Dermatologic adverse events from immune checkpoint inhibitors

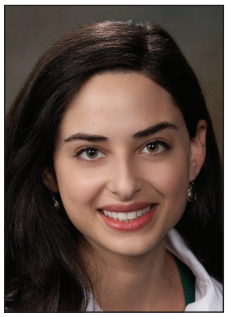
By Taylor Gray, DO, and Lisa Fronek, DO

Immune Checkpoint Inhibitors		
CTLA-4 Inhibitors	**PD-1 Inhibitors**	**PD-L1 Inhibitors**
Ipilimumab (*Yervoy*)	Pembrolizumab (*Keytruda*)	Atezolizumab (*Tecentriq*)
	Nivolumab (*Opdivo*)	Avelumab (*Bavencio*)
	Cemiplimab (*Libtayo*)	Durvalumab (*Imfinzi*)

*CTLA-4: cytotoxic T-lymphocyte-associated antigen
*PD-1: Programmed cell death protein-1
*PD-L1: Programmed death-ligand 1

Dermatologic Adverse Events				
Cutaneous Reaction	**Clinical Description**	**Timeframe**	**Treatment**	**Special Notes**
Maculopapular Rash	-Faint erythematous macules and papules that coalesce into plaques -Most commonly affects the trunk and extensor surfaces of extremities	-3-6 weeks after initial dose	-Grade 1 and 2 presentations are most common and are often self-limited but may be treated with TCS. Immunotherapy is continued -Grade 3 is treated with TCS + systemic CS taper. Immunotherapy is held until rash is grade 1 or less -Grade 4 warrants discontinuation of immunotherapy in addition to systemic CS administration	-Grade 1: rash covering <10% BSA +/- symptoms -Grade 2: rash covering 10-30% BSA +/- symptoms; limiting instrumental ADL; rash covering >30% BSA +/- mild symptoms -Grade 3: rash covering >30% BSA + moderate or severe symptoms; limiting self-care ADL **-Most common cutaneous AE overall** -More commonly induced by CTLA-4 inhibition
Pruritus	-May present with or without cutaneous eruption	-3-6 weeks after initial dose	-Grade 1 and 2 presentations are most common and management strategies include emollients, oral antihistamines, and TCS. -Gamma-aminobutyric acid analogs have also been utilized	-Grade 1: mild or localized -Grade 2: widespread and intermittent; skin changes from scratching noted -Grade 3: widespread and constant; limiting self-care ADL or sleep **-2nd most common cutaneous AE overall** -More commonly induced by CTLA-4 inhibition
Lichenoid Eruption	-Multiple, discrete, erythematous-to-violaceous papules and plaques -Often involve the chest and back and rarely the extremities, palmoplantar surfaces and oral mucosa -Up to 45% of the time the lichenoid infiltrate involves the hair follicle resulting in a clinical pattern reminiscent of lichen planopilaris or keratosis pilaris	-6-12 weeks after initial dose	-Usually manageable with TCS without disruption in immunotherapy dosing schedule -Systemic CS administration and immunotherapy cessation may be required in severe cases -Phototherapy and acitretin have also been utilized	-More commonly associated with anti-PD1/PD-L1 therapy
Bullous Pemphigoid	-A non-bullous prodromal phase characterized by pruritus may precede development of localized or generalized tense blisters -Oral mucosa involvement is seen 10-30% of the time	-Mean onset of 12-14 weeks following initiation of therapy, however, cases have been reported 3-84 weeks after initial dose	-Grade 1 eruptions may respond to TCS -Addition of systemic CS in grade 2 and rituximab in grades 3-4 may be warranted -For grade 2 events and higher, immunotherapy should be held until grade 0-1 is achieved -Nonsteroidal options including doxycycline, nicotinamide, methotrexate, and omalizumab have also been utilized	-Grade 1: asymptomatic; blisters covering <10% BSA -Grade 2: blisters covering 10-30% BSA + erythema or pruritus; limits instrumental ADL Grade 3: blisters covering >30% BSA; limits self-care ADL Grade 4: blisters covering >30% BSA; electrolyte abnormalities Grade 5: death **-May persist several months after discontinuation of therapy** -More commonly associated with anti-PD1/PD-L1 therapy
Vitiligo-like Eruption	-Characterized by macules of depigmentation evolving into large symmetric plaques on photo-exposed skin	-Cases have been reported to occur 6 days-36 weeks after initiation of therapy	-No specific treatment is required, however, photoprotection should be utilized to protect the depigmented/ hypopigmented skin -Potent TCS and calcineurin inhibitors can be used -Cosmetic camouflaging may limit negative psychosocial impact - Resolution with cessation of therapy does not occur	**-Vitiligo-like skin eruptions are associated with greater anti-cancer benefit from immunotherapy** -Hair depigmentation may also be observed -More commonly associated with anti-PD1/PD-L1 therapy
Neutrophilic Dermatoses -Sweet's syndrome -AGEP -Intracorneal pustular drug eruption -PG -Bullous lupus erythematosus	-Neutrophilic dermatoses secondary to immunotherapy are morphologically similar to these eruptions in circumstances that lack inciting immunotherapy trigger	-For cases presenting as Sweet's syndrome, AGEP and intracorneal drug eruption time to onset was approximately 9 weeks -Cases of PG and bullous lupus presented approximately 16 weeks after initiating therapy	-Sweet's syndrome eruptions have been treated successfully with systemic CS and immunotherapy dose interruptions -TCS and systemic CS, with and without dose adjustment, have been utilized for AGEP, intracorneal drug eruptions, and bullous lupus -For cases of PG, TCS, systemic CS, intralesional CS and infliximab have been utilized	-Cases of Sweet's syndrome have been reported secondary to ipilimumab

Taylor Gray, DO, is a PGY-4 dermatology resident at Largo Medical Center in Florida.



Lisa Fronek, DO, is a PGY-4 dermatology resident at Largo Medical Center in Florida.

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Cutaneous Reaction	**Clinical Description**	**Timeframe**	**Treatment**	**Special Notes**
Psoriasiform	-Well-defined, scaly, erythematous plaques on the trunk and extremities -May also present similarly to guttate, inverse, or palmoplantar psoriasis	-0-3 weeks after treatment initiation is common, however, cases have been reported after 3 weeks	-High potency TCS, vitamin D_3 analogues, and narrowband ultraviolet B therapy are commonly used -Retinoids, apremilast and biologics may be utilized if lesions persist -For grade 3 events and higher, immunotherapy should be held until grade 0-1 is achieved	**-Eruption has been shown to correlate with positive tumor response in melanoma patients** -Concurrent psoriatic arthritis has been reported **-Personal and family history of psoriasis are significant risk factors for development, or exacerbation, of psoriasiform dermatitis with treatment** -Has been associated with risk of endocrine immune-related adverse event -More commonly associated with anti-PD1/PD-L1 therapy
Severe Cutaneous Adverse Reactions (SCAR) -DRESS/DIHS -EM -SJS -SJS-TEN -TEN	-SCARs may manifest similarly to a maculopapular rash initially or may present immediately with blister formation, Nikolsky sign, mucosal ulceration, fever, or cutaneous pain	-Cases have been reported within 1-20 weeks of initiating therapy, however, the majority have occurred in the first 4 weeks	-Immunotherapy should be discontinued immediately and patient should be hospitalized for systemic treatment	-Mortality rate is 10% for SJS, 30% for SJS-TEN, and 50% for TEN
Granulomatous Reactions	-Subcutaneous nodules or indurated papules and plaques	-Typically occurs within 12 weeks of initiating therapy	-Systemic CS	**-In many cases patients go on to develop systemic granulomatous disease**
Lupus Erythematosus	-Presentations include: erythematous papules and plaques, annular papulosquamous plaques, bullous eruptions, and reactivation of discoid lesions	- 4-34 weeks	-TCS, systemic CS and hydroxychloroquine have all been utilized -In some cases, therapy was reinitiated following treatment with systemic CS	-Lupus erythematosus and lichenoid reactions may be difficult to distinguish clinically and histologically. Therefore, it is recommended immunofluorescence be performed. Anti-nuclear antibodies may be absent.
Hair Effects	-Alopetic patches are most common -Diffuse loss indicative of telogen effluvium may also be seen	-3-6 months after initial dose	-Intralesional triamcinolone and clobetasol foam are often used to treat alopetic patches	-Hair regrowth may manifest with poliosis -Appropriate work-up should be performed to rule out other causes of alopecia -Of note, PD-1 expression is believed to contribute to the immune privilege of hair follicles. Therefore, use of anti-PD1/PD-L1 therapy may result in follicular inflammation.
Mucosal Effects	-Nonspecific stomatitis, mucosal inflammation, periodontal disease, and lichenoid reactions have all been reported	-Median onset 3 weeks	-TCS and lidocaine are often utilized -If mucositis results in severe pain that interferes with oral intake CPI should be held until mucositis improves	-Xerostomia and lichenoid reactions are most common -Mucositis has been associated with risk of gastrointestinal immune-related adverse event including gastroenterocolitis -The differential diagnosis of candidiasis should be kept in mind for individuals who may be treated with CS

*CS: corticosteroids
*TCS: topical corticosteroids
*BSA: body surface area
*ADL: activity of daily living
*AE: Adverse effect
*CPI: Checkpoint inhibitor
*AGEP: Acute generalized exanthematous pustulosis
*PG: Pyoderma gangrenosum
*DRESS/DIHS: Drug rash with eosinophilia and systemic symptoms/ Drug induced hypersensitivity syndrome
*EM: Erythema multiforme
*SJS: Stevens-Johnson syndrome
*TEN: Toxic epidermal necrolysis

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