DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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S031: “What’s new in Dermatopathology”

DISCLOSURES
I do not have any relevant relationships with industry.
CTLA-4 inhibitor: ipilimumab

- Cytotoxic T-lymphocyte antigen-4 antibodies
  - Enhances immune response/antitumor activity
  - Inhibit **CTLA-4**, which is a negative regulator of T-cell activation

*Kandalaft et al., JCO 2011*
**PD-1 inhibitors: pembrolizumab and nivolumab**

- Programmed cell death-1 antibodies
  - Enhances immune response/antitumor activity
  - Inhibit **PD-1**, which plays an important role in downregulating the immune system by preventing the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance

*Kandalaft et al., JCO 2011*
**Checkpoint inhibitor skin reactions**

- Morbilliform eruptions
- Pruritus
- Vitiligo
- Psoriasis
- Eczema
- Disappearance of pigmented lesions
- Lichenoid dermatitis and mucositis
- Grover-like reactions

- Lupus-like reactions
- Erythema nodosum-like panniculitis
- Bullous pemphigoid and other autoimmune blistering diseases
- Granulomatous reactions
- Erythema multiforme and SJS/TEN-like reactions
- Alopecia areata
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PD-1 inhibitor associated bullous pemphigoid

Mochel et al., JCP 2016
PD-1 inhibitor associated bullous pemphigoid
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- BP ELISA testing positive in our patients
Ipilimumab-related dermatitis herpetiformis

- 27 year old woman with Stage III melanoma, received adjuvant ipilimumab
- Developed asymptomatic pink papules near the elbows, back, buttocks 1 month after starting ipilimumab
Ipilimumab-related dermatitis herpetiformis

Mochel et al., J Cutaneous Path 2016
Grover-like reaction

Chen et al., J Cutaneous Path 2018
PD-1 inhibitor-associated lichenoid reactions
Wang et al.,
JAMA Derm 2018
Figure 1. Cutaneous Eruptions Consisting of Erythematous Papules With Scale Due to Anti-Programmed Cell Death 1 and Anti-Programmed Cell Death Ligand 1 Therapy

A. Small number of discrete scaly papules on the chest (patient number 4).
B. Hypertrophic scaly papules and plaques on the lower extremity (patient number 13). C. Inflammation around seborrhoeic keratoses, in addition to new-onset scaly papules, on the back (patient number 14).

D. Coalescent pseudovesicular papules on the palm (patient number 6).
E. Scaly, discrete papules and plaques on the palm (patient number 19).
F. Numerous erosions on the penis, resembling erosive lichen planus (patient number 15).

Figure 2. Photomicrographs Showing Lichenoid Interface Dermatitis

A. H&E, ×4
B. H&E, ×10
C. H&E, ×20
D. CD3-positive
E. CD4-positive
F. CD8-positive
G. CD20-negative
H. CD45-positive
I. CD68-positive

A-C. Hematoxylin-eosin (H&E) staining, original magnification ×4, ×10, and ×20, respectively. Staining of lymphocytic infiltrate revealed the following immunoprofile: D, CD3-positive (both intraepithelial and intrapapillary lymphocytes); E, CD4-positive (intraepithelial lymphocytes); F, CD8-positive (intrapapillary lymphocytes); and G, CD20 negative.
Biopsies of PD-1 inhibitor lichenoid dermatitis are common

Table III. Summary of histopathologic diagnoses associated with inflammatory eruptions to checkpoint inhibitor therapy

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Patients, n</th>
<th>Corresponding histologic diagnoses (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichenoid</td>
<td>16</td>
<td>Lichenoid interface dermatitis (15), scattered foci of histiocytes and lymphocytes with epidermal collarettes (lichen nitidus-like) (1)</td>
</tr>
<tr>
<td>Eczematous</td>
<td>5</td>
<td>Eosinophilic spongiosis (5)</td>
</tr>
<tr>
<td>Maculopapular</td>
<td>7</td>
<td>Dermal hypersensitivity reaction (5), acute vacuolar dermatitis (1), lichenoid interface dermatitis with eosinophils (1)</td>
</tr>
<tr>
<td>Psoriasiform</td>
<td>4</td>
<td>Psoriasiform (4)</td>
</tr>
<tr>
<td>Immunobullous</td>
<td>8</td>
<td>Subepidermal bulla with eosinophils (4), subepidermal bulla with focal interface changes (1), eosinophilic spongiosis (1), erosion of epidermis with eosinophils (1), subepidermal bulla with neutrophils (LABD, 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DIF: linear IgG and C3 at the DEJ (5), linear IgG and C3 and IgA at the DEJ (LABD, 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIIF: serum linear deposition of IgG at DEJ of monkey esophagus (2), serum intercellular staining of IgG and IgA on monkey esophagus with 1:10 (IgA) and 1:80 (IgG) dilutions (LABD, 1)</td>
</tr>
<tr>
<td>Prurigo nodularis</td>
<td>1</td>
<td>Epidermal acanthosis and parakeratosis (1)</td>
</tr>
<tr>
<td>Grover-like</td>
<td>2</td>
<td>Epidermal acantholysis and dyskeratosis (2)</td>
</tr>
<tr>
<td>Acneiform</td>
<td>1</td>
<td>Suppurative and granulomatous folliculitis (1)</td>
</tr>
<tr>
<td>Granulomatous</td>
<td>3</td>
<td>Naked granulomas within the dermis with multinucleated cells (sarcoïdosis-like, 2), superficial and deep perivascular and interstitial infiltrate of histiocytes and lymphocytes with focal palisading (granuloma annulare-like, 1)</td>
</tr>
<tr>
<td>SJS-like</td>
<td>2</td>
<td>Epidermal necrosis with numerous apoptotic keratinocytes and lymphohistiocytic inflammation (SJS-like, 1), subcorneal pustules and mixed infiltrate with eosinophils and necrotic keratinocytes, and lichenoid interface dermatitis with necrotic keratinocytes (AGEP and SJS-like, 1).</td>
</tr>
<tr>
<td>PR-like</td>
<td>1</td>
<td>Patchy papillary dermal mixed infiltrate with plasma cells and eosinophils with red cell extravasation (1)</td>
</tr>
<tr>
<td>PRP-like</td>
<td>1</td>
<td>Epidermal acanthosis with orthokeratosis and parakeratosis, intact granular layer and mild spongiosis, perivascular inflammatory infiltrate within the superficial dermis (1)</td>
</tr>
</tbody>
</table>

AGEP, acute generalized exanthematous pustulosis; C3, complement 3; DEJ, dermal-epidermal junction; DIF, direct immunofluorescence; IIIF, indirect immunofluorescence; LABD, linear IgA bullous dermatosis; PR, pityriasis rosea; PRP, pityriasis rubra pilaris; SJS, Stevens-Johnson syndrome.
Smith et al.,
JCP 2018
PD-1 inhibitor infusion site sarcoidosis
Delayed cutaneous adverse reactions to PD-1 inhibitors are frequently observed.
Cutaneous adverse reactions may also occur after PD-1 inhibitor therapy has been discontinued.

**Table 2. Summary of Reactions That Occurred After Discontinuation of PD-1 Inhibitor Treatment**

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Malignant Neoplasm</th>
<th>PD-1 Inhibitor</th>
<th>Cutaneous Adverse Reaction</th>
<th>Time to Onset After PD-1 Inhibitor Discontinuation, mo</th>
<th>Tumor Response</th>
<th>Associated Extracutaneous irAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/60s</td>
<td>Melanoma</td>
<td>Pembrolizumab</td>
<td>Sarcoidosis</td>
<td>4.7</td>
<td>CR</td>
<td>Lung sarcoidosis</td>
</tr>
<tr>
<td>6/F/80s</td>
<td>Melanoma</td>
<td>Pembrolizumab</td>
<td>Lichenoid dermatitis</td>
<td>2.0</td>
<td>PR</td>
<td>None</td>
</tr>
<tr>
<td>10/I/80s</td>
<td>SCC</td>
<td>Pembrolizumab</td>
<td>Bullous pemphigoid</td>
<td>6.0</td>
<td>PD</td>
<td>None</td>
</tr>
<tr>
<td>14/M/40s</td>
<td>Melanoma</td>
<td>Pembrolizumab</td>
<td>Lichenoid dermatitis</td>
<td>1.0</td>
<td>CR</td>
<td>None</td>
</tr>
<tr>
<td>16/I/50s*</td>
<td>Melanoma</td>
<td>Pembrolizumab and nivolumab</td>
<td>Lichenoid dermatitis</td>
<td>1.0</td>
<td>PD</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; irAE, immune-related adverse event; PD, progression of disease; PD-1, programmed cell death protein 1; PR, partial response; SCC, squamous cell carcinoma.

*Received 3 cycles of pembrolizumab followed by 3 cycles of ipilimumab and nivolumab.
Lupus-like cutaneous reaction to PD-1 inhibitor
Bullous erythema multiforme

Wang et al., JAMA Derm 2018
Bullous erythema multiforme

- Patient had a markedly delayed onset of cutaneous reaction attributable to pembrolizumab (38 months)
- Developed painful papules, plaques, and bullae on hands, and several oral mucosal erosions
- Resolved with course of prednisone but recurred with next cycle of pembrolizumab given

Wang et al., JAMA Derm 2018
Alopecia areata induced by immune checkpoint inhibitors

Zarbo et al., BJD 2017

Fig 1. Histology. (a) Case 1. Photomicrograph of a section of the posterior scalp biopsy showing a perifollicular (predominantly peri-infundibular) lymphocytic infiltrate with nanogen hair and residual fibrovascular tracts (follicular streamers and stellae), and mild mucin deposit; terminal-to-vellus ratio 1 : 2 (haematoxylin and eosin, × 100). (b) Case 3. Sparse peribulbar lymphocytic infiltrate.

Fig 2. Clinical images of alopecia areata. (a) Case 1. Regrowth with poliosis on follow-up after 2 months. (b) Case 3. Focal areas of patchy hair loss in the midscalp region. (c) Case 4. Superficial proximal onychoschizia associated with Beau’s lines of the proximal nail fold.
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Talimogene Laherparepvec (T-VEC)

• Approved by the FDA in October 2015 for treatment of unresectable Stage IIIB, IIIC, or IV melanoma
• First in class oncolytic virus based on modified HSV-1
  – Injectable therapy, directed into tumor tissue
  – Modified via deletion of 2 nonessential viral genes
• Designed to selectively replicate in and lyse tumor cells while promoting regional and systemic antitumor immunity
  – Should not harm normal tissue
**T-VEC = engineered HSV-1**

<table>
<thead>
<tr>
<th>Genetic modification</th>
<th>Result</th>
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<tbody>
<tr>
<td>deletion of ICP34.5</td>
<td>prevents HSV infection of non-tumor cells, providing tumor-selective replication</td>
</tr>
<tr>
<td>deletion of ICP47</td>
<td>enables antigen presentation</td>
</tr>
<tr>
<td>insertion of human GM-CSF gene (behind CMV promoter)</td>
<td>enhances anti-tumor immune response by recruiting and stimulating dendritic cells to tumor site</td>
</tr>
</tbody>
</table>
Proposed mechanism of action of T-VEC

- T-VEC selectively replicates in tumor cells and lyses them → release of progeny virus and tumor-derived antigens (TDAs)
- T-VEC modified to include 2 copies of human GM-CSF → promotes maturation and function of dendritic cells → activate anti-tumor T-cells through presentation of processed TDAs

Harrington et al, 2015
Andtbacka et al., JCO 2015

78 patients in T-VEC arm showed response, 56/78 were ongoing at time of end point assessment

8 pts in GM-CSF arms responded
Clinical Course

- Patient with stage IIIB melanoma with recurrence s/p 1st WLE → received 4 cycles of ipilimumab
- 2nd WLE: Malignant melanoma, multiple satellite nodules, completely excised
- Additional satellite lesions developed subsequently
- Continued localized progression of disease with pembrolizumab therapy, no distant metastases
- Started on T-VEC
Our patient

- Following treatment with T-VEC, biopsy of pigmented macules revealed no residual melanoma
- A neutrophil-rich dermal inflammatory infiltrate is suggestive of a Sweet’s like reaction, and may be attributable to the GM-CSF component of T-VEC

Parekh et al, JAMA Derm 2017
T-VEC associated granulomatous reactions

Lee et al, JCP 2018
Septal and lobular panniculitis after T-VEC

Long et al, JCP 2018
The Dermatology Foundation has supported & advanced my research – and patient care.
Thank you!

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