ABOUT THE AUTHOR

Abdulhadi Jfri, MD, MSc, FRCPC

Dr. Abdulhadi Jfri holds certification as a Fellow of the Royal College of Physicians of Canada (FRCPC) in dermatology and as a Diplomat of the American Board of Dermatology (DABD). He completed both his Masters' degree in experimental medicine in the department of epidemiology and biostatistics and a five-year dermatology residency at McGill University. He also completed a fellowship in advanced surgical procedures at Icahn School of Medicine at Mount Sinai, New York. Dr. Jfri is currently completing his complex medical dermatology fellowship at Harvard School of Medicine, where he is rotating between Brigham and Women's Hospital and the Dana-Farber Cancer Institute.

DERMATOLOGIC IMMUNE-RELATED ADVERSE EVENTS WITH IMMUNE CHECKPOINT INHIBITORS

Introduction

Immune checkpoint inhibitors (ICIs) are mainstay treatments for diverse malignancies. Approved ICIs in Canada include anti-PD-1 agents (nivolumab, pembrolizumab, cemiplimab, and dostarlimab), an anti-CTLA-4 agent (ipilimumab), and anti-PDL-1 agents (atezolizumab, avelumab, and durvalumab).[1] ICIs are ground-breaking treatments, but have been associated with immune-related adverse events (irAEs) that can affect any organ system and which can be severe enough to necessitate treatment interruption or discontinuation.[2] While the intended effect of ICIs is to activate the immune system against malignant cells, irAEs occur when this activation inadvertently targets host tissue. These occurrences appear idiosyncratic; predicting which patients will develop irAEs seems impossible.[2]

This article examines dermatologic irAEs. While primarily classified as 'rash' or 'maculopapular rash', cutaneous IrAEs represent a diverse group of often specific morphologies. The most common are described below. **Table 1** summarizes all morphologies relative to onset-from-ICI-initiation time.

A. Morbilliform:

Morbilliform eruptions present as pruritic blanching macules and papules on the trunk and extremity extensor surfaces. They occur in 49 to 68% of patients treated with anti-CTLA-4 therapy and in 20% of patients treated with anti-PD-1 or anti-PDL-1 therapy.[3] The onset of a morbilliform eruption generally occurs within a few weeks of initiating ICI therapy, may be dose dependent, and typically resolves within 2-3 months of treatment continuation.[3] Most patients can be managed with mid- or high-potency topical steroids, but in severe or highly symptomatic cases, systemic corticosteroids can be used (i.e. 0.5-1mg/kg of prednisone or equivalent), tapering over 2-6 weeks depending on severity and symptoms.[4]

B. Eczematous:

Eczematous eruptions present as pruritic erythematous papules coalescing into plaques, often having scale or crust and overlying signs of excoriation. The distribution of these eruptions may be similar to classic atopic dermatitis, with trunk and flexural extremity areas favored over other body areas.5 Eczematous reactions are most commonly seen with PD-1 inhibitors, occurring in ≤17% of patients.[23] The mean onset of time to these eruptions with anti-PD1 therapy is 6 months, but eczematous eruptions can occur between 1 and 25 months after initiation of therapy.[5] Management is similar to measures taken with general dry skin care eczematous eruptions in non-ICI patients: topical moisturizers; compounded camphor 0.25% menthol 0.25% w/hydrocortisone 1% cream;5 topical steroids ranging from low- to high-potency depending on body area involvement; and physical skin-directed approaches including narrowband ultraviolet-B (NBUVB) therapy.[4]

C. Lichenoid:

Lichenoid eruptions typically present as pruritic flat-topped erythematous-to-violaceous papules coalescing into plaques on the trunk and extremities.[6] Between 5%-17% of patients receiving anti-PD-1 or anti-PDL-1 therapy are reported to have had lichenoid eruptions.[3] These eruptions present from 3 days to 13 months following initiation of anti-PD-1 or anti-PDL-1 therapy.[7] Low- to high-potency topical steroids, including betamethasone valerate 0.1% or clobetasol propionate 0.05%, can be used to manage grade 0-1 ICI-induced lichenoid eruptions and associated pruritus.[4] Safe oral treatments in patients with malignancies include oral prednisone which can be dosed between 30-60 mg daily for 4-6 weeks followed by tapering. Additionally, oral retinoids, namely acitretin, can be used at 30 mg daily for refractory lichenoid eruptions except in women of childbearing age.[8] Apremilast, can also be used at 30 mg twice daily after being titrated upwards from its initial dose of 10 mg over a period of 6 days.[8] Cyclosporine has been used in refractory cases and methotrexate has also been used at 10-25 mg oral or subcutaneous once-weekly to manage various ICI-induced eruptions including lichenoid eruptions.[9]

D. Psoriasiform:

Psoriasiform eruptions usually present between 2-12 weeks after treatment initiation as erythematous plaques with overlying silvery scales on the trunk and extremity extensor surfaces.[10] Scalp psoriasis, sebopsoriasis, and guttate psoriasis have been described in ICI-induced psoriasiform eruptions, as have psoriatic arthritis and uveitis.[7] The worsening of pre-existing psoriasis is more common than de novo psoriasis, but either may occur.[7] The treatment of ICI-induced psoriasiform eruptions depends on its clinical severity. Topical steroids including betamethasone valerate 0.1% or clobetasol propionate 0.05% are suggested for the treatment of grade 0-1 eruptions.[5] Other evidence suggests that psoriasiform eruptions can be managed with topical vitamin D analogs including calcipotriene (twice daily application at a maximum weekly dose of 100 g); retinoids including tazarotene (0.05%); tar; and anthralin.[10] Oral prednisone can be used cautiously, as severe rebound flares of psoriasis have been observed with tapering.[7] Acitretin has been used for psoriasiform eruptions at a daily oral dose of 25-30 mg.[11]Apremilast is another oral agent with an excellent safety record, dosed at 30 mg twice daily, after being titrated up from its initial dose over a period of 6 days to maintenance.[11] Methotrexate can also be used, at a dose of 10-25 mg oral or subcutaneous once-weekly.[11] Biologic medications are contraindicated in ICI-induced psoriasiform eruptions, specifically TNF-α inhibitors and IL-12/IL-23 inhibitors such as ustekinumab. Other biological agents that may be used with caution include IL-17 agents such as secukinumab, ixekizumab, and brodalumab. Additionally, clinicians can consider the use of IL-23 agents such as risankizumab, tildrakizumab and guselkumab. Biologic therapy should be discussed with the patient's oncologist before initiation.[10]

E. Vitiligo:

Vitiligo presents in patients receiving ICI therapy as depigmented macules coalescing into patches on photo-exposed areas which, unlike classic vitiligo, does not spread via koebnerization.[12] ICI-induced vitiligo develops in approximately 10% of patients receiving anti-PD-1 monotherapy or anti-PD-1/anti-CTLA-4 combination and in approximately 5% of patients receiving anti-CTLA-4 monotherapy.[8] Vitiligo is one of the later-occurring irAEs, generally presenting 7 to 65 weeks after anti-PD-1 therapy initiation.[12] Patients developing ICI-induced vitiligo in melanoma treatment generally have a favorable prognosis, as some studies have shown that vitiligo correlates with enhanced anti-tumor response.[3,12] Suggested treatment may include only sun protection and camouflage, as restoring skin pigment can be challenging during immunotherapy, but for localized disease, treatment using topical steroids followed by calcineurin inhibitors (tacrolimus/pimecrolimus) is suggested.[10] Phototherapy with narrowband ultraviolet-B (NBUVB) light has been used for vitiligo involving a large body surface area.[12]

F. Bullous pemphigoid (BP)

ICI-induced BP presents similarly to classic BP with prodromal or concurrent pruritic components followed by localized or generalized tense bullae. Of ICI-induced BP cases, 10 to 30% show oral mucosal involvement.[13] BP can present from 3 to 20 weeks following ICI therapy initiation, and is most commonly observed with anti-PD-1 and anti-PD-L-1 therapy.[14] Treatment of ICI-induced BP includes topical or systemic corticosteroids for refractory/extensive disease (0.5-1 mg/kg/day depending on severity); dapsone (starting oral dose of 25 or 50 mg daily with titration as required); methotrexate (15-25 mg oral or subcutaneous) with possible 5 mg daily oral folic acid supplementation used adjunctively; omalizumab (300 mg every 2-4 weeks); rituximab (375 mg/m2 weekly for 4 weeks); or intravenous immunoglobins (1-2 g/kg every 4 weeks).[10]

G. Severe Cutaneous Adverse Reactions (SJS/TEN/DRESS)

Severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening irAEs that may manifest with the use of ICI therapy. Clinically, SJS/TEN presents with prodromal malaise, fever, and conjunctival injection followed by diffuse erythema of skin, skin pain, blister formation with positive Nikolsky sign, and desquamation. Mucosal surfaces of the eye, respiratory, gastrointestinal, or genitourinary tract may also be involved.[15,16]

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is another uncommon but potentially life threatening irAE reported with the use of ICI therapy. DRESS typically presents with facial edema, diffuse erythema of skin, fever, malaise, and lymphadenopathy. Laboratory abnormalities including eosinophilia may be seen along with evidence of acute myocarditis, pericarditis, pneumonitis, hepatitis, colitis, and nephritis. When DRESS follows ICI therapy, determining the causal relationship between DRESS and toxicity associated with ICI therapy is difficult. Similar to classic

Eruption	Presentation	Onset from ICI initiation	Treatment options
Morbilliform	Pruritic blanching macules and papules on the trunk and extensor surfaces of extremities	First few weeks	• Mid- or high-potency topical steroids • Systemic steroids if severe
Eczematous	Pruritic erythematous papules that coalesce into plaques; often have scale or crust and often have overlying signs of excoriation on the trunk and flexural areas of the extremities	1-25 months	• Moisturizers • Compounded combination of camphor 0.25% menthol 0.25% with hydrocortisone 1% cream • Topical low- to high-potency steroids depending on the affected body part • Phototherapy (narrow band UVB)
Lichenoid	Pruritic flat-topped erythematous-to-violaceous papules coalescing into plaques on the trunk and extremities	3 days to 13 months	• Topical low- to high-potency steroids • Systemic steroids • Acitretin • Apremilast • Cyclosporine • Methotrexate
Psoriasiform	Erythematous plaques with overlying silvery scale on the trunk and extensor surfaces of extremities, on the scalp, or as guttate; can be de novo or flare of pre-existing disease	2-12 weeks	• Topical or systemic steroids • Topical vitamin D analogs such as calcipotriene • Tar • Anthralin • Topical tazarotene • Apremilast • Methotrexate • Acitretin • Anti-IL17 or IL-23 inhibitors
Vitiligo	Depigmented flecked macules coalescing into patches photo-distributed and lacks koebnerization.	7 to 65 weeks	• Photoprotection and camouflage • Trial of topical steroids followed by calcineurin inhibitors (tacrolimus/pimecrolimus) • Phototherapy (narrow band UVB)
Bullous pemphigoid	Prodromal or concurrent pruritic urticarial eruption followed by localized or generalized tense bullae	3 to 20 weeks	• Topical or systemic corticosteroids • Dapsone • Methotrexate • Omalizumab • Rituximab • Intravenous immunoglobin (IVIG)
Severe Cutaneous Adverse Reactions (SJS/TEN/DRESS)	SJS/TEN presents with prodromal malaise, fever, and conjunctival injection followed by diffuse erythema of skin, skin pain, blister formation with positive Nikolsky sign, and desquamation. DRESS presents with facial edema, diffuse erythema of skin and systemic symptoms	7-140 days	• Discontinuation of immunotherapy is needed. • Higher doses of prednisone are recommended for managing SCAR. • Switching oral to IV methylprednisone, cyclosporine and TNF-α inhibitors such as infliximab or etanercept are reserved for managing life-threatening SJS/TEN.
Eruptive keratoacanthomas	Firm erythematous papules or plaques that may have overlying crusting and tend to favor the extremities	4-18 months	• Topical therapy (Imiquimod or 5-Fluorouracil) • Intralesional therapy (5-Fluorouracil) • Surgical removal (Mohs or wide local excision) • Additional oral medications (Acitretin)

Table 1: *Cutaneous manifestations of inflammatory bowel diseases (IBD); courtesy of Dr Abdulhadi Jfri, MD*

DRESS, onset of ICI-associated DRESS is approximately 2 to 8 weeks after initiation.[17]

When life-threatening grade IV severe cutaneous adverse reactions (SCAR) occur (including DRESS, SJS, or TEN), immunotherapy discontinuation is needed.[18] Higher prednisone doses are recommended for managing SCAR.[18] Switching from oral to IV methylprednisone for associated ICI-induced gastrointestinal (GI) inflammation following oral steroid absorption may also be required.[18] Cyclosporine can be used in severe or steroid-unresponsive cases.[18] When using biologics with ICI-induced cutaneous irAEs in patients with active malignancies, TNF-α inhibitors including infliximab or etanercept are reserved for managing life-threatening SJS/TEN.10

H. Neoplastic

Neoplastic eruptions including eruptive keratoacanthomas (i.e. eruptive squamous atypia) and eruptive well-differentiated squamous cell carcinomas have been reported most notably with the use of anti-PD-1 therapy. These eruptions present with firm erythematous papules or plaques that may have overlying crusting, generally on the extremities. Many of these eruptions spontaneously resolve in immune activation during ICI therapy, but additional treatments including topical therapy (Imiquimod or 5-Fluorouracil), intralesional therapy (5-Fluorouracil), surgical removal (Mohs or wide local excision), or additional oral medications (acitretin) can be considered.[19-20]

I. Uncommon eruptions

Scleroderma has been reported with anti-PD-1 therapy.[21] Dermatomyositis has been reported with anti-PD-1 and anti-CTLA-4 therapy.[22] Cutaneous lupus can also occur with anti-PD-1 therapy.[23] The literature also shows that several case reports of sarcoidosis with cutaneous and internal involvement have been reported with anti-PD-1 therapy, anti-CTLA-4 therapy, and combination anti-PD-1/anti-CTLA-4 therapy.[24] Alopecia, including both areata and universalis types, is a less commonly seen irAE. Alopecia areata is seen in 1 to 2% of patients receiving ICI therapy and has been reported with anti-PD-1 therapy, anti-PDL-1 therapy, and anti-CTLA-4 therapy, usually within 3 to 6 months of treatment initiation.[25]

Conclusion

ICI-induced dermatologic irAEs have a broad range of presentations. Assessment and treatment should focus on the nature of the disease in conjunction with percentage of body surface area involved. Clinicians may consider a wide array of treatment options for these irAEs and should work with the patient's oncology team to ensure seamless coordination of care and information-sharing.

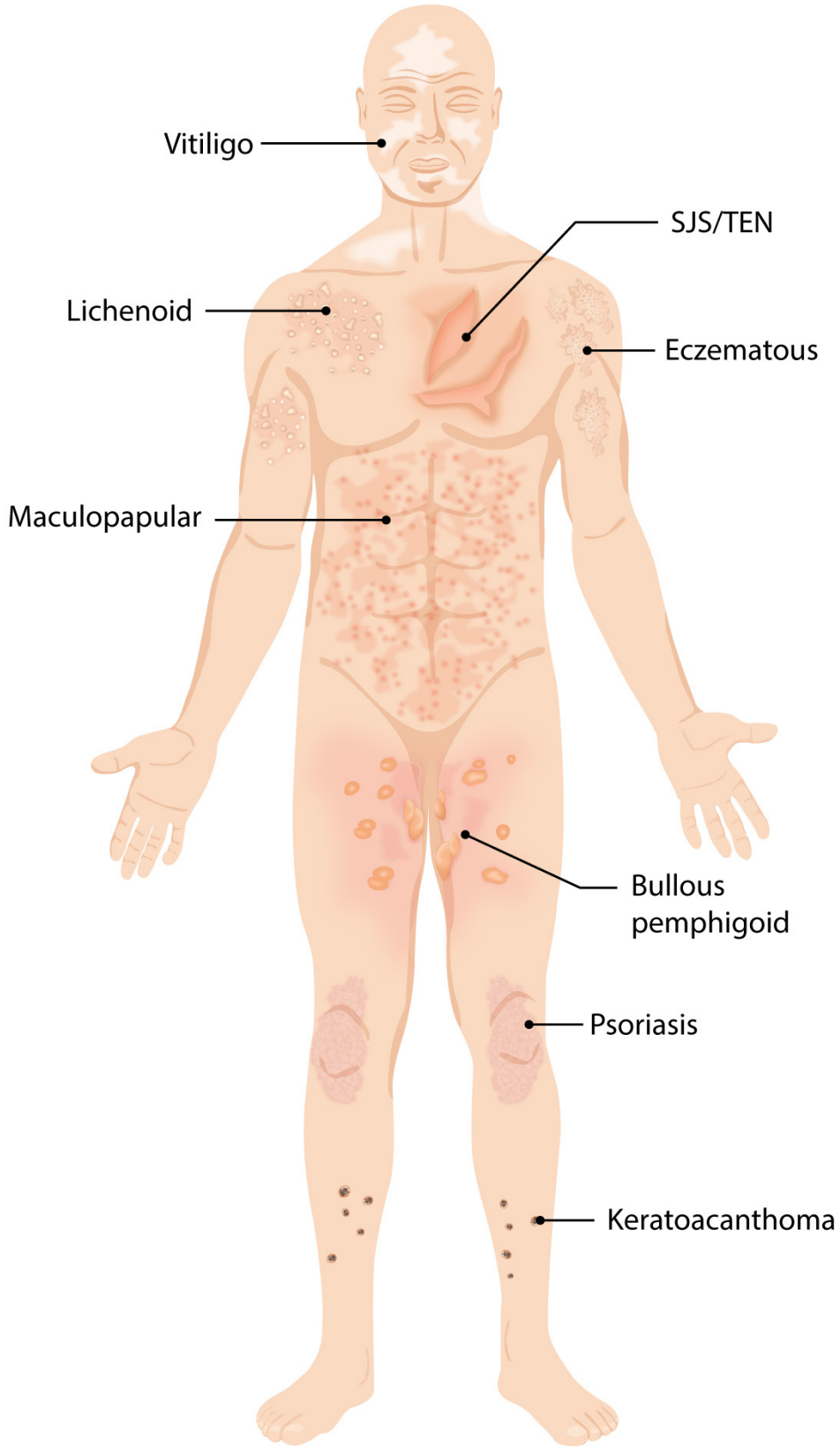

Figure 1: *Clinical morphologies of immune checkpoint inhibitors immune-related cutaneous adverse events; courtesy of Abdulhadi Jfri, MD*

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