Dermatologic adverse events from immune checkpoint inhibitors

By Taylor Gray, DO, and Lisa Fronek, DO

### Immune Checkpoint Inhibitors

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<th>CTLA-4 Inhibitors</th>
<th>PD-1 Inhibitors</th>
<th>PD-L1 Inhibitors</th>
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<tr>
<td>Ipilimumab (Yervoy)</td>
<td>Pembrolizumab (Keytruda)</td>
<td>Atezolizumab (Tecentriq)</td>
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<td>Nivolumab (Opdivo)</td>
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<td>Avelumab (Bavencio)</td>
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<td>Cemiplimab (Libtayo)</td>
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<td>Durvalumab (Imfinzi)</td>
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*CTLA-4: cytotoxic T-lymphocyte-associated antigen

*PD-1: Programmed cell death protein-1

*PD-L1: Programmed death-ligand 1

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<th>Dermatologic Adverse Events</th>
<th>Cutaneous Reaction</th>
<th>Clinical Description</th>
<th>Timeframe</th>
<th>Treatment</th>
<th>Special Notes</th>
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<tr>
<td>Maculopapular Rash</td>
<td>-Faint erythematous macules and papules that coalesce into plaques -Most commonly affects the trunk and extensor surfaces of extremities</td>
<td>-3-6 weeks after initial dose</td>
<td>-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</td>
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<td>Pruritus</td>
<td>-May present with or without cutaneous eruption</td>
<td>-3-6 weeks after initial dose</td>
<td>-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</td>
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<td>Lichenoid Eruption</td>
<td>-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</td>
<td>-6-12 weeks after initial dose</td>
<td>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</td>
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<td>Bullous Pemphigoid</td>
<td>-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</td>
<td>-Mean onset of 12-14 weeks following initiation of therapy; however, cases have been reported 3-84 weeks after initial dose</td>
<td>-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</td>
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<tr>
<td>Vitiligo-like Eruption</td>
<td>-Characterized by macules of depigmentation evolving into large symmetric plaques on photo-exposed skin</td>
<td>-Cases have been reported to occur 6 days-36 weeks after initiation of therapy</td>
<td>-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 camouflage may limit negative psychosocial impact -Resolution with cessation of therapy does not occur</td>
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<td>Neutrophil Dermatoses</td>
<td>-Sweet's syndrome -AGEP -Intraconal putular drug eruption -PG -Bullous lupus erythematosus</td>
<td>-For cases presenting as Sweet’s syndrome, AEGP and intraconal drug eruption time to onset was approximately 9 weeks -Cases of PG and bullous lupus presented approximately 16 weeks after initiating therapy</td>
<td>-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 AEGP, intraconal drug eruptions, and bullous lupus -For cases of PG, TCS, systemic CS, intralesional CS and infliximab have been utilized</td>
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Dermatologic Adverse Events

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<td>Psoriasis</td>
<td>- Well-defined, scaly, erythematous plaques on the trunk and extremities. May also present similarly to guttate, inverse, or palmoplantar psoriasis</td>
<td>-0.3 weeks after treatment initiation is common, however, cases have been reported after 3 weeks</td>
<td>- High potency TCS, vitamin D3 analogues, and narrowband ultraviolet B therapy are commonly used</td>
<td>- Eruption has been shown to correlate with positive tumor response in melanoma patients</td>
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<td>- Retinoids, apremilast and biologics may be utilized if lesions persist</td>
<td>- Personal and family history of psoriasis are significant risk factors for development, or exacerbation, of psoriasisiform dermatitis with treatment</td>
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<td>- For grade 3 events and higher, immunotherapy should be held until grade 0-1 is achieved</td>
<td>- More commonly associated with anti-PD1/PD-L1 therapy</td>
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**Severe Cutaneous Adverse Reactions (SCAR):**
- SCARs may manifest similarly to a maculopapular rash initially or may present immediately with blister formation, Nikolsky signs, 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
- Immunetherapy 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 infiltrated 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 papuloquamous 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:**
- Alopecic 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 alopecic patches
- Hair regrowth may manifest with polyma
- 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

References

*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: Pityroderma 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