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ORIGINAL ARTICLE

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USCOM Algorithm for the Prevention and Management of Cutaneous Immunotherapy-Related Adverse Events

Alana Deutsch MD,[a] Mario Lacouture MD,[b] Anneke Andriessen PhD,[c] Jennifer N. Choi MD,[d] Alice Y. Ho MD,[e] Beth N. McLellan MD,[f] Edith Mitchell MD,[g] Jonathan S. Leventhal MD[a]

[a]Department of Dermatology, Smilow Cancer Hospital at Yale, New Haven, CT
[b]Division of Oncodermatology, Memorial Sloan Kettering Cancer Center, New York, NY
[c]Radboud UMC, Nijmegen and Andriessen Consultants, Malden, The Netherlands
[d]Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL
[e]Department of Radiation Oncology, Duke University School of Medicine, Durham, NC
[f]Department of Medicine, Division of Dermatology, Albert Einstein College of Medicine, Bronx, NY
[g]Department of Medical Oncology, Center to Eliminate Cancer Disparities, Sidney Kimmel Cancer Center at Jefferson, Philadelphia, PA

ABSTRACT

Background: In 2023, nearly 2 million patients will be diagnosed with cancer in the United States and at least 40% will be eligible for treatment with an immune checkpoint inhibitor (ICI). Cutaneous immune related adverse events (cirAEs) from ICIs are common and include pruritus as well as maculopapular, eczematous, bullous, lichenoid, and psoriasiform reactions. All clinicians interfacing with cancer patients must expedite proper evaluation and diagnosis, treatment, and/or consultation that supports the need for evidence-directed guidelines.

Materials and Methods: A panel of advisors was selected, and a systematic literature review generated foundational evidence to develop a treatment algorithm for cirAEs via a modified Delphi process. Iterations of the algorithm were performed until the group met consensus.

Results: An algorithm that tailors the management of cirAEs was developed based on the CTCAE v.5 grading of skin disorders. Representative clinical images and suggested diagnostic measures, supplement the algorithm.

Conclusion: Recognition and treatment of cirAEs guided through a multidisciplinary, physician-developed algorithm will limit disruption of immunotherapy, optimize quality of life, and enhance overall outcomes in patients treated with ICIs.

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INTRODUCTION

In 2023, an estimated 1,958,310 Americans will be diagnosed with cancer.[1] Although overall incidence continues to rise, ongoing advancements in anticancer therapy have contributed to improved survival. Moreover, some historically fatal malignancies are now being treated akin to chronic disease, exposing a new spectrum of drug toxicities both from novel agents as well as extended duration of use. Immunotherapy, specifically immune checkpoint inhibitors (ICIs), has been a foundation of such management, with expanding indications for therapeutic interventions for cancer patients.

Broadly, immunotherapy activates the body's immune system to fight cancer. ICIs do so by blocking T-cell inactivation receptors, which are used by malignant cells for evasion, to maintain inherent immune mediated anti-cancer activity.[2,3] ICIs are approved for treatment of numerous solid-organ tumors and a few hematologic malignancies, acting as first-line therapy in many instances.[2,3] In 2019, approximately 40% of all cancer patients in the United States were eligible for treatment with immunotherapy,4 which may be administered as a single agent, combination immunotherapy, or alongside alternate classes of medications such as cytotoxic chemotherapy and targeted therapy.[2-4]

In parallel to immunotherapy use, the characterization of cutaneous immunotherapy-related adverse events (cirAEs) is becoming increasingly recognized and refined. Adverse skin reactions occur in 14% to 47% of patients treated with ICIs, which range from mild and localized to debilitating and widespread.[5,6] cirAEs vary based on class and dose of immunotherapy administered, type of cancer being treated, and patient-specific factors, and can arise at any time during treatment or after discontinuation.[5-15] Thus, dermatologists remain integral members of cancer care teams in which they provide expectant management, enhance preventative skin care practices, and

support patients through treatment to facilitate optimized anticancer management while limiting cutaneous toxicities and maximizing quality of life.[16] Patients receiving dermatologic care are more likely to resume their ICI after a cirAE and may even have better outcomes.

Project Update

The United States Cutaneous Oncodermatology Management (USCOM) project was developed to improve cancer patients' and survivors' quality of life by offering tools for preventing and managing cutaneous adverse events related to cancer therapy.

The USCOM consortium has previously published 2 foundational algorithms for skin management in cancer patients: 1) an algorithm to reduce the incidence of cirAEs, treat cirAEs, and maintain healthy skin using general measures and over-the-counter agents,[17] and 2) an algorithm to prevent and treat acute radiation dermatitis.[18] These algorithms aim to support all healthcare providers treating oncology patients, including physicians, nurses, pharmacists, and advanced providers.

The next step in the project is to develop a practical algorithm for the prevention and treatment of immunotherapy-related cutaneous adverse events, which we propose here.

MATERIALS AND METHODS

A selected group of multidisciplinary advisors used the AGREE II instrument following the modified Delphi method to develop the USCOM practical algorithm for the treatment of cirAEs.[19,20] The modified Delphi method is a communication technique for interactive decision-making for medical projects.[20]

During a face-to-face meeting on February 4, 2023 the outcome of a systematic literature review identifying the spectrum of cirAEs, specifically pruritus and the inflammatory dermatoses, and addressing their prevention and treatment was discussed and the practical algorithm was developed based on the assembled evidence coupled with the panel's experience and opinion. An online process was used to fine-tune the practical algorithm and prepare and review the publication.

Literature Review

The systematic literature review included guidelines, consensus papers, and clinical or other research publications on the prevention and management of cirAEs published in English from January 2010 to October 2022. Articles were excluded if they contained no original data (unless a review article was deemed relevant), if they were not relevant to cirAEs, or if the publication language was other than English.

A dermatologist and a physician-scientist conducted the searches on October 26 and 27, 2022. PubMed was the primary search engine, with Google Scholar as a secondary source. The search criteria used were as follows: *cirAEs AND isolated pruritus OR psoriasis OR lichen planus OR eczematous eruptions OR bullous eruptions AND QoL OR prevention OR treatment OR maintenance with prescription therapy OR skincare OR adjunctive skincare OR education of staff and patients.*

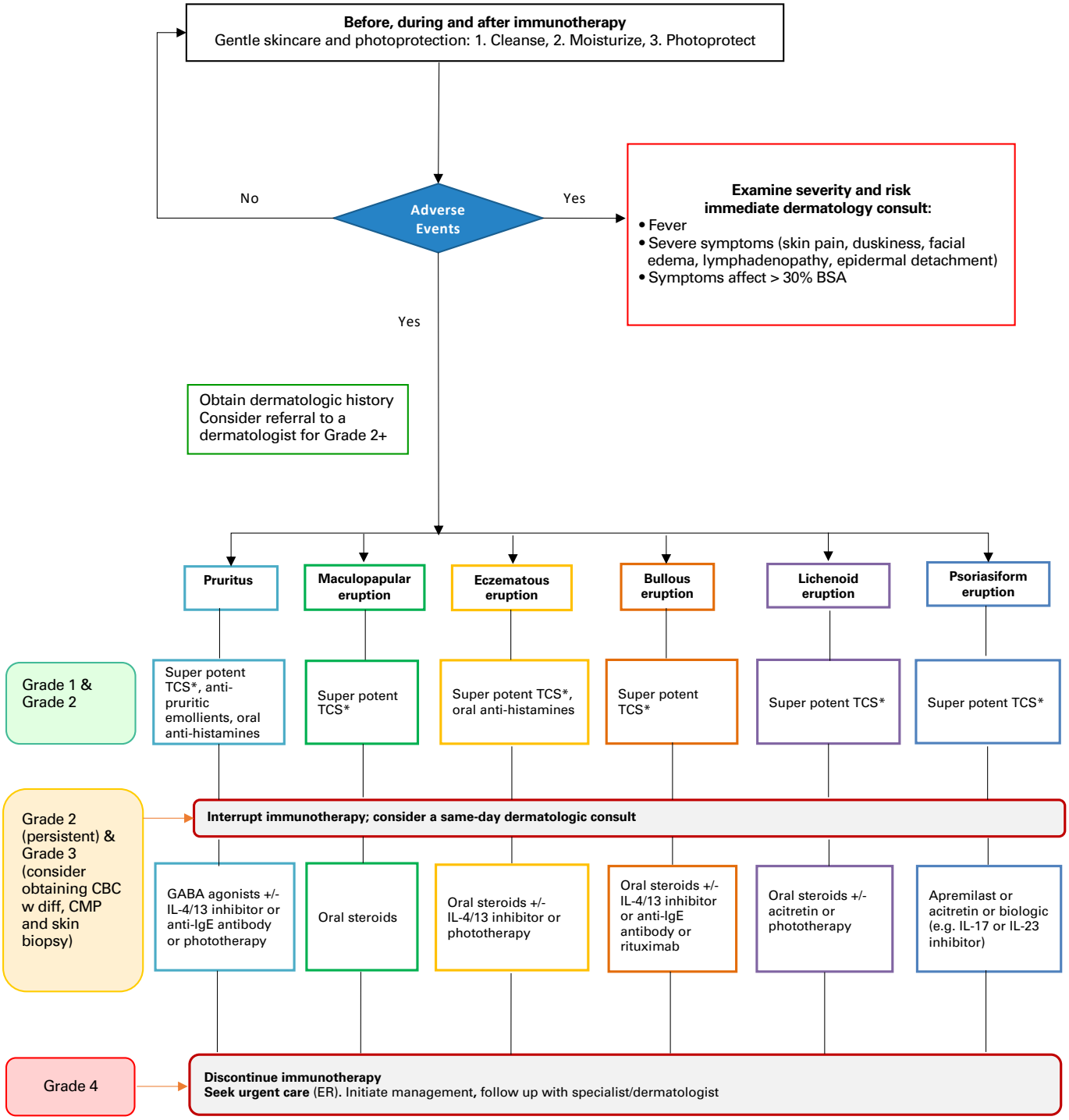
The results of the searches were evaluated independently by 2 reviewers who resolved discrepancies through discussion. The searches yielded 106 publications. Ninety-four papers remained after excluding duplicates and articles not deemed relevant (other subjects, low quality). The 94 included papers addressing cirAEs were comprised of: 2 guidelines and algorithms, 8 systematic literature reviews, 10 consensus papers, 17 reviews, 42 clinical studies, and 15 other research studies. Case reports were included because they provide valuable information in this fast-developing field. Moreover, cirAEs possess complex issues, including their presentation and appropriate management on a patient-to-patient basis, that are difficult to capture in randomized controlled settings. Two reviewers evaluated the literature search results and graded the clinical publications. Grading and rating of evidence included study type and quality (grade A to C) and level of evidence (level 1 to level 4) using pre-established criteria.18 The paucity of studies on cirAE treatment, with both general skincare and prescription medications, made grading less relevant; however, the guidelines, systematic literature reviews, and consensus papers provided valuable information.

The Algorithm

An algorithm for the prevention and management of cirAEs was created based on results of the systematic literature review as well as expert experience and opinion (Figure 1). As with the USCOM Algorithm II for the prevention and management of acute radiation dermatitis,[18] the proposed algorithm expands on the USCOM algorithm for cancer-treatment-related cAEs,[17] which uses the Common Terminology Criteria for Adverse Events (CTCAE) grading system v.5 (Table 1).

As with other anticancer therapies, early identification of severe cAEs – which may be detected by signs and symptoms including fever, skin pain, epidermal changes, high body surface area involvement, or laboratory abnormalities – is an important first step because, regardless of the cutaneous reaction, the patient will require immediate evaluation by a clinician and possibly a dermatologist. Often inpatient or ICU level care is required for management. When red flag signs or symptoms are not present, recommendations become specific to type of cutaneous reaction with therapeutic distinctions for the following classes: eczematous or maculopapular, bullous, lichenoid, and psoriasiform eruptions as well as pruritus. Evaluation for more systemic organ involvement should be performed imme-

FIGURE 1. United States Cutaneous Oncodermatology Management III algorithm for the prevention and management of immunotherapy-related cutaneous adverse events.



*Use with caution in sensitive areas (e.g. face, genitals, intertriginous zones)

TABLE 1.

Common Terminology Criteria for Adverse Events (CTCAE v.5) Grading of Skin Disorders					
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching; oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	--	--
Eczema	Asymptomatic or mild symptoms; additional medical intervention over baseline not indicated	Moderate; topical or oral intervention indicated; additional medical intervention over baseline indicated	Severe or medically significant but not immediately life-threatening; IV intervention indicated	--	--
Rash maculopapular	Rash covering <10% BSA with or without symptoms	Rash covering 10-30% BSA with or without symptoms; limiting instrumental ADL; rash covering >30% BSA with or without mild symptoms	Rash covering >30% BSA with moderate or severe symptoms; limiting self care ADL	--	--
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10-30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Skin disorders - Other	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or non-invasive, intervention indicated; limiting age-appropriate instrumental ADLs	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

ADL, activity of daily living; BSA, body surface

diately and established interventions instituted. Interventions are stepwise based on cirAE severity and offered alongside grade-based recommendations for discontinuation or interruption of immunotherapy. Treatment recommendations for each cirAE class will be expanded upon below.

Type of Cancers Treated With Immune Checkpoint Inhibitors

ICIs can be classified based on the proteins they inhibit: cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), lymphocyte activation gene-3 (LAG-3), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1). Except for the novel LAG-3 inhibitor, multiple drugs exist within each class with various oncologic indications (Table 2).

Immune Checkpoint Inhibitors and Associated Cutaneous Adverse Events

While the heightened immune response activated by ICIs has meaningful anti-cancer effects, the ensuing immunologic commotion can idiosyncratically confront any host organ system including the skin. Cutaneous immune related adverse events (cirAEs) develop in up to 60% of ICI-treated cancer patients, with the highest rate in those receiving combination immunotherapy (59-72%) followed by anti-CTLA-4 (44-59%), anti-PD1 (34-42%), and anti-PD-L1 (~20%) monotherapies.[5,25-27] The median time to onset of cirAEs is 4 weeks, often presenting as the first treatment-related toxicity; however, a broad temporal range has been reported from time of onset to years later, including beyond treatment discontinuation.[5,12]

Inflammatory dermatoses including maculopapular, eczematous, bullous, lichenoid, and psoriasiform eruptions predominate the cirAEs, as well as pruritus. Less common manifestations include granulomatous eruptions, keratinocyte carcinomas, alopecia, rheumatologic dermatoses, severe cutaneous adverse reactions, and others.[25] ICI-induced pigmentary changes are also important to recognize, particularly the development of vitiligo-like depigmentation in the setting of melanoma which is associated with improved response to treatment. While some patients with pre-existing dermatologic conditions may have ICI-induced exacerbation of their chronic skin disease, it is impossible to predict which patients will develop cirAEs and which type they will develop. According to CTCAE (v.5) categorization, cirAEs are generally mild to moderate with severe toxicity (grade 3-4) occurring in <5% of those receiving combination immunotherapy and <3% in monotherapy. Treatment discontinuation because of a cirAE is likewise approximately 5%.[27] Importantly, ICI anti-cancer efficacy has been correlated with extent of immune activation, and an association between the development of cirAEs and clinical benefit (ie, progression-free survival) has been shown.[28,29] Therefore, treatment of cirAEs, when safe and appropriate, can limit ICI-

TABLE 2.

Immunotherapy Classes, Molecules, and Indications[21-24]		
CTCAE Term	**Grade 1**	**Grade 2**
CTLA-4 inhibitors	Ipilimumab	Colorectal Kidney Liver Lung Melanoma
	Tremelimumab	Lung
LAG-3 inhibitors	Relatimab	Melanoma
PD-1 inhibitors	Cemiplimab	Basal cell carcinoma Lung Cutaneous squamous cell carcinoma
	Dostarlimub	Uterus Mismatch repair deficient recurrent or advanced solid tumors
	Nivolumab	Bladder Colorectal Esophagus Gastric Head and neck Kidney Liver Lung Lymphoma Melanoma Mesothelioma
	Pembrolizumab	Bladder Breast Cervix Colorectal Cutaneous squamous cell carcinoma Esophagus Gastric Head and neck Kidney Liver Lung Lymphoma Melanoma Merkle cell carcinoma Stomach
PD-L1 inhibitors	Atezolizumab	Bladder Breast Liver Lung Melanoma
	Avelumab	Bladder Kidney Merkel cell carcinoma
	Durvalumab	Bladder Lung

*Oncologic indications are non-all-encompassing for the listed organ. Each agent has specific FDA-approved indications for subvarieties of each type of cancer based on biology and/or behavior.

disruption or discontinuation, which is paramount to improved outcomes. Such treatment must be efficacious without adding additional harm; therefore, broad immunosuppression, including systemic corticosteroids, should be avoided when possible.

For each cirAE, specific treatment approaches will be discussed, but gentle skin care should be reviewed with all patients. This includes gentle cleansing with soap and water as well as daily use of hydrating emollients such as lotions, creams, or ointments based on the extent of xerosis as well as personal preference. Hygiene and cleaning products should be fragrance-free, and patients should avoid introducing new products into their routines whenever possible. As with gentle skin care, recommendations regarding the decision to discontinue or interrupt immunotherapy are fairly standardized. Such consideration is taken in patients with grade 3 reactions, during which immunotherapy can be held while addressing the cirAE. This warrants consideration of same-day consultation with a dermatologist when assistance is desired. When the cutaneous reaction has been addressed, immunotherapy may be restarted

with close follow-up; however, expectant management should be provided in that subsequent dosing could flare up cutaneous disease. While with grade 3 reactions there is room to harness control of cirAEs and treat through immunotherapy after brief interruption, grade 4 reactions should prompt immediate ICI discontinuation and urgent care should be sought.

Pruritus

ICI-related pruritus occurs in nearly half of patients and can be found in isolation or association with any cutaneous finding. With the former, secondary skin changes including excoriations and hyperpigmentation are frequently seen. Regardless of cutaneous associations, ICI-related pruritus is most common on the scalp, trunk, and extremities, with relative sparing of the head, neck, and acral surfaces. Notably, ICI-related pruritus has been demonstrated to be independently associated with lower patient quality of life.[30]

Treatment of pruritus of any severity includes oral antihistamines and frequent application of emollients. Topical corticosteroids may also be used, and intralesional corticosteroids can be helpful for secondarily developed prurigo nodules. While these measures are typically sufficient for mild-moderate pruritus, more severe disease necessitates additional systemic therapy, including oral agents like gabapentin/pregabalin (neuronal calcium channel inhibitors), naloxone/naltrexone (mu-opioid antagonists), and aprepitant (neurokinin-1 receptor antagonist). Dupilumab (anti-IL4-Ra monoclonal antibody), which is an injectable performed either in office or at home, is an alternative. Phototherapy with narrowband ultraviolet B, typically initiated at 2 to 3 times per week, may also provide benefit and is a useful option in patients motivated to avoid additional systemic therapeutics or when they are contraindicated. Systemic corticosteroids are only necessary in debilitatingly severe cases or those unresponsive to all above measures, which is uncommon.[25,31-34]

Maculopapular Eruption

Maculopapular or eczematous eruptions occur in ~25% of patients treated with anti-CTLA-4 therapy and ~10% to 20% treated with anti-PD-1/PD-L1 therapy, occurring early in treatment and within a dose-dependent manner. These cutaneous reaction patterns have historically been discussed jointly; however, given morphologic, histologic, and therapeutic differences, it is helpful to consider them as related yet distinct entities, as we will here.

Maculopapular eruptions are reminiscent of a morbilliform exanthem with coalescing erythematous macules and papules, which may become confluent. The trunk and extremities are most commonly involved, and patients often report pruritus. A subset of these patients may go on to develop lichenoid, psoriasiform, or eczematous reactions. As with other drug-induced maculopapular eruptions, it is prudent to monitor for progression into a severe cutaneous adverse reaction such as drug reaction with eosinophilia and systemic symptoms (DRESS) or Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN).[5,13,25,32] Treatment of maculopapular eruptions relies on topical corticosteroids for symptomatic management and hastened resolution. Systemic steroids are reserved for the mentioned severe cutaneous adverse reactions. Tocilizumab, a monoclonal antibody against IL-6R, has also demonstrated efficacy in managing severe, refractory ICI hypersensitivity reactions.[35]

Eczematous Eruption

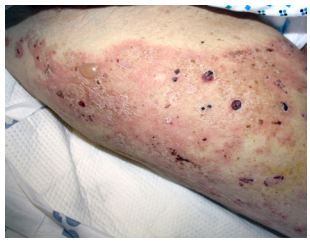
Eczematous eruptions present with pruritic erythematous papules and plaques with scale, which may appear like atopic, asteatotic, or nummular dermatitis. These reactions typically occur on the trunk and extremities and may become confluent.[5,25] Topical therapies, including moderate potency corticosteroids and calcineurin inhibitors, are the therapeutic mainstay for mild-moderate disease, which are used adjunctively with liberal application of emollient. Systemic antihistamines may benefit associated pruritus. More severe reactions can be addressed with dupilumab or narrowband UVB phototherapy in addition to increased potency of topical corticosteroids. Oral steroids should only be considered when persistent or severe.

Bullous Eruption

Bullous disorders are rare cirAEs, but they present more frequently in patients treated with anti-PD-1/PD-L1 therapy.[5] Mean time to onset is 14 weeks after ICI initiation, which is delayed compared with other cutaneous reactions.[13] Affected patients often develop intense pruritus followed by characteristic tense bullae and/or non-bullous urticarial or eczematous plaques (Figure 2).

The oral mucosa is involved in less than one-third of cases.[36,37] Diagnostic evaluation is akin to classic disease, which includes identification of a subepidermal split and numerous eosinophils on histopathology, linear deposition of immunoglobulin G and C3 along the basement membrane on direct immunofluorescence, and peripheral detection of antibodies against hemidesmosomal proteins (BP180 and BP230).[13,25]

FIGURE 2. Immune checkpoint inhibitor-induced bullous pemphigoid. Urticarial plaques with tense vesicles and bullae and erosions on the thigh of a light-skinned patient.



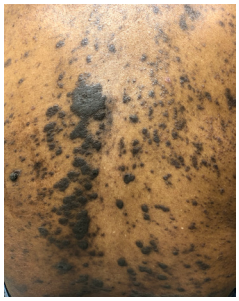
Wound care and infection prevention are essential when there is denuded skin. Gentle cleansing is a daily priority, as well as maintaining moist occlusion of affected areas. Limited disease may be managed with super potent topical corticosteroids; yet patients with bullous disease that is symptomatic, limits daily routine, or covers >30% of body surface area require systemic therapy. Systemic corticosteroids may provide immediate effect but should be limited when possible with preference for steroid-sparing agents for long-term maintenance therapy. Steroid-sparing agents include dupilumab, omalizumab, dapsone, methotrexate, and rituximab.[25,36-40] Doxycycline and niacinamide may be used in mild presentations, but careful consideration should be taken with ICI-induced bullous pemphigoid given the association of systemic antibiotic use with dysregulation of the gut microbiome, which has been shown to potentially restrict the intended immune response of ICIs.[41]

Lichenoid Eruption

Lichenoid eruptions are associated with anti-PD-1/PD-L1 therapy and occur in 6% to 25% of patients.[6,13,42] The clinical presentation is variable, with classic pruritic erythematous to violaceous flat-topped papules and plaques with Wickham striae seen frequently on the trunk and extremities (Figure 3). However, bullous, erosive, hypertrophic, inverse, papulosquamous, transient acantholytic dermatosis-like, and oral variants have been described. Lichenoid eruptions may also mimic eczematous or maculopapular reactions; however, their onset is typically later in the treatment course, with a mean time to onset of 4 months; and histopathologic features are distinguishing.[5,43,44]

Mild-moderate lichenoid eruptions can be treated with topical therapies including moderate strength corticosteroids, calcineurin inhibitors, or vitamin D analogues. Systemic corticosteroids can be considered for moderate-severe disease with transition to steroid-sparing agents such as acitretin, narrowband UVB phototherapy, doxycycline, and cyclosporine.[5,25,42,45] Classic lichen planus has been treated with dupilumab[46-48] as well as biologic inhibitors of interleukin-17 (IL-17) and tumor necrosis factor-a (TNF- a);[49,50] thus efficacy of these therapies for ICI-induced lichenoid eruptions is feasible and may be considered for refractory disease. Nonetheless, the benefits of biologic therapy are theoretical, and effects on a patient's malignancy must be considered, so shared decision-making with the oncologic team is essential.

FIGURE 3. Immune checkpoint inhibitor-induced lichenoid dermatitis. Violaceous to hyperpigmented flat topped papules and plaques on the back of a patient with a darker skin phototype.



Psoriasiform Eruption

ICI-associated psoriasiform eruptions are most common in patients with a history of psoriasis, and these patients tend to flare soon after initiation of immunotherapy. *De novo* disease represents a minority of reported cases and occurs later in the treatment course. Plaque psoriasis is typical, although guttate, pustular, inverse, and scalp-limited varieties have been described, along with psoriatic arthritis.[5,25,51,52]

Topical therapies including moderate strength corticosteroids, calcineurin inhibitors, and vitamin D analogues are foundational for psoriasiform eruptions and are typically sufficient in mild-moderate disease. Moderate-severe or recalcitrant disease can be treated with classic psoriasis therapeutics such as apremilast, acitretin, and narrowband UVB phototherapy.[5,53] Systemic steroids may be used in devastating disease, although it is generally avoided given the propensity for rebound flaring when discontinued. Oral immunosuppressives used in classic disease, such as methotrexate and cyclosporine, are generally discouraged given their contraindication in cancer patients. Similarly, biologics including inhibitors of TNF-a, IL-17, interleukin-12/23 (IL-12/23), interleukin-23 (IL-23), which are routinely used in classic psoriasis, are approached with hesitancy given the historical belief that they may propagate malignancy. Ongoing research suggests that these proinflammatory pathways may facilitate progression and metastasis in certain malignancies, so their inhibition may provide theoretical anti-cancer benefit in these cases while also treating the psoriasiform eruption.[54,55]

CONCLUSION

Widespread application of ICIs is improving cancer outcomes; however, cirAEs are common and necessitate rapid and appropriate recognition, diagnosis, and management in order to limit the severity and duration of toxicity that leads to the interruption of therapy and more severe complications and ultimately to promote an optimized quality of life. All clinicians interfacing with cancer patients should be able to recognize these common cutaneous reactions to expedite consultation or proper treatment, as suggested by the multidisciplinary physician-developed algorithm. Moderate-severe or recalcitrant cutaneous reactions are best managed cooperatively with a dermatologist and the oncologic team so that therapeutic interventions have enhanced effects, time away from intended anti-cancer treatment is minimized, and patient experience is improved.

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AUTHOR CORRESPONDENCE

Jonathan Leventhal MD

E-mail:..... jonathan.leventhal@yale.edu