Dermatologic toxicities to immune checkpoint inhibitor therapy: A review of histopathologic features

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Antineoplastic agents that use the immune system have revolutionized cancer treatment. Specifically, implementation of immune checkpoint inhibitors, monoclonal antibodies that block cytotoxic T-lymphocyte–associated antigen-4, programmed cell death protein 1, or programmed cell death ligand 1 show improved and sustained responses in patients with cancer. However, these agents are associated with a plethora of adverse events, many manifesting in the skin. As the clinical application of cancer immunotherapies expands, understanding the clinical and histopathologic features of associated cutaneous toxicities becomes increasingly important to dermatologists, oncologists, and pathologists to ensure timely diagnosis and appropriate care. This review discusses cutaneous reactions to immune checkpoint inhibitors, focusing on histopathologic features. (J Am Acad Dermatol 2020;83:1130-43.)

Key words: adverse event; atezolizumab; avelumab; bullous pemphigoid; checkpoint inhibitor; CTLA-4; cutaneous; durvalumab; immunotherapy; ipilimumab; lichenoid dermatitis; nivolumab; PD1; PD-L1; pembrolizumab; rash; skin; toxicity.

Immune checkpoint blockade has transformed cancer treatment by enabling sustained responses in patients with cancer.[1] Checkpoint blockade, including monoclonal antibodies that bind cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed cell death ligand 1 (PD-L1), inhibits the downregulation of cytotoxic T lymphocytes, shifting the immune system to an activated, anticancer state.[1,2] However, checkpoint inhibition can lead to numerous adverse events (AEs), often manifesting in the skin. As the use of checkpoint inhibitor therapy continues to expand, delineating the clinical and histopathologic findings of various cutaneous toxicities secondary to checkpoint inhibition helps improve early and accurate diagnosis and guide therapeutic interventions.

CHECKPOINT INHIBITORS

Checkpoints maintain immunologic homeostasis by limiting T-lymphocyte activity toward host antigens but can also inadvertently decrease immune

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surveillance of cancer cells.[3-5] CTLA-4, expressed on the cell surface of activated T cells, prevents continued T-cell activation when bound to costimulatory signals. Ipilimumab blocks this interaction, allowing the immune system to activate against neoplastic cells.[6-9] Similarly, binding of PD-1 expressed on activated T cells prevents T-cell proliferation and excessive inflammatory responses, which tumor and stromal cells evade by expressing PD-1 ligands (PD-L1, PD-L2).[3,10-15] By deploying PD-1 or PD-L1 inhibitors that block this interaction, T cells remain unsuppressed, performing antitumor activity.[16-18] The CTLA-4 inhibitor ipilimumab was approved as the first checkpoint inhibitor in 2011 by the United States Food and Drug Administration for treatment of metastatic melanoma,[19,20] followed by PD-1 inhibitors nivolumab and pembrolizumab in 2014 and PD-L1 inhibitors atezolizumab in 2016, and by durvalumab and avelumab in 2017 to treat various solid organ malignancies.[21]

CAPSULE SUMMARY

- Immune checkpoint inhibitors have revolutionized cancer treatment but can lead to a variety of cutaneous toxicities that may influence decisions to continue therapy.
- Recognizing the various cutaneous reactions to immune checkpoint blockade and their associated histopathologic findings is imperative for accurate diagnosis and appropriate patient care.

Checkpoint inhibition can lead to numerous AEs, often immune-related AEs, manifesting in the gastrointestinal tract, liver, and skin, although any organ may be affected. Patient characteristics, such as cytokine profiles and human leukocyte antigen types, may be predictive of immune-related AEs, including pruritus, but their specific influence on cutaneous eruptions remains largely unknown.[22,23] Interestingly, patients who develop dermatologic AEs may demonstrate greater therapeutic responses and outcomes.[24-26] Cutaneous toxicities are prevalent among all checkpoint inhibitor therapies but appear twice as often during anti–CTLA-4 therapy compared with PD-1 and PD-L1 inhibitors, in 60% vs 20% of patients, respectively.[1,18,27-38] Cutaneous toxicities often manifest earlier than other AEs, generally within 3 to 6 weeks after starting ipilimumab and 5 to 9 weeks after PD-1 and PD-L1 inhibitors, although the manifestation may occur months after the initiation of therapy.[1,24,27,28,39-41] Most cutaneous AEs are low-grade, with fewer than 3% progressing to a grade 3 or 4 reaction (for Common Terminology Criteria for Adverse Events, see the Appendix), and even fewer with PD-1 and PD-L1 inhibitors.[33-35,39] In general, maculopapular eruptions are reported most commonly, followed by pruritus and vitiligo, although many other reactions can occur, as discussed below.[35,42-46] Lastly, although these reactions occur after initiation of therapy, a subset of them may be incidental occurrences, paraneoplastic phenomena, or related to the patient's past personal or family history, introducing a bias as well as a limitation of this study that should be taken into consideration when evaluating these patients.

CUTANEOUS TOXICITIES

Inflammatory reactions

Predominantly superficial perivascular dermatitis. Maculopapular eruptions, occurring in up to 60% of patients treated with CTLA-4 inhibitor therapy, typically show superficial perivascular dermatitis on histopathology. Perivascular dermatitis, occasionally with eosinophils, may occur during PD-1 blockade but is less common.[47] Patients demonstrate variably pruritic, erythematous macules and dome-shaped papules, some of which coalesce into patches and plaques.[42,44,45,48] Reticulated patterns or koebnerization can be seen.[43,44] Eruptions usually present on the trunk or extremities, or both, often on extensor surfaces.[43,44,48] Rarely, flexural skin, scalp, palms, and the face are involved.[44,49] Onset varies from 3 days to 3 weeks after treatment initiation.[43,48,50]

Varying densities of superficial perivascular lymphocytes, often associated with interstitial eosinophils, are present (Table I).[42-45,48,49,51] Less frequently, concomitant parakeratosis, spongiosis, exocytosis, papillary dermal edema, and deep perivascular lymphocytes can be seen.[42,45,48,49,51] There are increased numbers of $CD4^+$ lymphocytes compared with $CD8^+$ lymphocytes, as well as regulatory T cells.[45,48,51]

Interface dermatitis (vacuolar, lichenoid). *Lichenoid dermatitis.* Lichenoid dermatitis is an AE associated with anti–PD-1 and anti–PD-L1 use and rarely occurs during ipilimumab treatment.[28,29,35,38,45,52-59] Onset is on average 12 weeks after medication initiation (range, 1-266 days).[28] Pruritus is common, but the clinical presentation is otherwise broad, ranging from classic lichen planus with flat-topped violaceous papules to a morbilliform eruption,[29,52,55,56,58] and rarely, pustules.[58] Trunk and extremities are typically affected, and less commonly palms, soles,

Abbreviations used:

AA:	alopecia areata
AE:	adverse event
BP:	bullous pemphigoid
CTLA-4:	cytotoxic T-lymphocyte–associated antigen 4
CXCL:	chemokine (C-X-C motif) ligand
PD-1:	programmed cell death protein 1
PD-L1:	programmed cell death ligand 1

and genitalia.[57,58,60] Oral mucosa may also be involved.[29]

A band-like lymphohistiocytic infiltrate along the dermoepidermal junction is present in all checkpoint-inhibitor–associated lichenoid dermatoses, with variable parakeratosis, hypergranulosis, acanthosis, spongiosis, vacuolar interface alteration, dyskeratosis, dermal eosinophils, and melanophages (Fig 1).[35,54-58] Subepidermal edema or clefting can occur. Reactions indistinguishable from lichen planus, with wedge-shaped hypergranulosis and saw-tooth rete ridges, are not uncommon.[54,58] Compared with classic lichen planus, histiocyte counts are typically higher with anti–PD-1 therapy as is the degree of spongiosis and epidermal necrosis.[56] Contrary to mixed $CD4^+$ and $CD8^+$ infiltrates often with predominance of $CD8^+$ infiltrates typically seen in lichen planus, those induced by anti–PD-1 therapy are $CD4^+$ T-cell predominant.[55,56] In addition, $CD163^+$ histiocytes are more abundant in immunotherapy-associated reactions, whereas the percentages of CD3, CD20, PD-1, CD25, forkhead box P3, chemokine (C-X-C motif) ligand 1 (CXCL13), and PD-L1 are similar to lichen planus.[56] The epithelial antigen driving the lichenoid response remains unknown, but PD-1 inhibitors likely unmask autoreactive T cells.[61,62] Finally, other dermatoses with a lichenoid infiltrate, including lichen sclerosus, pityriasis lichenoides chronica, and lichen planus pemphigoides, have also been reported.[56,60,63]

Stevens-Johnson syndrome/toxic epidermal necrolysis–like reaction. Stevens-Johnson syndrome/toxic epidermal necrolysis–like reactions with CTLA-4, PD-1, or PD-L1 inhibitors are rare but portend a poor prognosis.[53,54,64-70] Patients may present with a morbilliform eruption, eventually developing targetoid patches, epidermal detachment, and mucous membrane ulcerations.[65,66] Importantly, Stevens-Johnson syndrome/toxic epidermal necrolysis can have a delayed onset, as most incidents manifest weeks to months after treatment initiation.[54,65,66,71]

Variable epidermal necrosis is present, associated with vacuolar interface alteration, cleavage along the dermoepidermal plane, and subepidermal lymphocytes.[53,54,64-67,71] Leukocytoclastic vasculitis has been reported.[68,69] $CD8^+$ T cells are present, as well as increases in PD-L1 expression of lymphocytes and keratinocytes in the epidermis.[53,64] Increased PD-L1 expression may indicate an attempt to counter lymphocyte hyperactivity induced by anti–PD-1 agents.[64] Skin toxicities associated with anti–PD-1 agents that show necrotic keratinocytes display characteristic gene expression profiles that resemble Stevens-Johnson syndrome/toxic epidermal necrolysis, with upregulation of *CXCL9*, *CXCL10*, *CXCL11*, *PRF1*, *GZMB*, and *FASLG*.[53,64]

Psoriasis. Psoriasis is a well-established AE secondary to PD-1 and PD-L1 blockade. It develops days to months after therapy initiation and presents as well-demarcated, scaly, erythematous papules and plaques on the trunk and extremities.[47,72-77] Guttate, inverse, and palmoplantar presentations have been reported.[47,60,73,76-78] Individuals with established psoriasis may flare while undergoing treatment.[72,77,79-81]

Several classic features of psoriasis are present, including parakeratosis, neutrophils within or beneath the stratum corneum, granular layer absence, acanthosis, suprapapillary plate thinning, dilated superficial dermal capillaries, and mononuclear cells in the dermis.[47,60,73-75,78] Concomitant spongiosis may be seen, especially with inverse presentation similar to classic psoriasis.[47,60,76] PD-1 blockade appears to cause a shift to a proinflammatory T-helper cell 1/17 response, increasing levels of interferon-γ, tumor necrosis factor-α, and interleukins 2, 6, and 17.[82] These changes may contribute to psoriasis in patients undergoing PD-1 inhibitor therapy.[73,74]

Acantholytic dermatitis. Acantholytic dermatitis has been reported with CTLA-4– or PD-1–inhibitor therapy or combination therapy.[35,45,83-86] It presents as intensely pruritic erythematous papules or papulovesicles on the trunk and occasionally the proximal extremities.[45,83-85] Occasionally, hyperkeratotic, annular or targetoid papules or plaques are present.[86]

Acantholysis is characteristic, and some cases are accompanied by dyskeratosis resembling Grover disease.[45,83-85,87] Dermal lymphocytic infiltrates, occasionally with eosinophils and neutrophils, are present.[45,84,85] Infiltrates are often band-like when associated with PD-1 inhibitors. Predominance of $CD4^+$ T cells over $CD8^+$ T cells may be noted.[84] Direct immunofluorescence is typically negative, although one reported case of a paraneoplastic pemphigus-like reaction exists.[86] However, acantholytic dermatitis has not been associated

Table I. Dermatologic toxicities reported with cytotoxic T-lymphocyte–associated antigen 4 (*CTLA-4*) inhibitor (ipilimumab), programmed cell death protein 1 (*PD-1*) inhibitor (nivolumab, pembrolizumab), and programmed cell-death ligand 1 (*PD-L1*) inhibitor (atezolizumab, avelumab, durvalumab) therapy

Dermatologic toxicity		Histopathologic features	Histologic differential diagnosis	Quality of evidence (study designs)*		
				CTLA-4 inhibitor	PD-1 inhibitor	PD-L1 inhibitor
Inflammatory	Acantholytic dermatitis	• Acantholysis and dyskeratosis • Superficial dermal lymphocytic infiltrate, occasionally with interstitial neutrophils and eosinophils • Predominance of $CD4^+$ T cells	Pemphigus Hailey-Hailey disease Darier disease Acantholytic acanthoma	●	●	○
	Acneiform/follicular dermatitis or rosacea	• For rosacea, perivascular and perifollicular lymphocytes and dilation of superficial blood vessels	Acne vulgaris Seborrheic dermatitis Suppurative folliculitis	●	●	●
	Acute generalized exanthematous pustulosis	• Collections of subcorneal neutrophils, often with eosinophils	Pustular psoriasis Impetigo *Candida* infection Subcorneal pustular dermatosis	●	●●	○
	Bullous pemphigoid	• Subepidermal cleft with eosinophils within the blister cavity and the dermis • DIF: Linear C3 or C3 and IgG along the BMZ • Salt-split DIF: Linear C3 or C3 and IgG at the epidermal aspect of the blister • IIF: often positive on monkey esophagus • ELISA: BP180, sometimes BP230	Bullous arthropod reaction Allergic contact dermatitis Drug reaction Pemphigus vulgaris	●	●●	●●
	CD30 lymphomatoid reaction	• $CD30^+$ lymphocytic infiltrate in the dermis	Lymphoma Lymphomatoid papulosis	●	○	○
	Dermatomyositis-like reaction	Not reported	Lupus erythematosus	●	○	○
	Drug reaction with eosinophils and systemic symptoms	Not reported	Histologic features are variable, thus differential diagnosis is broad Spongiotic dermatitis Pustular dermatitis Interface dermatitis Interstitial granulomatous dermatitis	●●	○	○
	Sarcoidal granulomatous dermatitis	• Multifocal nodular collections of epithelioid histiocytes and scant accompanying lymphocytes • May contain polarizable material	Infection (including tuberculoid leprosy) Foreign body granuloma Sarcoidal variant of granuloma annulare Cutaneous Crohn's disease Necrobiosis lipoidica Granuloma annulare	●	●	○

Continued

Table I. Cont'd

Dermatologic toxicity	Histopathologic features	Histologic differential diagnosis	Quality of evidence (study designs)*		
			CTLA-4 inhibitor	PD-1 inhibitor	PD-L1 inhibitor
Interstitial granulomatous dermatitis	• Superficial interstitial dermal histiocytic infiltrate with scant lymphocytes • No associated epidermal changes, multinucleated giant cells, mucin deposition, or necrobiosis reported	Interstitial granuloma annulare	●	●	○
Lichenoid dermatitis	• Dense band-like dermal lymphocytic infiltrate obscuring the dermoepidermal junction • Variable degree of hyperkeratosis, hypergranulosis, dyskeratotic keratinocytes, vacuolar interface alteration, acanthosis, spongiosis, and parakeratosis • Occasionally inflammation around adnexal structures • Not uncommonly hyperkeratosis, wedge-shaped hypergranulosis, dyskeratosis, and irregular acanthosis with saw-tooth rete ridges indistinguishable from lichen planus	Lichen planus Lichenoid keratosis Lichen nitidus Lichen striatus Fixed drug reaction Discoid lupus erythematosus	●	●●	●●
Neutrophilic dermatosis of the dorsal hands	See Sweet syndrome (below)	Infection Vasculitis Pyoderma gangrenosum Granuloma faciale Behçet disease	●	○	○
Panniculitis	• Septal and lobular inflammatory infiltrates, including lymphocytes, histiocytes, multinucleated giant cells, rare eosinophils, and neutrophils • Fibrous septal thickening • Stains for microorganisms negative	Erythema nodosum Lupus panniculitis Other panniculitides Infection	●	●	○
Photosensitivity	• Spongiosis with eosinophils, parakeratosis, and acanthosis	Other spongiotic dermatitides	●	●	○
Prurigo nodularis	Not reported	Verruca vulgaris Pseudocarcinomatous hyperplasia Keratoacanthoma	●	○	○

Psoriasis	• Parakeratosis, diminished granular layer, acanthosis, thinning of suprapapillary plates, dilated superficial dermal capillaries, and mononuclear cells in the dermis • Varying degrees of concomitant spongiosis	Chronic spongiotic dermatitis Seborrheic dermatitis Pityriasis rubra pilaris Syphilis Lichen simplex chronicus	○	●●	●●
Pyoderma gangrenosum	• An ulcer with dermal neutrophilic infiltrates	Infection Vasculitis Sweet syndrome Granuloma faciale Behçet disease	●	○	○
Radiation-associated dermatitis	Not reported	Not available	●	●	○
Sclerodermoid reaction	• Extensive dermal sclerosis with perivascular lymphocytic infiltrates	Morphea Sclerodermoid GVHD Chronic porphyria cutanea tarda Keloid Late-stage radiation dermatitis Lichen sclerosus *Borrelia* infection	○	●	○
Spongiotic dermatitis	• Spongiosis, perivascular inflammatory cell infiltrates	Allergic contact dermatitis Atopic dermatitis Psoriasis Stasis dermatitis Id reaction Pityriasis rosea Tinea infection	●●	●	●
Stevens-Johnson syndrome/toxic epidermal necrolysis-like reaction	• Apoptotic keratinocytes and necrosis of the epidermis • Sparse mononuclear infiltrate in the dermis • $CD8^+$ T cells within epidermis and at dermoepidermal junction • Increased PD-L1 expression on epidermal keratinocytes near T cells • Upregulation of *CXCL9*, *CXCL10*, *CXCL11*, *PRF1*, *GZMB*, and *FASLG* (anti−PD-1 agents) • Leukocytoclastic vasculitis	Erythema multiforme GVHD Lupus erythematosus Dermatomyositis	●	●	●

Continued

Table I. Cont'd

Dermatologic toxicity		Histopathologic features	Histologic differential diagnosis	Quality of evidence (study designs)*		
				CTLA-4 inhibitor	PD-1 inhibitor	PD-L1 inhibitor
	Superficial perivascular dermatitis	• Superficial perivascular lymphocytic infiltrates with interstitial eosinophils • Rarely deep dermal lymphocytic perivascular infiltrates, exocytosis, parakeratosis, papillary dermal edema, spongiosis • Increased numbers of $CD4^+$ lymphocytes (CTLA-4 inhibitor)	Urticaria Arthropod bite reaction Drug reaction Scabies Urticarial bullous pemphigoid Allergic contact dermatitis Itchy red bump disease	●●	●	●
	Sweet syndrome	• Dense neutrophilic dermal infiltrates, often extending to the subcutis, occasionally with plasma cells and eosinophils • Prominent papillary dermal edema • No evidence of infection or leukocytoclastic vasculitis	Infection Vasculitis Pyoderma gangrenosum Granuloma faciale Behçet disease	●	○	○
	Xerosis	• Not reported	Ichthyosis "Invisible" dermatoses (macular amyloidosis, dermal melanocytosis, mastocytosis, anetoderma, vitiligo, tinea infection)	○	●	○
Alopecia	Alopecia, nonscarring	• Peribulbar lymphocytic infiltrate • Predominantly $CD4^+$ T-cells	Androgenetic alopecia Telogen effluvium Syphilitic alopecia	●	●	○
Alteration of melanocytes	Nevi with halo-like reaction	• Melanocytes surrounded by lichenoid lymphohistiocytic infiltrates • Commonly of $CD8^+$ T cells, with few $CD4^+$ and $CD45R0^+$ cells	Melanoma Lymphoma Lichenoid keratosis	●	●	○
	Vitiligo	• $CD8^+$ T cells expressing CXCR3 and producing elevated levels of interferon-γ and tumor necrosis factor-α	Postinflammatory hypopigmentation "Invisible" dermatoses (see above)	●●●	●●	●
Alteration of keratinocytes, including tumors	Actinic keratosis	Not reported	Squamous cell carcinoma in situ	○	●	○
	Basal cell carcinoma	Not reported	Squamous cell carcinoma Sebaceous carcinoma Other adnexal neoplasms	○	●	○

Keratoacanthoma	• Crateriform keratinocytic proliferation • Squamous cells with glassy-appearing cytoplasm with minimal cytologic atypia • An associated lichenoid infiltrate composed of $CD3^+$ T cells with scattered $CD20^+$ B cells	Squamous cell carcinoma Pseudocarcinomatous hyperplasia Verruca vulgaris Prurigo nodularis	○	●	○
Seborrheic keratosis	Not reported	Verruca vulgaris Hidroacanthoma simplex Squamous cell carcinoma in situ	○	●	○
Squamous cell carcinoma	Not reported	Hyperplastic actinic keratosis Keratoacanthoma Pseudocarcinomatous hyperplasia	○	●	○

BMZ, Basement membrane zone; C3, complement component 3; *DIF*, direct immunofluorescence; *ELISA*, enzyme-linked immunosorbent assay; GVHD, graft-versus-host disease; *IIF*, indirect immunofluorescence.
*Quality of evidence: unknown/no reported studies, ○; case report(s) and case series, ●; observational studies (≥1 case-control, cross-sectional, or cohort study), ●●; comprehensive studies (≥1 nonrandomized controlled trial, randomized control trial, meta-analysis, or systematic review), ●●●.

Fig 1. Bullous lichenoid dermatitis secondary to nivolumab. Biopsy specimen shows a band-like lymphocytic infiltrate associated with a cleft formation at the dermoepidermal junction.

with identifiable immunoreactant deposition, circulating autoantibodies, or clinical blistering.

Granulomatous dermatitis. *Interstitial granulomatous dermatitis.* Interstitial granulomatous dermatitis is rarely seen secondary to CTLA-4– or PD-1–inhibitor therapy or combination therapy and may be secondary to the cancer itself.[45,88] Interstitial granulomatous dermatitis may present as asymptomatic erythematous papules and plaques on the trunk and extremities shortly after initiating treatment. Interstitial histiocytic infiltrates in the superficial dermis with scant lymphocytes are characteristic. Eosinophils and giant cells may be present. Epidermal changes, mucin deposition, or necrobiosis are absent.[45]

Sarcoidal granulomatous dermatitis. Sarcoid-like lesions involving the skin, lungs, and hilar/mediastinal lymph nodes may occur in patients undergoing CTLA-4– or PD-1–inhibitor therapy.[89-93] Onset is typically at least 1 month after treatment initiation.[92,94-96] Because lesions may be clinically or radiographically concerning for cancer recurrence, an accurate diagnosis is imperative.[29,93] Cutaneous presentation varies from solitary to multiple erythematous to brown papules, plaques, or nodules on the trunk, extremities, or head and neck.[89-92] Prior scars may be involved.[92,95,97] Multifocal discrete nodular collections of epithelioid histiocytes with scant accompanying lymphocytes (ie, sarcoidal granulomas), are present in the dermis, in some cases extending into the subcutis.[89-91,95,96] Polarizable material may be present.[90,98] Infection should be excluded.[94-96]

Acute generalized exanthematous pustulosis. Acute generalized exanthematous pustulosis, occasionally observed with checkpoint inhibitor therapy, presents as diffuse edematous

erythema with sterile pustules involving the extremities, trunk, and groin. Collections of subcorneal neutrophils and often eosinophils are characteristic.[54,99]

Panniculitis. Panniculitis with clinical erythema nodosum-like features rarely occurs in combination therapy with ipilimumab and nivolumab. It presents as tender nodules on lower extremities and possibly forearms.[58] Eruptions show a septal and lobular panniculitis, with fibrous septal thickening and a mixture of lymphocytes, histiocytes, multinucleated giant cells, and rare eosinophils and neutrophils.[58] Findings are indistinguishable from erythema nodosum, especially early forms, secondary to other causes. Stains for microorganisms are negative.

Neutrophilic dermatoses. *Sweet syndrome.* Sweet syndrome may present during CTLA-4–inhibitor therapy as painful, erythematous and edematous or pseudovesicular papules and plaques.[100-102] Hands may be exclusively involved (neutrophilic dermatosis of the dorsal hands).[102] Papillary dermal edema and dense neutrophilic dermal infiltrates, often extending to the subcutis, are present, without evidence of infection or leukocytoclastic vasculitis.[100-102] Plasma cells, which are a unique finding and may be a distinguishing factor of ipilimumab-induced Sweet syndrome, and eosinophils may be present.[100]

Pyoderma gangrenosum. Pyoderma gangrenosum is infrequently reported in association with anti–CTLA-4 treatment.[49,103] Pyoderma gangrenosum presents as ulceration(s) with violaceous, undermined borders. Ulceration with dermal neutrophilic infiltrates is characteristic.[103] Ipilimumab may cause pyoderma gangrenosum through triggering tumor necrosis factor-α from activated natural killer cells, in addition to lowering regulatory T-cell function.[104]

Immunobullous reactions

Bullous pemphigoid. Bullous pemphigoid (BP) is another well-established AE associated with PD-1 and PD-L1 inhibition.[47,54,59,71,105-111] Onset varies from weeks to several months after therapy initiation.[47,59,106,107,110,111] Bullous eruptions are often preceded by pruritus and may initially present as nonspecific maculopapular or urticarial eruptions.[59,106,107,112] Tense bullae and vesicles eventually develop on the trunk and extremities.[47,59,105-112] Mucosal involvement is not uncommon.[59,71,106,110]

Subepidermal clefting with eosinophils is characteristic, although clefting is not always present (Fig 2). Superficial dermal infiltrates composed of lymphocytes, eosinophils, and, occasionally, neutrophils are present.[59,71,105,106,112] As with classic BP, direct immunofluorescence demonstrates linear deposits of complement component 3 and IgG along the basement membrane zone, localizing to the epidermal aspect of the blister on salt-split direct immunofluorescence.[59,71,106-108] Indirect immunofluorescence on monkey esophagus is positive in many cases.[59,106] Enzyme-linked immunosorbent assay detects antibodies against the hemidesmosomal protein BP180 and sometimes BP230 antibodies.[59,106-110,112]

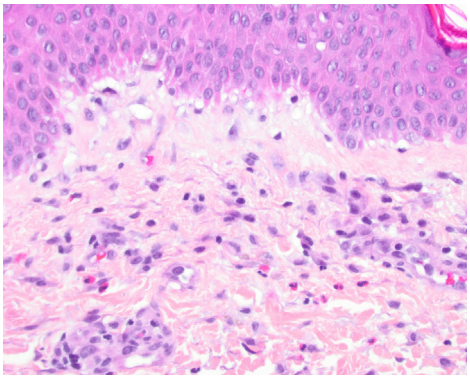

Fig 2. Bullous pemphigoid secondary to pembrolizumab. Biopsy specimen shows perivascular eosinophils and vacuolar alteration along the junction. Bullae were not present histologically in the biopsy specimen. Direct immunofluorescence showed deposition of component 3 and IgG along the junction (not shown). Clinically, the patient had intact and eroded bullae on an erythematous base.

BP may develop secondary to recognition of common antigens BP180 and BP230 shared between the cutaneous basement membrane and tumor cells.[106,113] Antibody-secreting B cells may also play a role, because PD-1 inhibition can activate B cells and inhibit immunosuppressive B-regulatory cells.[114] PD-1 blockade may also unmask incipient BP. BP does not resolve in some patients after cessation of checkpoint inhibition.[107]

Alopecia and other hair abnormalities

Nonscarring alopecia can occur during CTLA-4– or PD-1–inhibitor treatment.[44,50] Nonscarring alopecia associated with ipilimumab may show features of alopecia areata (AA) and be accompanied by signs of autoimmune dysregulation, including hypophysitis and widespread vitiligo.[50] A peribulbar, predominantly $CD4^+$ T-cell infiltrate with scant $CD8^+$ cells, is present.[44] Interestingly, CTLA-4 gene variants are linked with AA.[115,116] In AA mouse models, supplementation with CTLA-4 IgG prevents development of AA.[117] In patients with melanoma, activated T cells may be targeting melanocyte antigens in the hair bulb, leading to hair loss.[118]

Repigmentation of gray hair during anti–PD-1 and anti–PD-L1 therapy for non-small cell lung cancer has been observed.[119]

Alteration of melanocytes

Vitiligo. Vitiligo has the highest level of evidence for association with all checkpoint inhibitor therapy, particularly ipilimumab, occurring in up to 11% of patients with metastatic melanoma.[18,38,54,60,120,121] Development of vitiligo may be associated with improved treatment response and survival.[26,122] It typically presents with depigmented macules occurring on photoexposed sites and without personal or family history of vitiligo or other autoimmune disorders. Albeit rarely biopsied, the presence of $CD8^+$ T cells expressing CXCR3 and producing elevated levels of interferon-γ and tumor necrosis factor-α has been reported.[123] PD-1 inhibitor–associated vitiligo may result from allowing immune effector cells to target a shared antigen among melanoma cells and healthy melanocytes.[121,124]

Regression of melanocytic nevi. In addition to tumoral melanosis (ie, nodular aggregates of melanophages without melanocytes consistent with regression of melanoma)[125] regression of melanocytic nevi can happen with anti–CTLA-4 or anti–PD-1 treatments.[126,127] Melanocytes are obscured by lichenoid lymphohistiocytic infiltrates, commonly of $CD8^+$ T cells, with few $CD4^+$ and $CD45R0^+$ cells.[126] Melanocytic nevi may express melanoma-related antigens and become targets of anti-CTLA therapy, leading to local destruction by activated T cells.[128]

Alteration of keratinocytes

Benign, precancerous, and cancerous keratinocytic lesions are rarely associated with PD-1 inhibition.[54,129,130] These include seborrheic keratosis, actinic keratosis, keratoacanthomas, and squamous cell carcinoma.

Other dermatologic toxicities

Folliculitis, acneiform reactions, or rosacea can occur during CTLA-4– or PD-1–inhibitor therapy.[6,55,85,131] Rosacea may present with erythema, papules, and pustules that respond to topical metronidazole and doxycycline.[131] Histopathologic features include perivascular and perifollicular lymphocytes as well as dilation of superficial blood vessels.[131]

Sclerodermoid reactions are a rare complication of pembrolizumab therapy, presenting with generalized skin thickening and stiffness and progressive decline in joint flexibility. Histopathologic examination shows extensive dermal sclerosis with perivascular lymphocytes.[132]

Radiation-associated dermatitis is rarely seen with CTLA-4 or PD-1 inhibitors.[132] Other rare cutaneous toxicities related to ipilimumab include dermatomyositis and drug reaction with eosinophils and systemic symptoms and photosensitivity reactions related to PD-1 inhibitors.[35,49,54,60,67,127,133-135]

CONCLUSIONS

Immune checkpoint blockade has demonstrated remarkable outcomes for patients with various types of cancer. Checkpoint inhibitors are associated with a range of cutaneous AEs, highlighting the complexity of the immune response and the importance of clinical-histopathologic correlation in accurate recognition of AEs, allowing for appropriate intervention and patient care.

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APPENDIX

Common Terminology Criteria for Adverse Events. Adverse event: Rash/desquamation. Grade 1: Macular or papular eruption or erythema without associated symptoms. Grade 2: Macular or papular eruption or erythema with pruritus or other associated symptoms or localized desquamation or other lesions covering<50% of body surface area. Grade 3: Severe, generalized erythroderma or macular, papular, or vesicular eruption, or desquamation covering ≥50% body surface area. Grade 4: Generalized exfoliative, ulcerative, or bullous dermatitis. Grade 5: Death.