Dermatologic toxicities and other complications from cancer therapy: Updates, challenges and lessons learned from the oncodermatology trenches

Jonathan Leventhal, MD
Director, Oncodermatology Clinic
Associate Director, Residency Program
Assistant Professor, Department of Dermatology
Yale University School of Medicine
Disclosures

Regeneron and Sanofi: Advisory Board – Honoraria

Bristol-Myers Squibb: Advisory Board – Honoraria

La Roche-Posay: Advisory Board – Honoraria

Azitra, Inc. & OnQuality: Research funding – Clinical trials

‘Off-label’ use of medications will be discussed.
Objectives

• Recognize common dermatologic toxicities to cancer therapy, including traditional chemotherapy, targeted therapy, immune checkpoint inhibitor therapy, endocrine therapy, radiation therapy and stem cell transplantation.

• Understand how these dermatologic conditions impact cancer patients’ quality of life and their cancer treatment.

• Evaluate and manage dermatologic conditions in a multidisciplinary fashion with the oncology services.
Oncodermatology Program at Yale Cancer Center
Established 2008 (Jennifer Choi)
2015-2021 (Jonathan Leventhal)
Location in the cancer center matters!

- Timely evaluation and management (expedited referrals)
- Close communication with all members of the oncology team
- Clinical trials & collaborations
Supportive Oncodermatology

- Growing field dedicated to managing cutaneous conditions in cancer patients

- Dermatologic adverse effects are among the most frequent from cancer therapy:
  - May significantly impact quality of life
  - May lead to dose-limitation or interruption of cancer therapy when severe

- Prompt recognition and treatment allows for continuation of potentially life-saving cancer therapy when possible
Impact on quality of life (QoL)

- **Women:** often affected to a greater degree than men by toxic cutaneous effects of cancer therapy
  - Self-image, cultural identity, femininity, sexuality and mental health (depression, anxiety)

- **Chemotherapy-induced alopecia:** ~60% women with breast cancer considered this to be the worst chemo-associated side effect, and almost 10% considered declining treatment in fear of it

- **Acneiform rash, hand-foot syndrome, nail changes & mucositis:** frequently lower quality of life

Unique considerations in patients with skin of color

- Retrospective study 200 patients: Black/Non-Hispanic (110), Other/Hispanic (63), Asian/Non-Hispanic (24), or Black/Hispanic (3)
- Most common toxicity: acneiform (19.5%), xerosis/dermatitis (19.1%), nail changes (8.7%)
- **Hyperpigmentation** (post-inflammatory) (38.6%); **scarring alopecia, nail dystrophy, keloids** were most recalcitrant to therapy
- Oncoderm consult: clinical improvement in 85.9%, continuation of cancer therapy in 92.8%
Dermatologic care improves outcomes in cancer patients

- Outpatient oncodermatology consults: decreased interruption of immunotherapy compared to cases managed by oncologists (5% vs 30%).

- Inpatient dermatology consults: reduced systemic immunosuppression (18% vs 55%) and reduced immunotherapy discontinuation (0% vs 36%) compared to cases without dermatology involvement.

- Yale Cancer Center (outpatient & inpatient dermatology consults): >90% remained on immunotherapy.

- **Improved survival**: when dermatologists evaluated and treated cutaneous adverse events.
Oncodermatology Service:

**Toxicities & direct complications**
- Systemic therapy (targeted, immunotherapy, conventional, endocrine)
- Radiation therapy
- Stem cell transplantation
- Cutaneous metastases

**Indirect complications**
- Paraneoplastic conditions
- Infectious complications (immunosuppression)
- Late complications (skin cancer, fibrosis, Survivorship program)

**Cutaneous oncology**
- Melanoma, squamous cell, basal cell, merkel cell, dermatofibrosarcoma protuberans, angiosarcoma, cutaneous lymphoproliferative disorders
- High-risk skin cancer screening
- Cancer genetics program

**Infectious complications** (immunosuppression)

**Late complications** (skin cancer, fibrosis, Survivorship program)
Focus on cutaneous toxicities

**Toxicities & direct complications**
- Systemic therapy (targeted, immunotherapy, conventional, endocrine)
- Radiation therapy
- Stem cell transplantation
- Cutaneous metastases

**Indirect complications**
- Paraneoplastic conditions
- Infectious complications (immunosuppression)
- Late complications (skin cancer, fibrosis, Survivorship program)

**Cutaneous oncology**
- Melanoma, squamous cell, basal cell, merkel cell, dermatofibrosarcoma protuberans, angiosarcoma, cutaneous lymphoproliferative disorders
- High-risk skin cancer screening
- Cancer genetics program
Highlighting cutaneous toxicities

Toxicities & direct complications
- Systemic therapy (targeted, immunotherapy, conventional, endocrine)
- Radiation therapy
- Stem cell transplantation
- Cutaneous metastases

Indirect complications
- Paraneoplastic conditions
- Infectious complications (immunosuppression)
- Late complications (skin cancer, fibrosis, Survivorship program)

Cutaneous oncology
- Melanoma, squamous cell, basal cell, merkel cell, dermatofibrosarcoma protuberans, angiosarcoma, cutaneous lymphoproliferative disorders
- High-risk skin cancer screening
- Cancer genetics program
- Dozens of FDA-approved targeted agents for cancer therapy & the list is growing…
- Cutaneous adverse events are among the most frequently reported with classical and novel targeted drugs.
EGFR inhibitors: common dermatologic AEs (*PRIDE*)

- **Papulopustules** (initially sterile, commonly secondarily infected with MSSA or MRSA) & **paronychia**
- **Regulatory abnormalities of hair growth**
- **Itching, Dryness due to EGFRIs**
## Grade & management approach

<table>
<thead>
<tr>
<th>Grade</th>
<th>Body surface area</th>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;10% BSA</td>
<td>Mildly symptomatic</td>
<td>Emollients, low-potency topical steroids, anti-H1</td>
</tr>
<tr>
<td>2</td>
<td>10-30% BSA</td>
<td>Impact functional ADL</td>
<td>Mid-high potency topical steroids, Oral antibiotics (acneiform), Intolerable: prednisone &amp; hold cancer therapy</td>
</tr>
<tr>
<td>3</td>
<td>&gt;30% BSA</td>
<td>Impact self-care ADL, Fails to respond to Rx</td>
<td>Grade 2 treatment, IV steroids, Hold cancer therapy, Consider restarting cancer therapy once low-grade</td>
</tr>
<tr>
<td>4</td>
<td>Severe/life-threatening</td>
<td>Superinfection</td>
<td>Discontinue cancer therapy, Hospitalize &amp; IV steroids, IV Abx (superinfection)</td>
</tr>
</tbody>
</table>

*Common Terminology Criteria Adverse Events (CTCAE), American Society of Clinical Oncology (ASCO)*
Management of acneiform rash (+MSSA) from EGFR inhibitor in a patient with lung cancer with doxycycline, high-potency topical steroid/mupirocin ointment, antiseptic soaks
Management of acneiform rash with associated alopecia from EGFR inhibitor in a patient with lung cancer
Management of acneiform rash with associated scarring alopecia from EGFR inhibitor in a patient with lung cancer.
Management of Grade 3 acneiform rash from cetuximab with prednisone, doxycycline, high-potency topical steroids
Treatment of late onset purpuric acneiform drug eruption with doxycycline 100 mg twice daily and high-potency topical steroid ointment in patient with H&N cancer on cetuximab/afatinib
Management of paronychia and pyogenic granulomas from EGFR inhibitor in a patient with head & neck cancer with topical timolol gel, silver nitrate to stubborn PGs, doxycycline/antibiotic ointments, vinegar soaks.
Hot topics & challenges

• Preventive vs. reactive therapy: differs at each cancer center
  • Oral tetracycline/topical steroids/sunscreen/emollients (may reduce severity, not incidence)
  • Skin toxicity program: help enact preventive therapy & decreased EGFRI dose changes

• Prognostic relevance
  • Several trials demonstrated correlation with tumor response and rash severity

• Future directions
  • Clinical trials evaluating novel preventive methods (e.g. topical BRAF inhibitor, topical probiotics)

HER2, MEK inhibitors: similar AE profile (less frequent & severe)
Anti-angiogenesis multi-kinase inhibitors:
(VEGFR/PDGFR, also FGFR, KIT among others)

Hand-foot skin reaction (most common): impact ADLs, associated dysesthesia; dose-reduction often required

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical features</th>
<th>Treatment approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Minimal changes, asymptomatic</td>
<td>• Emollients, keratolytics (urea cream, ammonium lactate)</td>
</tr>
<tr>
<td>2</td>
<td>Peeling, blisters, edema, hyperkeratosis, pain interfering with functional ADLs</td>
<td>• High-potency topical steroid ointments (e.g. clobetasol); antiseptic soaks for blisters (e.g. dilute dakin’s, vinegar soaks); <em>dose interruption then reduction may be necessary</em></td>
</tr>
<tr>
<td>3</td>
<td>Severe changes, pain interfering with self-care ADLs</td>
<td>• Associated dysesthesia: gabapentinoids (e.g. pregabalin)</td>
</tr>
</tbody>
</table>
Challenges & future directions:

- Multi-institutional clinical trial (phase 1 complete, phase 2 pending) using a novel topical nitroglycerin ointment to treat grade 2/3 HFSR; results pending

Topical sildenafil in the treatment of hand-foot syndrome and hand-foot skin reaction: A retrospective study. Arrowood et al. J Clin Oncology, 2018

- This study recorded a 78% rate of clinically meaningful improvement to HFS/HFSR after topical sildenafil.
Other select targeted agents: BRAF, BCR-ABL, BTK, c-KIT, P13K, FGFR

**BRAF:** Phototoxicity, SCC, verrucae (reduced with MEK1), erythema nodosum

**BCR-ABL, c-KIT:** keratosis pilaris

**BTK:** Purpuric rash, folliculitis

**FGFR:** alopecia, nail changes, calciphylaxis/calcinosis cutis

**P13K:** Exanthem (erythroderma)

Hirner et al, JAMA Derm, 2020
Highlighting cutaneous toxicities

Toxicities & direct complications
- Systemic therapy (targeted, immunotherapy, conventional, endocrine)
- Radiation therapy
- Stem cell transplantation
- Cutaneous metastases

Indirect complications
- Paraneoplastic conditions
- Infectious complications (immunosuppression)
- Late complications (skin cancer, fibrosis, Survivorship program)

Cutaneous oncology
- Melanoma, squamous cell, basal cell, merkel cell, dermatofibrosarcoma protuberans, angiosarcoma, cutaneous lymphoproliferative disorders
- High-risk skin cancer screening
- Cancer genetics program
Immune checkpoint inhibitors: dermatologic side effects are common (30-50%)

Exanthems/dermatitides (frequent)
- Morbilliform
- Lichenoid
- Eczematous/pruritus
- Psoriasiform

Autoimmune disorders
- Vitiligo
- Bullous pemphigoid
- Connective tissue disease
- Alopecia areata

Severe cutaneous adverse reactions (rare)
- SJS/TEN
- AGEP, DRESS

Miscellaneous: dermal/subcutaneous/fascial
- Granulomatous
- Panniculitis
- Eosinophilic fasciitis

Retrospective study from Oncodermatology Clinic:
- 103 rashes: various clinical & histologic morphologies; most resembled idiopathic dermatoses (lichen planus, eczema, psoriasis, bullous pemphigoid)
- Most responded to topical therapy; 20% required prednisone; other targeted agents uncommonly used (e.g. omalizumab)
- >90% remained on immunotherapy, <10% permanently discontinued (Steven-Johnson Syndrome, pemphigoid, lichenoid)

Table 1. Summary of patient demographics, associated immunotherapy class, rash characteristics, and other irAE

<table>
<thead>
<tr>
<th>Rash type</th>
<th>No. patients, (M, F)</th>
<th>Age, y, mean</th>
<th>Anti–CTLA-4</th>
<th>Anti–PD-1 or PD-L1</th>
<th>Both</th>
<th>Latency, mon, mean (range)</th>
<th>Pruritus, n</th>
<th>Grade, median (range)</th>
<th>Other irAE, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichenoid</td>
<td>26 (17, 9)</td>
<td>64</td>
<td>2</td>
<td>23</td>
<td>1</td>
<td>6.2 (0.5-20)</td>
<td>25</td>
<td>1 (1-3)</td>
<td>9</td>
</tr>
<tr>
<td>Maculopapular</td>
<td>18 (5, 13)</td>
<td>61</td>
<td>2</td>
<td>11</td>
<td>5</td>
<td>1.0 (0.2-5.7)</td>
<td>16</td>
<td>2 (1-3)</td>
<td>7</td>
</tr>
<tr>
<td>Psoriasisform</td>
<td>17 (8, 9)</td>
<td>67</td>
<td>1</td>
<td>12</td>
<td>4</td>
<td>5.7 (0.2-28.8)</td>
<td>10</td>
<td>1 (1-3)</td>
<td>8</td>
</tr>
<tr>
<td>Eczematous</td>
<td>12 (6, 6)</td>
<td>66</td>
<td>0</td>
<td>9</td>
<td>3</td>
<td>5.8 (0.6-25)</td>
<td>12</td>
<td>1 (1-3)</td>
<td>5</td>
</tr>
<tr>
<td>Immobullous</td>
<td>8 (4, 4)</td>
<td>68</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>4.5 (0.5-10)</td>
<td>8</td>
<td>3 (2-3)</td>
<td>2</td>
</tr>
<tr>
<td>Prurigo</td>
<td>7 (3, 4)</td>
<td>71</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>10.1 (1.8-16)</td>
<td>7</td>
<td>1 (1-3)</td>
<td>3</td>
</tr>
<tr>
<td>Grover-like</td>
<td>4 (4, 0)</td>
<td>71</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4.2 (0.2-14.4)</td>
<td>4</td>
<td>1 (1-2)</td>
<td>1</td>
</tr>
<tr>
<td>Acneiform</td>
<td>4 (3, 1)</td>
<td>47</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4.3 (0.2-11)</td>
<td>1</td>
<td>1 (1-2)</td>
<td>1</td>
</tr>
<tr>
<td>Granulomatosus</td>
<td>3 (0, 3)</td>
<td>65</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>17.7 (7-36)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>SJS-like</td>
<td>2 (1, 1)</td>
<td>62</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1.4</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>PR-like</td>
<td>1 (1, 0)</td>
<td>75</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.2</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PRP-like</td>
<td>1 (1, 0)</td>
<td>63</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.46</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>103 (54, 49)</td>
<td>65</td>
<td>5</td>
<td>81</td>
<td>17</td>
<td>5.13 (0.1-36)</td>
<td>77</td>
<td>1 (1-4)</td>
<td>36</td>
</tr>
</tbody>
</table>

Coleman et al, J Am Acad Dermatol, 2019
Overview of management of dermatologic toxicities (ASCO guidelines):

<table>
<thead>
<tr>
<th>Grade</th>
<th>Severity</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No affect on quality of life</td>
<td>- Continue immunotherapy</td>
</tr>
<tr>
<td></td>
<td>Controlled topically/anti-H1</td>
<td>- Emollients, low-mid potency topical steroids &amp; anti-H1</td>
</tr>
<tr>
<td>2</td>
<td>Affect quality of life</td>
<td>- Hold immunotherapy if intolerable</td>
</tr>
<tr>
<td></td>
<td>Requires intervention</td>
<td>- Prednisone 1 mg/kg, taper over 4 weeks; mid to high-potency topical steroids</td>
</tr>
<tr>
<td>3</td>
<td>Fails to respond to intervention</td>
<td>- Hold immunotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- IV methylprednisolone 1–2 mg/kg, taper over 4 weeks</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>- Permanently discontinue immunotherapy</td>
</tr>
<tr>
<td></td>
<td>Fails to respond to intervention</td>
<td>- IV methylprednisolone 1-2 mg/kg, taper slowly</td>
</tr>
</tbody>
</table>

- **Restart immunotherapy**: when Grade 1 (unless SCAR); prednisone <10mg/day

- **Dermatology pearl**: use disease-targeted approaches whenever possible (e.g. phototherapy, dupilumab)

*Brahmer et al. J Clin Oncology, 2018*
“Lichenoid” dermatitis: up to 25% on PD-1/PD-L1

Resembling lichen planus: pink-violaceous, scaly papules

Bolognia et al, Dermatology, 4th ed
Lichenoid dermatitis treated with topical steroids and acitretin in a patient with lung cancer on PD-1 therapy.
Darker skin phototypes
Mucosal involvement (oral/genital) – Low threshold for prednisone & drug holiday; hydroxychloroquine
Inverse psoriasiform eruption from pembrolizumab improved with high-potency topical steroid ointment & mupirocin.

Flare of psoriasis on PD-1 therapy responded well to nbuvb phototherapy.
Morbilliform exanthems: most common with ipilimumab or combination ipi/nivo

- Onset usually weeks (shorter latency than LP/BP).
- Mild cases: self-limited, topical steroids; if persists/intolerable → prednisone 0.5-1mg/kg
- Severe cases: monitor for SCAR; prednisone 1-2 mg/kg taper over 4 weeks
Severe cutaneous adverse reactions (SCARs): rare, include SJS/TEN, DRESS, AGEP
- Stop immunotherapy + medical management: IV steroids, consider IVIG or cyclosporine; TNF inhibitors

TEN due to ipi/nivo – skin improved with IV steroids/infliximab (also colitis); died from sepsis.

DRESS due to ipi – responded to IV steroids (long taper)

AGEP due to ipi – responded to IV steroids, infliximab (also colitis)

SJS/TEN-like: delayed onset from exanthem or lichenoid, often with a concurrent high-prob drug; ‘progressive immunotherapy-related mucocutaneous eruption’ (PIRME)

Molina et al, J Am Acad Dermatol, 2020
**Bullous pemphigoid**: autoimmune blistering disease
- ~1% patients on PD-1/PD-L1, typical latency of onset ~4-6 months
- +BP180 antibodies in serum and +IgG and complement stain at dermoeidermal junction on skin biopsy
- Particularly challenging to treat (most require prednisone); rituximab, omalizumab, dupilumab, methotrexate (steroid-sparing)
- May persist after stopping immunotherapy

Pruritus often precedes rash

Mucosal

Widespread urticarial plaques and blisters/erosions

Siegel et al, J Am Acad Dermatol, 2018
Future directions: targeted approach toward dermatologic irAE

- Several studies demonstrated that brief or low-dose use of systemic steroids for skin irAE is not associated with impaired tumor response; however, better targeted strategies are needed
- IL-4-13, IgE, CD20 – bullous pemphigoid
- IL-4-13, IgE – dermatitis, recalcitrant pruritus
- IL-12-23, IL-23, IL-17, TNF inhibitors – psoriasiform
- TNF inhibitors – Steven-Johnson Syndrome, toxic epidermal necrolysis
- Studies to evaluate impact of targeted biologics for skin irAE on tumor response are ongoing

Omalizumab as steroid-sparing maintenance therapy for BP in a patient with metastatic melanoma on adjuvant PD-1 therapy

Thompson et al, JAMA Dermatol, 2021
Dermatologic irAE as positive prognostic marker

Maculopapular, pruritus, vitiligo


Vitiligo in melanoma

Sanlorenzo, et al. JAMA Derm 2015

Lichenoid/spongiotic dermatitis

Min Lee, et al. JAAD. 2018
Highlighting cutaneous toxicities

Toxicities & direct complications
- Systemic therapy (targeted, immunotherapy, conventional, endocrine)
- Radiation therapy
- Stem cell transplantation
- Cutaneous metastases

Indirect complications
- Paraneoplastic conditions
- Infectious complications (immunosuppression)
- Late complications (skin cancer, fibrosis, Survivorship program)

Cutaneous oncology
- Melanoma, squamous cell, basal cell, merkel cell, dermatofibrosarcoma protuberans, angiosarcoma, cutaneous lymphoproliferative disorders
- High-risk skin cancer screening
- Cancer genetics program
Cytotoxic chemotherapy dermatologic toxicities (most common)

Alopecia (anagen effluvium)
(permanent less common)

Nail changes (paronychia, onycholysis, pigment change)

Mucositis

‘Toxic erythema of chemotherapy'
(hand-foot syndrome, malignant intertrigo)
Cytotoxic chemotherapy dermatologic toxicities (treatment pearls)

Alopecia (anagen effluvium) (permanent less common)

Nail changes (paronychia, onycholysis, pigment change)

Topical minoxidil
Scalp cooling (preventive)

Mucositis

Topical antiseptics, anesthetics, steroids
Treat thrush, HSV

‘Toxic erythema of chemotherapy'
(hand-foot syndrome, malignant intertrigo)

Dilute vinegar soaks
Topical antibiotics (culture)
Gentle nail care, lacquer/emollients
Localized cooling (preventive)

Topical steroids/wound care, NSAIDs
Drug holiday, slower infusion rate or dose reduction
Localized cooling (preventive hand-foot syndrome)
Cytotoxic chemotherapy dermatologic toxicities (less common)

- Periorbital edema
- Lipodermatosclerosis-like
- Radiation recall
- Extravasation reactions
- Sclerodermoid reactions
- Hyperpigmentation
- Inflamed keratoses
Cytotoxic chemotherapy dermatologic toxicities (treatment pearls)

- **Periorbital edema**
  - Lymphedema mask

- **Lipodermatosclerosis-like**
  - Avoid misdiagnosis of cellulitis
  - Topical steroids
  - Compressive therapy

- **Radiation recall**
  - Topical steroids (low grade)
  - Drug holiday/reduce dose (high grade)

- **Extravasation reactions**
  - Check for antidote
  - Wound care
  - Treat superinfection
  - Surgical consult (severe)

- **Sclerodermoid reactions**
  - Stop cancer therapy (taxane usually)

- **Hyperpigmentation**
  - No treatment needed

- **Inflamed keratoses**
  - No treatment needed
  - Topical steroids

*De Angelis et al. Clinical Rheumatology 2003*
New strategies & challenges: localized cooling

- Regional cooling may reduce the incidence, severity and delay the onset of hand-foot syndrome, nail changes & neuropathy according to several (but not all) prospective & retrospective studies.
- Caution cold injury; painful

- RCTs demonstrated efficacy of scalp cooling for alopecia prevention in women with breast cancer (taxane, anthracycline, or both); efficacy ~50% (less for anthracyclines)
- Challenges: cost ($3000, lack of insurance coverage), adverse effects (headache, frost bite), concern for scalp metastasis (rarely seen in breast cancer, contraindicated in H&N, CNS, hematologic)


Kruse and Abraham, 2018, Nangia et al, 2016, Marks et al, 2019
Highlighting cutaneous toxicities

**Toxicities & direct complications**
- Systemic therapy (targeted, immunotherapy, conventional, endocrine)
- Radiation therapy
- Stem cell transplantation
- Cutaneous metastases

**Indirect complications**
- Paraneoplastic conditions
- Infectious complications (immunosuppression)
- Late complications (skin cancer, fibrosis, Survivorship program)

**Cutaneous oncology**
- Melanoma, squamous cell, basal cell, merkel cell, dermatofibrosarcoma protuberans, angiosarcoma, cutaneous lymphoproliferative disorders
- High-risk skin cancer screening
- Cancer genetics program

**Toxicities & direct complications**
- Systemic therapy (targeted, immunotherapy, conventional, endocrine)
- Radiation therapy
- Stem cell transplantation
- Cutaneous metastases

**Indirect complications**
- Paraneoplastic conditions
- Infectious complications (immunosuppression)
- Late complications (skin cancer, fibrosis, Survivorship program)

**Cutaneous oncology**
- Melanoma, squamous cell, basal cell, merkel cell, dermatofibrosarcoma protuberans, angiosarcoma, cutaneous lymphoproliferative disorders
- High-risk skin cancer screening
- Cancer genetics program
Endocrine (hormonal) therapy dermatologic toxicities

Female pattern alopecia: topical minoxidil may promote regrowth

Other side effects:
- Flushing
- Xerosis
- Vulvovaginal atrophy/dryness
- Radiation recall (rare)
Highlighting cutaneous toxicities

**Toxicities & direct complications**
- Systemic therapy (targeted, conventional, immunotherapy, endocrine)
- Radiation therapy
- Stem cell transplantation
- Cutaneous metastases

**Indirect complications**
- Paraneoplastic conditions
- Infectious complications (immunosuppression)
- Late complications (skin cancer, fibrosis, Survivorship program)

**Cutaneous oncology**
- Melanoma, squamous cell, basal cell, merkel cell, dermatofibrosarcoma protuberans, angiosarcoma, cutaneous lymphoproliferative disorders
- High-risk skin cancer screening
- Cancer genetics program
Acute radiation dermatitis: majority of patients – typically low grade presentations

- Recommend mometasone cream 1-2x daily for breast RT prophylaxis, and in setting of an underlying inflammatory dermatosis (e.g. psoriasis, autoimmune blistering disease).
- Variety of topical agents and dressings used in practice to prevent and treat radiation dermatitis, but minimal evidence to support their use.
Acute radiation dermatitis: less common severe presentations with moist desquamation

- Holding further radiotherapy until clinically improved.
- High-potency topical steroids (if no infection), mupirocin or Silvadene cream
- Superficial wound culture; consider oral antibiotics (e.g. cephalexin).
- Open-wet dressings, dilute dakin's (sodium hypochlorite) soaks, gentle debridement of crusts.
- Biologic dressings: hydrogel, hydrocolloid, silver-based.
Many cutaneous toxicities complications of radiotherapy: include acute and chronic, as well as late carcinogenesis.

- Acute radiation dermatitis
- Chronic radiation changes (atrophy, dyspigmentation, fibrosis)
- Radiation persistent alopecia
- Radiation enhancement (e.g. EGFRi)
- Radiation recall phenomenon (usually chemo)
- Radiation-associated neoplasms (atypical vascular lesions, basal cells)

Aragonés, et al, Actas Dermo-Sifiliográficas, 2017
Diversity of rashes triggered by radiotherapy
localized or enhanced within radiation field, but often generalizes

Radiation-triggered bullous pemphigoid
Psoriasis flare & koebnerization
Radiation-induced morphea & GVHD

Radiation-triggered erythema multiforme or severe cutaneous adverse reactions (SJS)
Eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy
• Biopsy inflammatory rashes of irradiated breast!
• Early inflammatory morphea can be mistaken for cellulitis, acute radiation dermatitis, mastitis, or inflammatory breast cancer.
Highlighting cutaneous toxicities

Toxicities & direct complications
- Systemic therapy (targeted, conventional, immunotherapy, endocrine)
- Radiation therapy
- Stem cell transplantation
- Cutaneous metastases

Indirect complications
- Paraneoplastic conditions
- Infectious complications (immunosuppression)
- Late complications (skin cancer, fibrosis, Survivorship program)

Cutaneous oncology
- Melanoma, squamous cell, basal cell, merkel cell, dermatofibrosarcoma protuberans, angiosarcoma, cutaneous lymphoproliferative disorders
- High-risk skin cancer screening
- Cancer genetics program
Post-hematopoietic stem cell transplantation: Acute graft versus host disease

Moriilliform exanthem – common

Toxic epidermal necrolysis-like GVHD (stage 4) – rare
Post-hematopoietic stem cell transplantation: Acute GVHD (treatments)

Morbilliform exanthem – common

Toxic epidermal necrolysis-like GVHD (stage 4) – rare

Low grade: topical steroids
High grade: prednisone, increase immunosuppression, JAK inhibitor
Post-hematopoietic stem cell transplantation: chronic graft versus host disease

- Lichenoid
- Dyspigmentation
- Morpheaform/sclerodermoid + ulcers
- Eosinophilic fasciitis
Challenging to treat!
Prednisone, increase immunosuppression, JAK inhibitor, BTK inhibitor
Photopheresis
Phototherapy
Hydroxychloroquine, methotrexate, acitretin
Clinical trials..

Post-hematopoietic stem cell transplantation: chronic GVHD (treatment)
When to refer patients to dermatology?

- Cutaneous toxicities that impact QoL; severe cases which may interrupt cancer therapy.
- Grade 2 & beyond rashes; recalcitrant to emollients, topical steroids, anti-histamines, local wound care.
- Red flags (e.g. skin pain, blisters, pus, mucositis, facial edema).
- Lesions concerning for malignancy or infection.
- Clinical trials that require surveillance skin biopsies.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic, managed topically &lt;10% BSA</td>
</tr>
<tr>
<td>2</td>
<td>Affect QoL (functional ADLs) 10 - 30% BSA</td>
</tr>
<tr>
<td>3</td>
<td>Affect QoL (self-care ADLs) &gt;30% BSA</td>
</tr>
<tr>
<td>4</td>
<td>Systemic complications, life-threatening (e.g. Steven-Johnson)</td>
</tr>
</tbody>
</table>

CTCAE
Conclusions

• Dermatologic toxicities are frequent from cancer therapy, commonly impact patients’ quality of life:
  • Targeted & immunotherapy: high correlation with rash (e.g. acneiform from EGFRi, hand-foot from VEGFRi, lichenoid & pemphigoid from PD-1/PD-L1).
  • Conventional chemo and radiation: variety of complications (e.g. alopecia, hand-foot, nail changes, radiodermatitis).
  • Chronic graft versus host disease: challenging to treat, multiple agents often required.
• Dermatology consultation can be an important component of the multi-disciplinary care of cancer patients, treating toxicities and reducing disruption of cancer therapy!
Thank you & Questions?

Please email me any questions: Jonathan.Leventhal@yale.edu