized treatment approaches based on diagnostic tools and biomarkers [31]. Current treatment strategies are based on adapted recommendations for primary ADs; however, personalized immunohistopathologically guided treatment may be appropriately based on predominant immune infiltrate types in affected areas [32–35]. Ultimately, we recommend a biopsy at least in clinical situations where eruptions are refractory to topical corticosteroids, and in cases with diagnostic uncertainty or suspicion for SCARs exist. Additional diagnostic studies include direct and indirect immunofluorescence and enzyme-linked immunosorbent assays. Outlined in Table 1 are cirAEs that may require biopsy for diagnosis, their corresponding histologic findings, and the need for a dermatology referral.

4.3 Non-steroidal Treatment Options

Although cirAEs are etiologically distinct from their idiopathic counterparts, they have similar clinical presentations and are thus treated similarly. Most cirAEs are treated based on existing management strategies with additional considerations of the underlying malignancy and effect on immunotherapy efficacy, which can theoretically be impacted by specific drugs.

Most cases of cirAEs can be treated with supportive therapy, corticosteroids, and/or cessation of treatment. However, some corticosteroid-refractory and severe cases may require additional therapies, and in some cases, these agents may be preferable to upfront corticosteroids. Retrospective studies and case reports have reported preliminary benefits of targeted biologics and other immunosuppressants including: infliximab, mycophenolate mofetil, tacrolimus, intravenous immunoglobin, rituximab, dupilumab, and other agents as shown in Table 2. Current consensus guidelines by the National Comprehensive Cancer Network, Society for Immunotherapy of Cancer, and European Society for Medical Oncology recommend escalating immunosuppression with the addition of one or more additional immunosuppressants in the case of corticosteroid-refractory cirAEs and in specific diagnoses that warrant alternative therapies (such as rituximab in bullous pemphigoid) [21, 23, 24].

In general, the use of immunomodulators is based on recommendations and evidence for their efficacy in autoimmune and idiopathic forms of the same condition (e.g., non-ICI related). Because of this lack of validated evidence

Table 1 Biopsy, referral, and histopathology findings

cirAE	Biopsy [36]	Dermatology referral/consult [22, 25, 26]	Histologic findings [35, 37–39]
Lichenoid reactions [19, 38, 40]	Yes	Non-acute referral	Band-like crowded lymphocytic infiltrate along the dermoepidermal junction with variable hyperkeratosis and hypergranulosis
Cutaneous sarcoidosis [38, 41, 42]	Yes	Non-acute referral	Noncaseating granulomatous infiltrates of epitheloid histiocytes and minimal inflammatory cells
Bullous pemphigoid [43, 44]	Yes	Acute referral	Subepidermal cleft with eosinophils, intradermal vesicles, and necrotic keratinocytes at the blister roof of the dermoepidermal junction ELISA[a]: BP180/BP230 Direct immunofluorescence[a]: linear depositions of IgG and C3 along the dermoepidermal junction
SJS/TEN [40, 43]	Yes	Acute referral	Epidermal necrosis with numerous necrotic keratinocytes, lymphocytes with CD8+ predominance, and increased PD-L1 expression in lymphocytes and keratinocytes
DIHS/DRESS [34, 45]	Yes	Acute referral	Non-specific but may commonly include spongiosis, lymphocyte exocytosis, scattered keratinocyte necrosis, interface dermatitis, perivascular infiltration, and basal cell vacuolization
Grover's disease [46, 47]	Yes	Non-acute referral	Acantholytic dyskeratosis with dermal lymphocytic infiltrates composed primarily of CD4+ and CD8+ T cells
Psoriasiform [40]	Sometimes	Non-acute referral	Parakeratosis, psoriasiform epidermal hyperplasia, acanthosis, diminished granular layer, elongated rete ridges, and inflammatory infiltrate of lymphocytes

BP bullous pemphigoid, *cirAE* cutaneous immune-related adverse events, *DIHS/DRESS* drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms, *ELISA* enzyme-linked immunosorbent assay, *PD-L1* programmed death-ligand 1, *SJS/TEN* Stevens–Johnson syndrome/toxic epidermal necrolysis

[a]Refers to additional non-biopsy diagnostic methods and findings

in the context of cirAEs, these treatments should be used carefully and considered on an individual patient basis. General recommendations for the use of tumor necrosis factor inhibitors, mycophenolate-containing medicines, intravenous immunoglobin, cytokine inhibitors, and other agents have been included in consensus guidelines [22, 36, 48]. Additional non-steroidal treatment options based on a literature review are summarized and further divided by localized or systemic application in Table 2. Of note, corticosteroids alone are usually avoided in the treatment of SJS; however, as the underlying mechanism of ICIs is based on T-cell activation, corticosteroids are appropriate for ICI-mediated SJS, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome, or other severe blistering eruptions mimicking epidermal necrolysis [36, 49].

Anti-tumor necrosis factor-α monoclonal antibodies have traditionally been used to treated various autoimmune conditions and empirically for irAEs. This treatment has had some reported success with irAEs, most notably for corticosteroid-refractory colitis [50–53]. Because of limited data on interactions between non-steroidal immunosuppression and ICIs, some suggest that immunosuppression should take a step-by-step approach utilizing high-dose corticosteroids as a base before additional agents based on empiric treatment strategies [54]. However, other schools of thought would suggest that agents with a less presumed T-cell impact should be prioritized over corticosteroids (e.g., narrow-band UVB, acitretin, dupilumab, hydroxychloroquine). Ultimately, more studies are needed to assess the impact of these immunomodulating agents on tumor-specific immunity. Close collaborations between oncologists and dermatologists are needed to balance the risks and benefits of specific immunotherapies, taking into consideration the co-morbidities of each patient.

4.4 Balancing Toxicity and Treatment

While some treatment discontinuation decisions may be straightforward based on existing guidelines, other situations (e.g., chronic bothersome toxicities, unclear attribution of event) may be more challenging. This is particularly true as studies have suggested that irAEs may serve as a marker for anti-tumor efficacy and better prognosis [79, 80]. This concept is further supported by the significant variation between clinicians in assessing the occurrence, type, timing, and severity of irAEs [81]. Thus, the decision to discontinue ICIs for cirAEs may be more fluid and individualized with the input from dermatologists, ultimately improving patient outcomes [27].

Table 2 Summary of non-steroidal treatment options based on a review of the literature

Skin-directed therapy	Drug class	Proposed indications
Narrow-band UVB therapy [26, 30, 39, 55]	Phototherapy	Psoriasiform, lichenoid
Calcipotriol, maxacalcitol, tacalcitol, calcitriol [56, 57]	Vitamin D_3 analog	Psoriasiform
Tacrolimus, pimecrolimus [30]	Calcineurin inhibitor	Lichenoid, psoriasiform, pruritus
Tazarotene [58, 59]	Retinoid	Psoriasiform
Diphenhydramine, doxepin [60]	Antihistamine	Pruritus
Systemic therapy	**Drug class**	**Proposed indications**
Infliximab, adalimumab, etanercept [26, 30, 61, 62]	Tumor necrosis factor inhibitor	SJS/TEN, psoriasiform, lichenoid
Tacrolimus [30]	Calcineurin inhibitor	Lichenoid, psoriasiform, pruritus
Ustekinumab, guselkumab [30, 61]	Cytokine inhibitor (IL-12 and/or IL-23)	Psoriasiform
Dupilumab [63, 64]	Cytokine inhibitor (IL-4 and IL-13)	Immunobullous, pruritus
Intravenous immunoglobulin [22, 30, 48, 65]	Human immunoglobulin (IgG, IgA, IgM)	SJS/TEN, immunobullous
Cyclosporine [22, 30, 61, 66]	Calcineurin inhibitor	SJS/TEN
Mycophenolate mofetil [48, 67, 68]	Inosine-5′-monophosphate dehydrogenase inhibitor	Immunobullous, lichenoid
Tocilizumab [43, 54]	Cytokine inhibitor (IL-6)	Lichenoid
Apremilast [26, 30, 61]	Phosphodiesterase-4 inhibitor	Psoriasiform, lichenoid
Methotrexate [26, 30, 61]	Folate antagonist	Psoriasiform, immunobullous, lichenoid
Hydroxychloroquine [26, 66, 69, 70]	Unknown	Lichenoid
Acitretin [26, 30, 39, 61]	Retinoid	Psoriasiform, lichenoid
Ritixumab [22, 30, 71]	Anti-CD20 monoclonal antibody	Immunobullous
Aprepitant [72]	Substance P/neurokinin 1 receptor antagonist	Pruritus
Omalizumab [30, 73]	IgE inhibitor	Pruritus, immunobullous
Pregabalin, gabapentin [26, 39]	GABA agonist	Pruritus
Amitriptyline, doxepin, nortriptyline [60, 74–76]	Tricyclic antidepressant and antihistamine	Pruritus
Mirtazapine [77]	Atypical antidepressant	Pruritus
Hydroxyzine [78]	Antihistamine	Pruritus

IL interleukin, *NB-UVB* narrowband UVB, *SJS/TEN* Stevens–Johnson syndrome/toxic epidermal necrolysis

As noted, existing guidelines can guide most treatment continuation/discontinuation decisions. Severe or life-threatening events certainly necessitate discontinuation, whereas mild asymptomatic eruptions do not. However, there are "gray areas" where this decision can be quite challenging, specifically patients with persistent bothersome grade 1–2 cirAEs. There are no absolute guidelines here, but a few principles may be useful. First, dermatology referral is essential to ensure all potential options for the management of cirAE symptoms are being optimized (e.g., optimal-strength topical corticosteroids). Second, concurrent systemic therapy and ICIs may be indicated in some patients; for example, we often continue patients with a low dose of corticosteroids (e.g., 5–10 mg) along with ICIs for ongoing skin or joint irAEs. Another example would include a patient with severe lichenoid eruption who may be able to successfully continue ICI therapy while also receiving apremilast and phototherapy. Third, the patient's cancer situation should be assessed: patients who have obvious progressive disease or an alternatively complete response after a long duration of therapy may appropriately discontinue ICIs, whereas patients who are benefiting from ICIs, or are in the early stages of therapy may need more aggressive measures to continue ICI treatment.

4.5 Rechallenge

Current guidelines recommend permanent discontinuation of ICIs following severe cirAEs; however, rechallenge is often possible after treatment with corticosteroids and temporary discontinuation in less severe cases [82, 83]. Rechallenge is considered in two settings: (1) responding patients who discontinue treatment for toxicity and later progress and (2) patients who complete a course of corticosteroids with improvement. There is a current lack of prospective data regarding the outcomes of rechallenge for specific toxicities and cancer types.

Immune-related adverse event recurrence after rechallenge may present as the same initial irAE or a new clinically distinct entity. Although death or severe morbidity from rechallenge is fairly rare, recurrence is still relatively common [84]. The incidence of all-grade irAEs after an ICI rechallenge has been reported to range from 27.5 to 57.5% [85, 86]. A cross-sectional pharmacovigilance cohort study of 24,079 cases found a recurrence rate of 28.8% of the same irAE associated with initial discontinuation. Other retrospective studies have found similar irAE rates with a range from 18 to 42% [82, 83, 87]. The incidence of clinically significant but distinct toxicities ranges from 4.4 to 26%, and probably lower than the risk of the same irAE recurring [87–89]. Rash has been reported to be among the most common irAEs after rechallenge [90].

Several important questions should be considered with rechallenge including the timing, agent, survival benefits, and irAE recurrence risk factors. Meta-analyses of outcomes have shown that rechallenge is associated with survival benefits but with irAE recurrence rates that are slightly higher than those reported for naïve patients treated with ICIs [85, 86, 90]. Overall antitumor response rates to rechallenge have been reported between 20 and 43.1% for multiple cancer types including melanoma, non-small cell lung cancer, colorectal cancer, and renal cell carcinoma [87, 91, 92]. Response to ICI reinduction is possible even after disease progression [86, 93, 94]. Some studies have reported that patients with cancer who develop high-grade irAEs before being rechallenged actually have a superior response to treatment and survival outcomes than patients who do not develop irAEs [90, 95, 96]. This is based on the postulation that toxicities reflect underlying immunotherapy activity, acting as a surrogate marker for efficacy, and has been best demonstrated with the correlation of de novo vitiligo-like rash with survival benefits in patients with metastatic melanoma [15].

Clinical predictors and risk factors for irAE recurrence may include the need for immunosuppression for initial irAE, longer duration of symptoms, and rechallenge with anti-CTLA-4 therapy [82]. Conversely, anti-PD-1/PD-L1 antibodies by be associated with a lower recurrence rate of irAEs compared with anti-CTLA-4-containing regimens [85]. Patients rechallenged after previous toxicity have a decreased risk for recurrence compared with those rechallenged after progression [86]. Another question surrounds patients treated with anti-CTLA-4 and anti-PD-1 combination therapy who experience toxicity and whether they should be rechallenged with anti-PD-1 monotherapy. In these cases, the rates of recurrent irAEs and clinically distinct toxicities appear to be somewhat lower [83].

Most recurrent toxicities are low grade and manageable with treatment [89]. Ultimately, with the exception of patients with a history of drug reaction with eosinophilia and systemic symptoms or SJS/TEN, rechallenge may be a safe and effective treatment option for a subset of patients and should be considered on an individual basis. Of note, skin testing and drug desensitization are additional options for rechallenge that have been described for ICI-drug hypersensitivity reactions, an etiologically distinct but clinically similar entity [97]. As one of the most common irAEs with initial ICI treatment, the rate of cirAE recurrence is relatively high compared with other toxicities, but most are mild and treatable. However, the risk-benefit ratio should be considered and in patients who have had a durable response to ICIs prior to toxicities, observation may be considered over resumed maintenance therapy.

4.6 Management in Patients with Pre-existing Autoimmune Disease, Skin Conditions, and Solid Organ Transplant

Because ICIs augment immune system activity, irAEs present similarly to ADs. Cytotoxic T-lymphocyte-associated protein 4 and PD-1 have both shown to be involved in the pathogenesis of several autoimmune conditions [98, 99]. As such, exacerbations of pre-existing autoimmune conditions and a potentially increased risk of de novo irAEs is possible. Patients with pre-existing autoimmune conditions were previously excluded from clinical trials because of concerns surrounding disease exacerbations [100, 101]. Thus, most existing data for ICI use in patients with ADs are from retrospective reviews and case series. A significant proportion of patients with cancer have active comorbid ADs or a history of ADs (approximately 10% of older patients with lung cancer); thus, these patients must be considered for ICI therapy [102]. Skin ADs are relatively common and include psoriasis, vitiligo, scleroderma, cutaneous lupus, dermatomyositis, Behcet's disease, pemphigus vulgaris, and bullous pemphigoid. While the prevalence of more common cutaneous ADs range from 0.5 to 2% in vitiligo to 3.0% in psoriasis [103, 104], the prevalence of more severe conditions such as bullous pemphigoid (0.012%) is much lower [105].

Pre-existing AD flares are frequent during with ICI treatment, with a range from 41 to 55%, while de novo irAEs are less common with a range from 25 to 42% [101, 106–108]. Notably, there does not seem to be a substantially increased risk of classical irAEs in patients with active ADs versus inactive pre-existing Ads [101]. Studies have reported that overall survival and tumor response rate do not appear to differ between patients with or without ADs, but additional studies are needed to confirm this [101, 107].

Immune checkpoint inhibitors have been documented to lead to worsening or flares of pre-existing cutaneous conditions, most notably psoriasis [109]. Specifically, we observed that approximately half of patients with pre-existing psoriasis experienced a flare, although only 7% required

ICI discontinuation, and topical therapy was often sufficient to manage the usually low-grade flares. Case series have reported generally similar findings for a wide spectrum of pre-existing skin disease including cutaneous lupus erythematosus and scleroderma, with most flares being mild, and/or responsive to standard therapies, and not requiring treatment discontinuation [110, 111]. Thus, in most cases, underlying AD is not a contraindication for ICI therapy, and patients should be monitored closely and managed appropriately for disease flares. We propose that dermatologists and oncologists collaborate to develop treatment strategies for patients with active ADs. This may include the selection of specific selective immunosuppressive agents that minimize side effects and unnecessary long-term corticosteroid exposure.

Another population with challenging management and unique considerations is the solid organ transplant (SOT) patient population. They have been excluded from clinical trials because of the risk of organ rejection, thus little is known about ICI use in this population. However, as a result of the actions of immunosuppressive drugs used to prevent graft rejection, these patients are predisposed to the development of malignancies such as non-Hodgkin lymphoma, melanoma, non-melanoma skin cancers, lung cancer, liver cancer, and kidney cancer, many of which are indications for ICIs [112]. Systematic reviews of ICIs in SOT patients report that between 37 and 41% of patients experience graft rejection due to ICIs [113, 114]. Most studies report that PD-1 therapies, particularly nivolumab (52% vs 25–27% in other agents), have the highest risk of graft rejection [113, 115, 116]. A pharmacovigilance study of SOT patients found an overall mortality rate of 40.4% [117]. However, most deaths were not related to graft failure or rejection, but to disease progression or secondary to underlying comorbidities [113].

Despite the very considerable toxicities, disease control was reasonable in these patients. One review found a total disease control rate of 35% with a concurrent antitumor response and durable graft tolerance in 21% of patients [118]. Notably, tumor response seems to be higher in patients with skin cancer including melanoma and squamous cell carcinoma [114]. Although no specific immunosuppressive regimen seems to have an advantage in preventing graft failure, the maintenance of prior immunosuppressive regimens may play a protective role, and additional studies are needed in this area [119].

Immunosuppressive regimens include monotherapy or a combination of the following: tacrolimus, sirolimus, mycophenolate mofetil, everolimus, cyclosporine, azathioprine, or prednisone [116]. Currently, there is no treatment consensus in this population. In general, acute cellular rejection in the setting of ICI therapy should follow acute rejection guidelines consisting of high-dose corticosteroids [120, 121]. The efficacy of these guidelines are unknown in ICI-treated patients as graft loss rates have been reported to be as high as 80% even with high-dose corticosteroids and immunosuppressive escalation [117]. Clinical trials are currently being conducted to characterize how tacrolimus, nivolumab, and ipilimumab interact in kidney transplant recipients with cancer, with a focus on malignancies that respond well to ICIs, especially skin cancers [122].

Ultimately, ICI use in SOT with cutaneous malignancies is a very complex decision. As cutaneous malignancies respond particularly well to ICIs and untreated disease may equal a death sentence, a frank discussion of the risks and benefits is needed for each patient. For example, anti-PD-1 could be considered for kidney transplant patients with metastatic melanoma, whereas a patient with a heart transplant and a less responsive tumor type may not want to consider therapy. A careful approach with a multidisciplinary team including transplant surgeons, oncologists, dermatologists, and transplant organ-specific experts is needed for treatment planning and management of these patients. Patients should receive full disclosure of the risks and benefits of treatment.

5 Conclusions

As the indications for ICIs continue to expand, the role of oncodermatology and interdisciplinary collaborations with oncologists are increasingly important. Immune checkpoint inhibitors are associated with a wide range of cutaneous toxicities with varied morphologic presentations, providing challenging and unique dermatologic considerations. Involvement of dermatologists is essential to facilitate early diagnosis and effective treatment strategies to minimize unnecessary harm for patients.

Declarations

Funding No external funding was used in the preparation of this article.

Conflicts of interest/competing interests BCP, SJ, STC, AD, and DBJ have no conflicts of interest that are directly relevant to the contents of this article.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials Not applicable.

Code availability Not applicable.

Author contributions BCP, SJ, STC, AD, and DBJ wrote the main manuscript text. BCP and DBJ prepared Tables 1 and 2. All authors reviewed the manuscript.

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