Advanced Oncology Certified Nurse Practitioner

REVIEW COURSE 2024

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Side Effects and Symptom Management: Dermatologic and Pulmonary Toxicities

Marcia Holloway MSN APRN ANP-C AOCNP
Department of Genitourinary Medical Oncology
UT MD Anderson Cancer Center

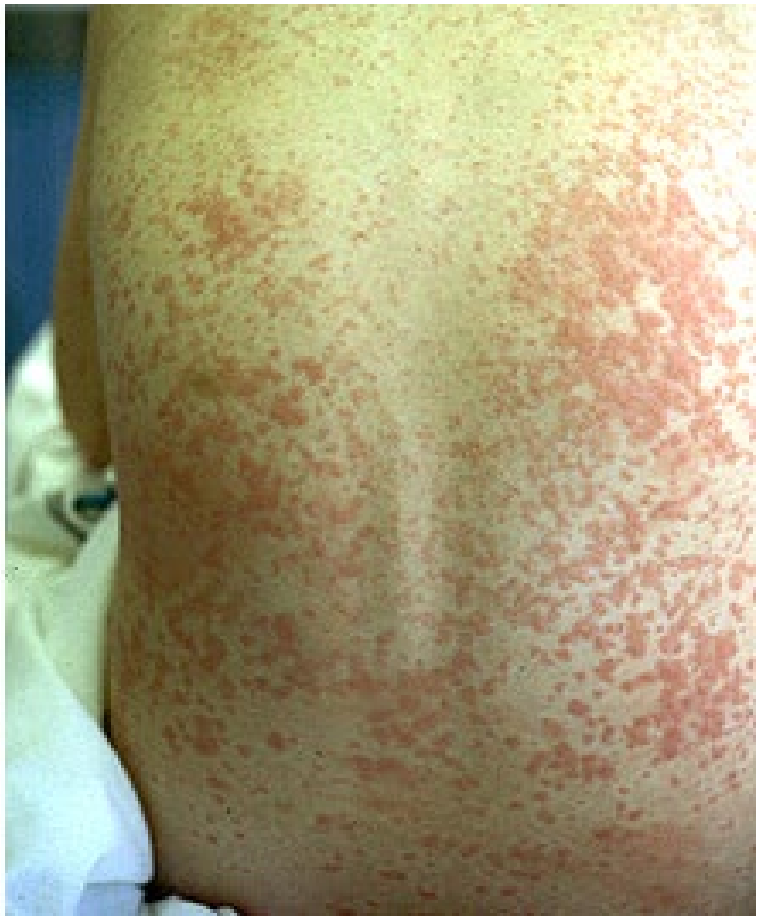
Dermatologic Toxicities

- Treatment related
  - Chemotherapy, targeted therapies, biologics, ICIs
    - Cytotoxic agents cause interruption in specific stages of the cell cycle, areas of rapid cellular proliferation & turnover more susceptible (skin, mucous membranes, hair follicles)
    - Cutaneous irAEs occur in 40% treated with anti-CTLA-4 or PD-1 monotherapy; 60% of combination of both classes
  - Radiation therapy
  - Hematopoietic Stem Cell Transplant (HSCT)
    - Graft versus host disease
- Clinical presentation
  - Rash/itching
  - Blisters, acneiform eruptions
  - Dryness, peeling, flaking, crusting
  - Hand-foot syndrome (palmar-plantar erythrodysesthesia)
  - Changes in pigmentation of skin
  - Photosensitivity
  - Nails: cracked/brittle/yellowing, swelling/tenderness of cuticles, paronychia
  - Hair: alopecia, change in pigment/ hair color
  - Burning, erythema, painful skin

Maculopapular eruption

Drugs	Clinical Presentation
Bortezomib, lenalidomide, cladribine, fludarabine, gemcitabine, pemetrexed, cytarabine. BCR–ABL TKI's: *imatinib, dasatinib* BRAF inhibitors: *vemurafenib* PI3K inhibitors: *dacomitinib, alpelisib, duvelisib* ADCs: *enfortumab vedotin* ICIs (most common cutaneous irAE) *Imatinib may be dose dependent *Pemetrexed: May be premedicated with dexamethasone 4mg BID x 3 days starting day before tx.	Eruption of small, erythematous macules or papules Involve the trunk, proximal extremities With or without pruritis, low-grade fever, and/or mild eosinophilia Eruption may occur 7-10 days after start of tx ICI: 3-6 wks after start of treatment, most cases involve the trunk, extensor aspect of extremities, pruritic

Maculopapular eruption



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Management

Dictated by severity, goals of care
Some may resolve over time despite continuation of tx

CTCAE:
Grade 1: Medium to high potency topical corticosteroid. Continue treatment.

Grade 2: High-potency topical corticosteroid. Consider systemic (oral) corticosteroids for rash unresponsive to topical tx alone. May require interruption of cancer tx.

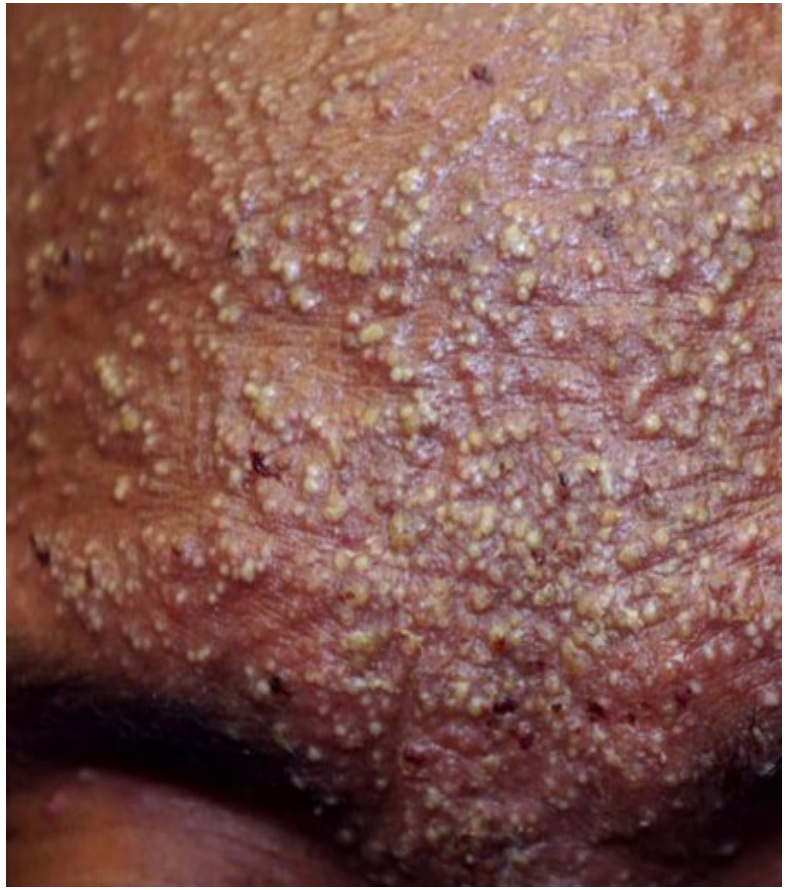
Grade 3: Interrupt cancer tx. Systemic corticosteroids (ex. prednisone 0.5-1 mg/kg/day) until improvement then taper over 2-4 wk.

No response: Add Inflixumab or tocilizumab

Acneiform Eruption

Drugs	Clinical presentation
EGFR-inhibitors- Occurs in up to 2/3 of patients -Monoclonal Ab*: cetuximab, panitumumab*, - Oral small molecules*: erdafitinib, gefitinib, afatinib, lapatinib, dacomitinib, osimertinib, neratinib* MEK-inhibitors *-trametinib, cobimetinib, binimetinib*	Diffuse, erythematous follicular papules, pustules May be dose dependent Begins within 1-2 weeks of tx onset Lesions occur on face, scalp, chest and back (not extremities)- frequent in sun exposed areas, sebaceous glands Pruritis (in up to 1/3) Severe in 10-20% Older, light pigmented skin Initial presentation as dysesthesias, edema, erythema. Later crusts form from purulent material, necrotic debris. Dry skin, scattered telangiectasias w/ erythema. Clinical course: Can wax & wane. May resolve/improve despite continuation of treatment. May be a "surrogate marker" for efficacy: Increased ORR w/ presence of AE. Not contraindication to continue. Combination tx with BRAF-inhibitor + MEK inhibitor: LESS skin toxicity

Acneiform Eruption



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Management

Prevention: Prophylactic oral abx + topical corticosteroids for 6 weeks

- Doxycycline, minocycline, cephalosporin
- Hydrocortisone 2.5% cream to face/chest

CTCAE:

Grade 1: Topical corticosteroids + topical antibiotics (clindamycin 1%)

Grade 2: Topical corticosteroids (low potency on face/back + flucinonide 0.05% cream to chest/back) plus oral antibiotics (tetracycline) for 4-6 wks. Consider alternative abx (cephalexin, cefadroxil, trimethoprim/ sulfamethoxazole) if already on tetracycline.

Grade ≥3 or intolerable Grade 2: Interrupt cancer tx, short course systemic steroids, oral doxycycline (or alternative) x 4 weeks.

- Assess for viral/bacterial superinfection, cx & treat accordingly

Refractory Grade ≥3: If no improvement in 2 weeks, low dose isotretinoin or acitretin

- Continue therapy for at least 2 months if resume cancer tx

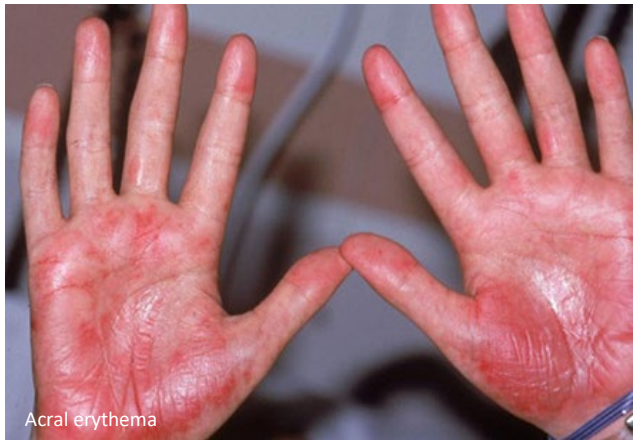
Hand Foot Syndrome (HFS)/ Hand Foot Skin Reaction (HFSR)

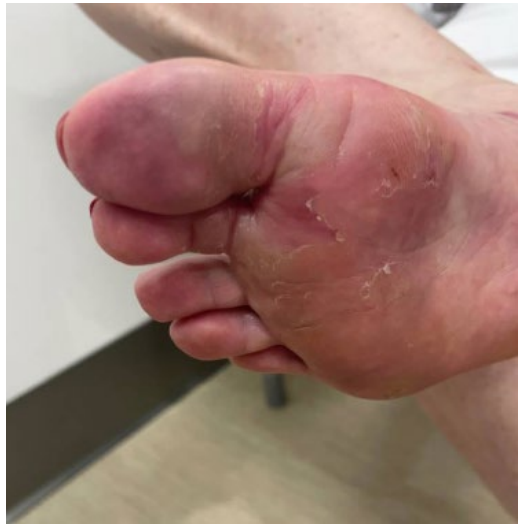
Drugs	Pathogenesis
Chemotherapy: *doxorubicin, pegylated liposomal doxorubicin, fluoropyrimidines (fluorouracil, capecitabine), cytarabine, docetaxel* VEGR/PDGFR inhibitors (TKIs): *cabozantanib, axitinib, lenvatanib, regorafenib, vandetanib, sorafenib, sunitinib, pazopanib* FGFR-inhibitors: *Pemigatinib, erdafitinib*	HFS: Also known as palmo-plantar erythrodysesthesia, toxic erythema of chemotherapy (TEC), acral erythema Not well understood- TEC may be direct toxic effect on eccrine glands (highest density on palms/soles) HFSR: TKIs- proposed that inhibition of both VEGF and PDGF receptors is necessary to cause, local tissue damage w/ insufficient repair

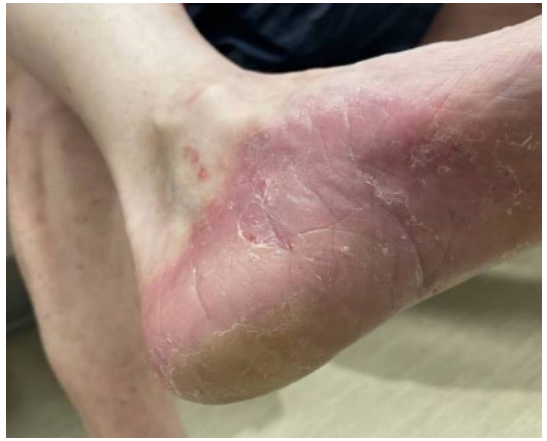
Hand Foot Syndrome (HFS)/ Hand Foot Skin Reaction (HFSR)

Clinical presentation	Grading
HFS: Onset: 1-3 weeks after chemotherapy, capecitabine- within 5-7 days. Manifests initially as tingling sensation → edema, tenderness, symmetric erythema → may progress to pallor, blistering, desquamation, & necrosis. Dose related: May resolve within 2-4 weeks after discontinuation of offending agent. **HFSR**: All grade incidence: 35% (high grade in 10%) *Highest risk in cabozantanib (all grade), regorafenib (high grade) in patients with thyroid cancer* Onset: Within 2-4 weeks of starting treatment Manifests as focal, hyperkeratotic, callus-like lesions on erythematous base, yellow plaques; occurring in areas of pressure or friction (fingertips, heels/ balls of feet, great toe). Can present as bullae or blisters. May be painful, burning Impact on QOL: affects gait, grasping objects	CTCAE Grade 1: Minimal skin changes or dermatitis (erythema, edema, or hyperkeratosis) without pain Grade 2: Skin changes (peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting iADLs. Grade 3: Severe skin changes (peeling, blisters, bleeding, edema, hyperkeratosis) with pain, limiting self-care ADLs

Hand Foot Syndrome (HFS)/ Hand Foot Skin Reaction (HFSR)







HFSR on TKI

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Management

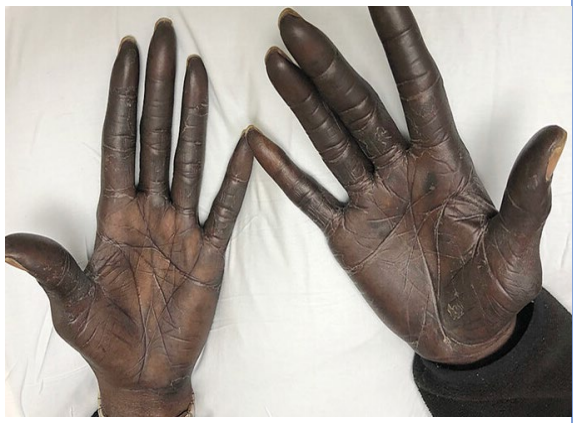
Skin bx usually not indicated.
Prevention is important!
3 C's (control *calluses*, *cushion*, *creams*)
Avoid hot water, tight fitting shoes

Topical keratolytic agents (urea based) to hands & feet (all grades)
Considerations (no consensus):
Hydrocolloid dressing containing ceramide
Topical corticosteroids (≥ grade 2)- reduce inflammation
Celecoxib
Topical diclofenac

*Drug interruption/dose modification depending on severity. Consider discontinuation of drug for Grade 3 that is not responding.

Pigmentation changes

Drugs	Clinical presentation
Chemotherapy: Hyperpigmentation **Diffuse**: *Fluorouracil, busulfan, pegylated liposomal doxorubicin, hydroxyurea, methotrexate* **Localized**: *cyclophosphamide, busulfan, fluorouracil, doxorubicin, daunorubicin, thiotepa, ifosfamide, docetaxel, capecitabine, cisplatin, bleomycin* **Patterned:** *(serpentine) fluorouracil, vincristine, vinorelbine, docetaxel, (linear) bleomycin; (reticular) paclitaxel, cytarabine, fluorouracil, idarubicin. Combination regimens.* **TKIs:** Reversible *hypo*pigmentation of skin/hair (sunitinib, pazopanib). Resolves with stopping therapy. **ICIs:** vitiligo-like depigmentation	Can affect skin, hair, nails, and oral mucosa <u>Localized</u>: Intrinsic features of the skin • Mucous membranes, skin creases • Flexural or intertriginous areas • Palms or soles, face Extrinsic factors • Trauma, pressure, sun exposure • Sites of adhesive on the skin

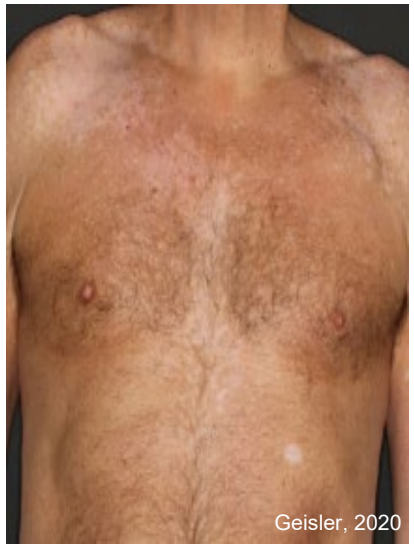


After d/c treatment

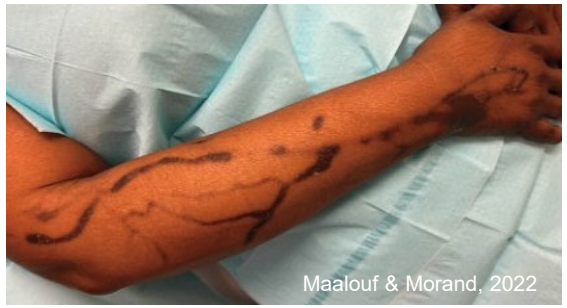
Schaefer & Ramnath, 2020

Pigmentation changes

Clinical presentation

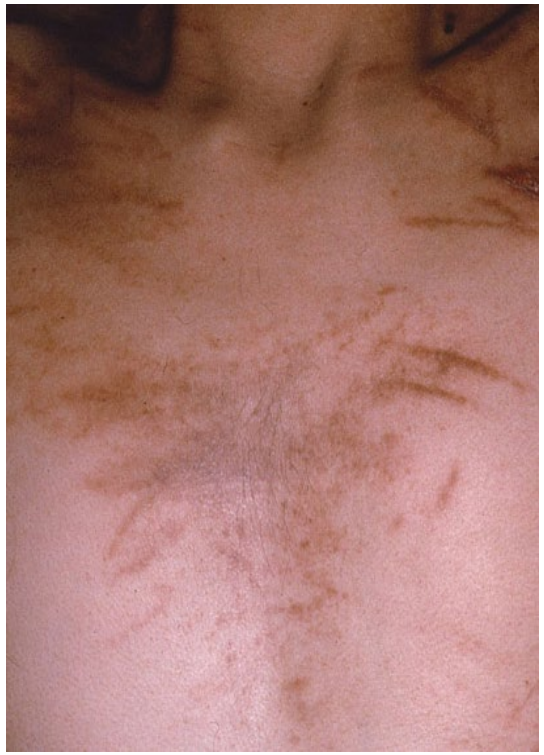

Geisler, 2020

Vitiligo-like depigmentation:
Incidence: Anti-PD1: 25%, Anti-CTLA4: 11%
Manifests as flecked macules, progress to large patches on sun-exposed area.
- In melanoma, correlation with favorable response to therapy


Maalouf & Morand, 2022

← Serpentine

Linear (flagellate) →



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Management

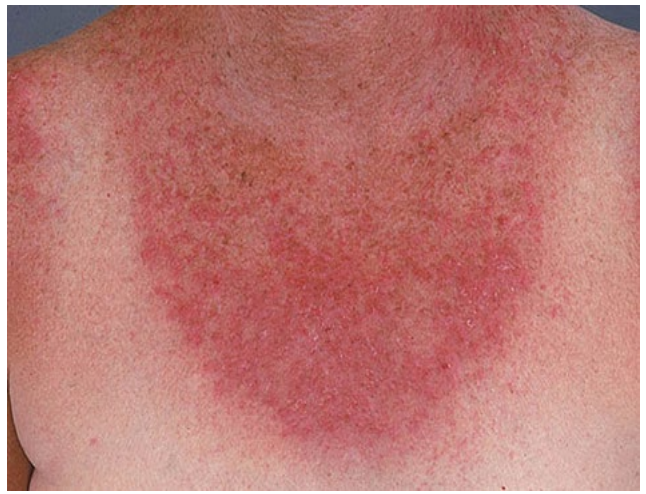
Most cases improve once treatment stopped. May take several weeks to months for resolution.

Nail hyperpigmentation may persist for longer

Vitiligo:
Photoprotection to avoid sunburn, no other tx
Does not resolve after cessation of therapy

Photosensitivity

- Pathogenesis: Concentration of drug within the skin + subsequent absorption of UV light → apoptosis of keratinocytes

Drugs	Clinical presentation	Management
Chemotherapy: methotrexate, fluorouracil, dacarbazine, vinblastine Oral targeted therapies: • EGFR inhibitors • BCR–ABL TKI's • MET inhibitors	• Resembles an exaggerated sunburn, with erythema, edema, pain, and tenderness in sun-exposed areas. • Blistering in severe cases. • Severe erythema, can occur within minutes to hours after exposure. • May have post-inflammatory hyperpigmentation.	• D/C offending agent. • Avoid direct sunlight exposure, use of sunscreen  www.visualdx.com. Retrieved from: https://www.uptodate.com/contents/cutaneous-adverse-effects-of-conventional-chemotherapy-agents?csi=ab13d3d3-5737-4d85-862a-aa697647bcbd&source=contentShare

Radiation recall dermatitis

- Uncommon, acute inflammatory skin reaction- occurs in area of previously irradiated skin after administration of promoting agent

Drugs	Clinical presentation	Management
Most common with chemotherapy • Arsenic trioxide, bleomycin, cytarabine • Capecitabine, cyclophosphamide • Dactinomycin, daunorubicin, docetaxel • doxorubicin (Free and liposomal) • Etoposide, fluorouracil, gemcitabine • Hydroxyurea, idarubicin, lomustine • Melphalan, methotrexate, paclitaxel • Pemetrexed, tamoxifen, vinblastine	Erythema, maculopapular eruptions, vesicular development, and desquamation within previously irradiated site. Symptoms range from mild rash to severe necrosis	Topical Ointments Steroid based ointments Stopping precipitating agent

Hair Changes: Alopecia

- Pathogenesis: Cytotoxic chemotherapy affects rapidly dividing cells, including the dividing hair matrix cells.

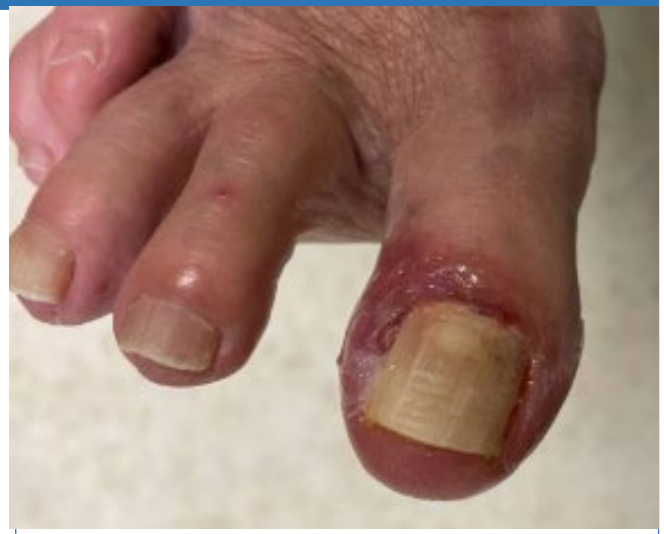
Drugs	Clinical presentation
Chemotherapy: Bleomycin, cyclophosphamide, cytarabine, dactinomycin, daunorubicin, docetaxel, doxorubicin, etoposide, idarubicin, 5-fluorouracil, ifosfamide, interferon, irinotecan, methotrexate, mitoxantrone, paclitaxel, vincristine Mild/partial alopecia: Antibody drug conjugates Targeted biologic agents: BRAF, BCR-ABL, CDK Tamoxifen Aromatase inhibitors	• Onset within 2-3 weeks of start of chemotherapy (dependent upon regimen, dose, schedule) • Temporary, reversible hair loss. May be minimal, moderate, or severe. Infrequent: permanent alopecia • Regrowth of hair around 3-5 months (complete regrowth up to 1-2 years after discontinuation • Changes in hair color, hair texture, and hair type • Some may experience scalp itching and discomfort within 1-2 days prior to alopecia and during period of hair loss

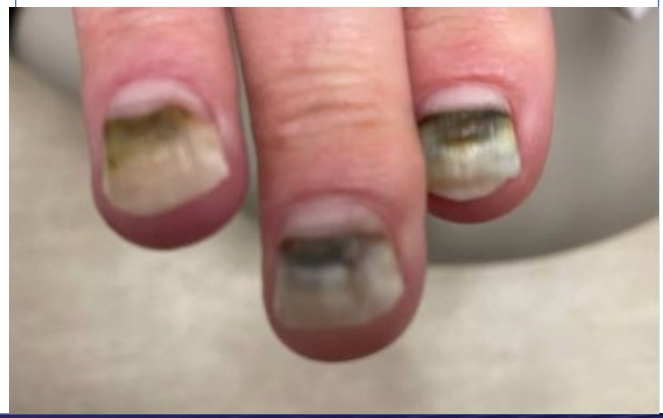
Hair Changes- alopecia

Prevention	Management	Other Changes
Scalp hypothermia (scalp cooling) - Causes local vasoconstriction of blood vessels→ reduced delivery to scalp, decreased follicle cell metabolic rate, reduced cellular drug uptake - Two automated hypothermia systems approved by FDA - Used in particular regimens (solid tumors)	Scalp care- cleansing, sun protection Topical and oral minoxidil Topical bimatoprost 0.03% for eyelash loss	**Pigment Changes:** Chemotherapy: Cisplatin, cyclophosphamide, methotrexate, and combination regimens Monoclonal antibodies/ small molecule inhibitors targeting: EGFR, BRAF, BTK, BCR/ABL, KIT, VEGFR/PDGFR ICI: Rare alopecia (1-2%). Patchy hypopigmentation.

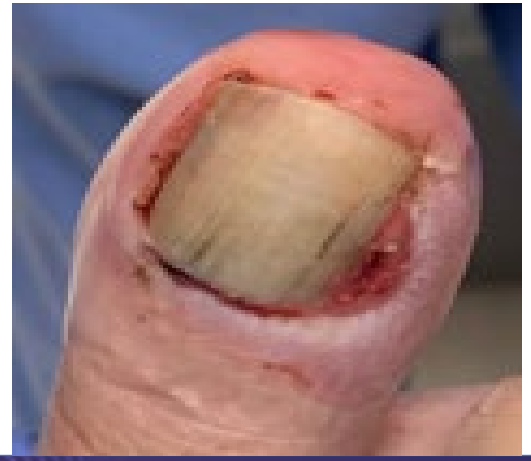
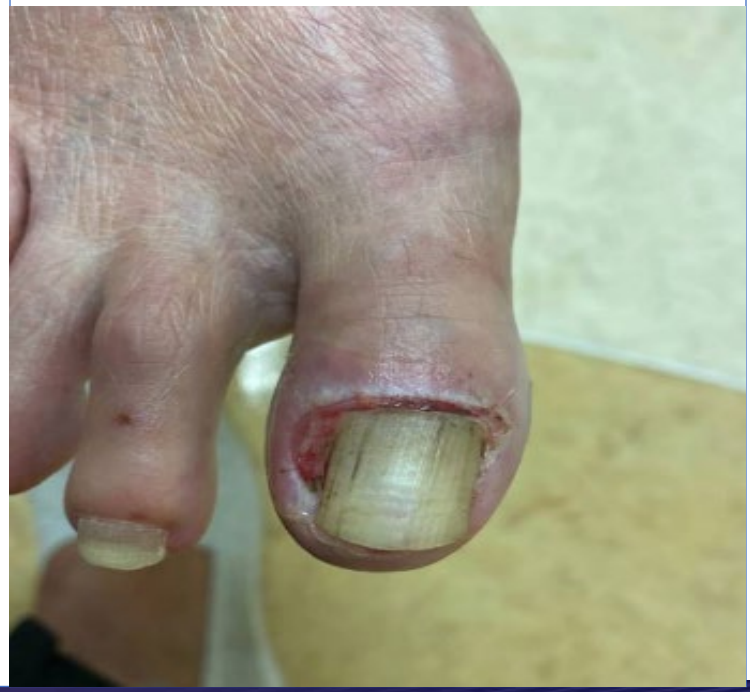
Nail Toxicities

Drugs	Clinical presentation
Chemotherapy: • Melanonychia: *fluorouracil, alkylating agents, taxanes, antimetabolites, anthracyclines, and other antitumor antibiotics* • Onycholysis: *Paclitaxel, docetaxel, gemcitabine, capecitabine, cyclophosphamide, doxorubicin, etoposide, fluorouracil, hydroxyurea* • Inflammatory changes: *Capecitabine, docetaxel, paclitaxel* EGFR inhibitors: paronychia BRAF inhibitors FGFR inhibitors: paronychia, onychomadesis BTK inhibitors: splitting/ridging of nails	**Pigment Changes**: Usually occur at base of nail, can cause transverse ridges ("Beau lines") **Oncholysis:** Inflammation of the nail bed → "lifting"/detachment of nail plate from the nail bed **Melanonychia:** Diffuse hyperpigmentation or banding of the nail plate or bed **Paronychia**: Inflammation of the nail fold. May present with pyogenic granulomas (bacterial or fungal). Case: Patients on FGFR-inhibitor (erdafitinib)





Nail Toxicities

Prevention	Management	
• Trimming nails, avoiding artificial and acrylic nails • Moisturize hands/ nails • Avoid irritants, chemicals, detergents, etc that may damage nails. • Gloves	• Antiseptic washes (diluted vinegar, peroxide) • Topical and/or oral antibiotics • Topical corticosteroids • Topical antifungals 	Case study: mUC, on erdafitinib; 3 weeks following tx hold, antibiotics, & diluted vinegar soaks. 

Serious skin toxicity

Drugs	Clinical presentation	Management
Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) SJS: affecting BSA <10% TEN: affecting BSA >30% • Several chemotherapy agents • Lenolidomide • Imatinib	Extensive necrosis and detachments of the epidermis due to massive keratinocyte a proptosis. • Onset of fever and influenza-like symptoms→ 1-3 days irruption of ill-defined, coalescing, erythematous macules with atypical target lesions → formation of vesicles and bullae → skin sloughing. Mucosal involvement >90%.	• Requires inpatient management, often in a burn unit, because of extensive skin detachment • Risk for hyponatremic dehydration and sepsis. • Acute complications may include massive loss of fluids, electrolyte imbalance, hypovolemic shock and multi organ dysfunction. • Must permanently discontinue causative agent.

Serious skin toxicity

Drugs	Clinical presentation	Management
Drug reaction with eosinophilia and systemic symptoms (DRESS) • Chlorambucil • Lenalidomide	Hypersensitivity reaction presents with skin eruption, hematologic abnormalities (eosinophilia, atypical lymphocytosis), lymphadenopathy, and/or internal organ involvement (liver, kidney, lung). • Onset is 2-6 weeks after initiation of causative agent. Starts as a morbilliform eruption that progresses rapidly to a diffuse, confluent, and infiltrated erythema. • Liver involved in 60-80% of patients	Prompt withdrawal of the causative agent is the mainstay of treatment for DRESS. Supportive Care: Fluid, electrolyte, nutritional support Consider topical or oral steroids– depending on symptoms/severity, degree of organ involvement

ICI cutaneous AEs

Lichen planus eruption

Incidence: Up to 25% of patients w/ cirAEs

Presentation:
Flat, violaceous papules in localized or generalized distribution, often associated with pruritis.

Management:
Grade 1: Medium to high potency topical steroids, emollients. Continue ICI.

Grade 2: High potency topical steroids. If no response, add systemic steroids (prednisone 0.5-1 mg/kg/day), phototherapy. Continue ICI.

Grade 3: Interrupt ICI. Systemic steroids, taper over 2-4 weeks. Second line therapy: acitretin (10-25 mg daily, methotrexate).

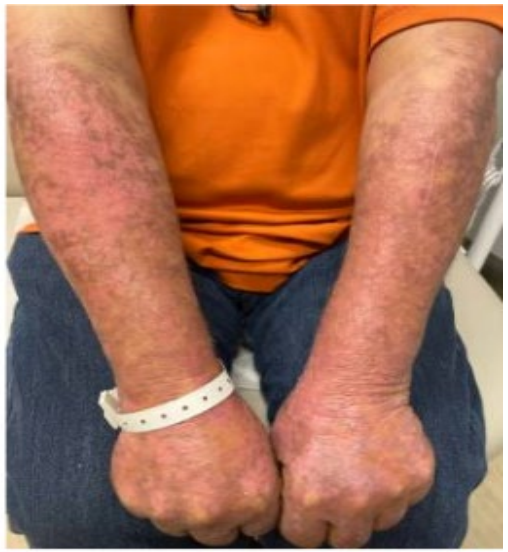
Case Study

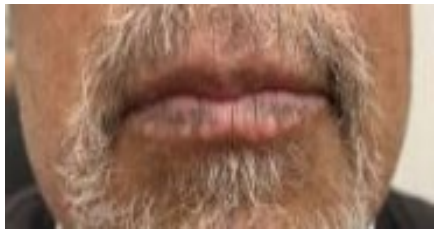
57 yo male with mCRPC, on clinical trial with ICI (cetrelimab) + niraparib. Dermatologist felt to be related to ICI, exacerbated by sun exposure.

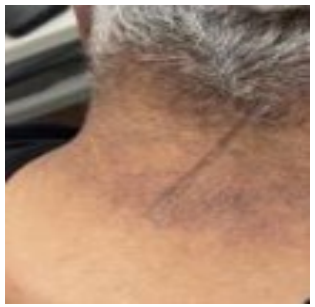
Managed with medium-high potency topical steroids to affected areas, tacrolimus ointment to lip; advised strict sun protection.

Clinic notes: Violaceous patches in photodistribution with overlying erythematous depigmented patches

4/2024







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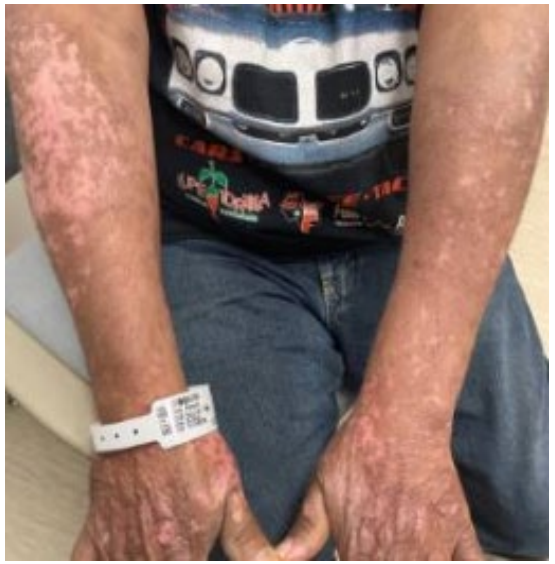


ICI cutaneous AEs

Bullous pemphigoid

Usually appears 13-16 weeks after start of tx, but can present after d/c

Clinical presentation:

- Prodromal pruritis, then development of tense blisters filled with serous or hemorrhagic fluid; urticarial plaques or papules

Work-up:

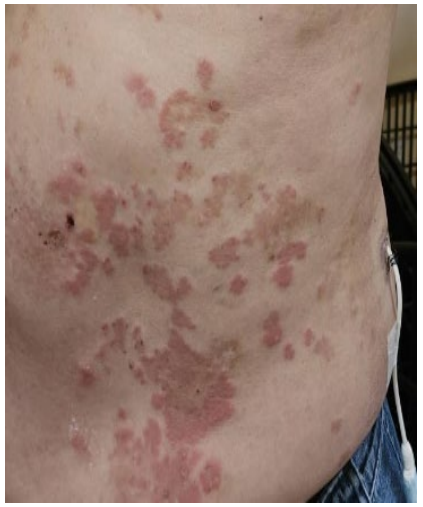
- Perilesional skin bx for histopathogical dx and direct immunofluorescence (DIF)
- Serologic testing by ELISA for circulating Ab against BP antigen
- *Pathology*: Dermal infiltrates with lymphocytes, eosinoprils, neutrophils. DIF shows deposits of IgG and complement component 3 (C3) at the dermal-epidermal junction.

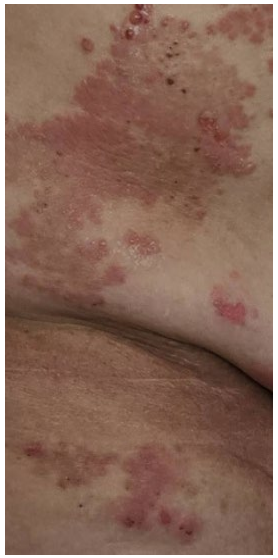
Case study

68 yo w/ mCRPC, MSI-H; hx of pembrolizumab tx in 2021, d/c after 5 mo due to bullous dermatitis, resolved with steroids/stopping ICI. Presented to our center after progression on chemotherapy, discussed with dermatology and rechallenged in 8/2022. Did well until dose increase from 200 mg to 400 mg in 4/2023 and rash recurred in 7/2023.

Clinic Notes: Scattered urticarial papules and plaques with overlying tense bullae and erosions on trunk and extremities. Admixed hyperpigmented macules and patches at sites of previous disease.

8/1/2023





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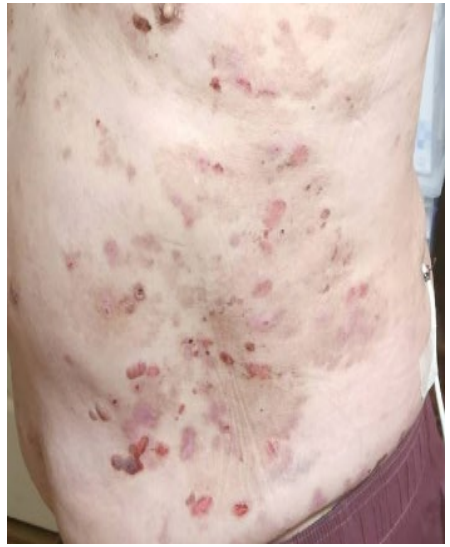
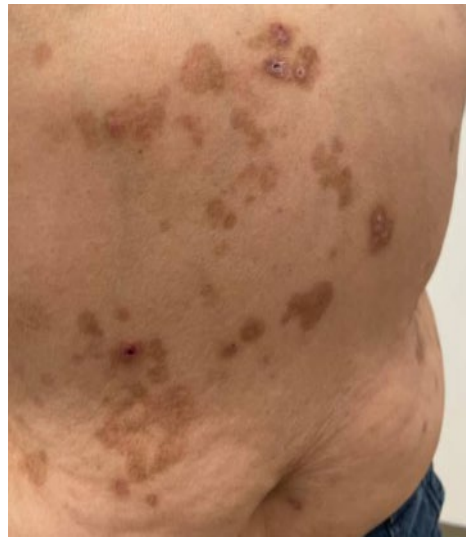


2/2024



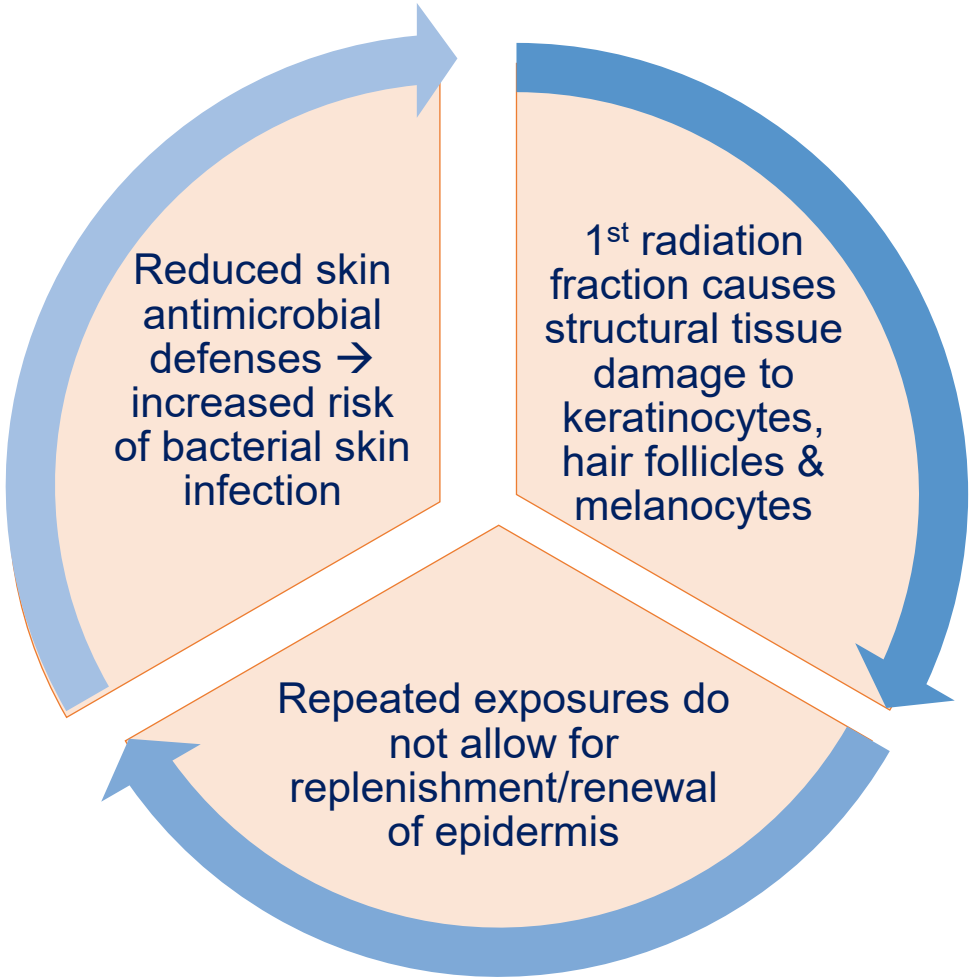
Management: High potency topical corticosteroids, systemic corticosteroids (prednisone 1 mg/kg/day), doxycycline

Refractory to steroids: immunomodulators (dupilumab, IVIG, rituximab)

Radiation dermatitis

Pathogenesis

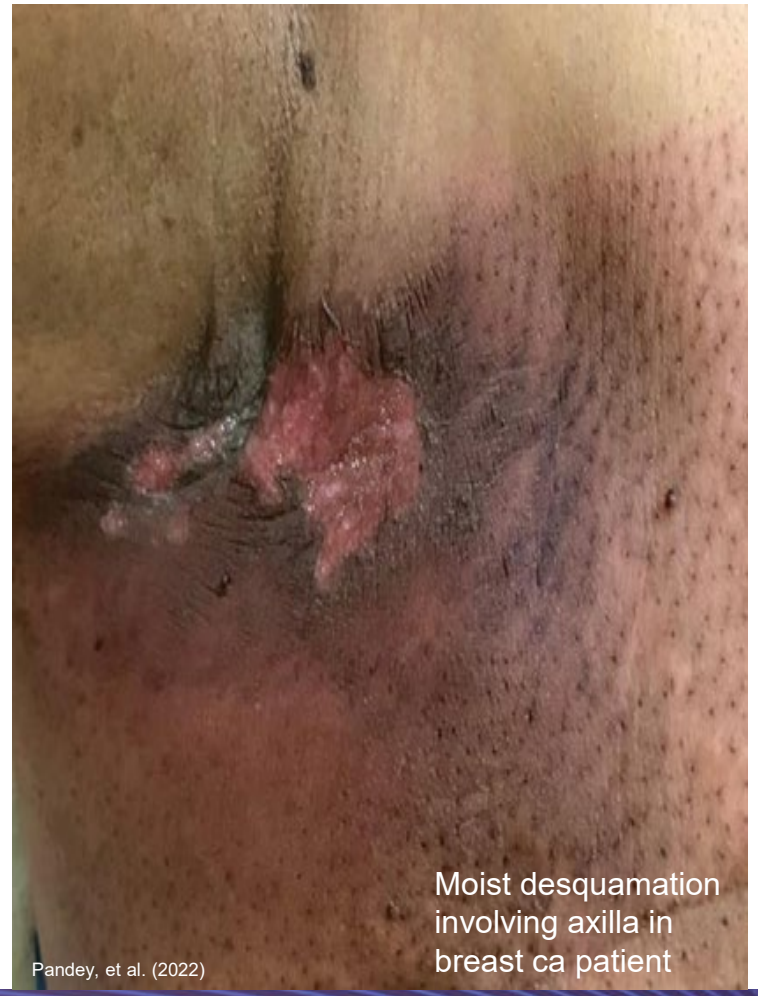
Basal keratinocytes, stem cells in hair follicles and melanocytes are highly radiosensitive.



Radiation dermatitis

Incidence	Clinical presentation
Over 90% of patients receiving RT Higher incidence in cancers of breast, lung, skin, head/neck, sarcoma due to higher radiation dose. Approximately 20-45% may experience higher grade dermatitis. * RT + EGFR inhibitor may cause severe radiodermatitis	Onset: within 2 weeks of starting RT, can progress up to 10-14 days after completion RTOG/ CTCAE: **Grade 1:** Faint erythema with dry desquamation +/- pruritis, hair loss, decreased sweating **Grade 2:** Moderate-brisk erythema, patchy moist desquamation in the skin folds/creases– epidermal necrosis, fibrinous exudates, can be painful **Grade 3:** Confluent, moist desquamation in areas other than skin folds +/- bleeding with trauma **Grade 4:** Skin necrosis or ulceration of full thickness dermis, spontaneous bleeding from site

Radiation dermatitis



Moist desquamation involving axilla in breast ca patient

Pandey, et al. (2022)

Management

Goals: decrease inflammation/risk of infection, improve comfort/healing

Grade 1: Hydrophyllic moisturizers, medium potency topical steroids to control itching, irritation (continue for 2 wks post RT

Grade 2-3: Prevent secondary infection, if occurs→ topical and/or systemic antibiotics
Daily dressing change (Nonadherent,soft, absorbant, silicone, foam bandage) with/without topical agent. Grade 3 may require interruption of RT.

Grade 4: Specific to patient. May require discontinuation of RT and multidisciplinary approach, treatment may include surgical debridement, full-thickness skin graft or myocutaneous pedicle flaps. Abx as indicated

Extravasation

Drugs	Clinical presentation	Management
Chemotherapy: Vesicant agents • Cisplatin • Dactinomycin • Daunorubicin • Doxorubicin • A previously • Idarubicin • Mechlorethamine • Melphalan • Mitomycin • Paclitaxel • Vinblastine • Vincristine • Vindesine • Vinorelbine	• Infrequent • Inadvertent leakage of drug or solution from a vein into surrounding healthy tissues causing skin and tissue damage • May range from mild to severe tissue destruction and may include erythema and ulceration • May lead to full-thickness skin necrosis with damage to underlying tendons, muscles, neurovascular structures	• Stop chemotherapy infusion • Disconnect IV tubing and aspirate residual chemotherapy • Apply **ice** (if not Vinca alkaloid) for 15-20 minutes at least 4 times per day and elevate affected extremity • Apply **heat** if the causative agent is a vinca alkaloid. • Consider referral to plastic surgeon

Pulmonary Toxicities

- Cancer related
  - Malignant pleural effusion

- Treatment related
  - Interstitial Lung Disease/pneumonitis
  - Malignant pleural effusion
  - Organizing pneumonia
  - Diffuse alveolar damage
  - Radiation recall pneumonitis
  - Eosinophillic pneumonia
  - Diffuse alveolar hemorrhage
  - Non-thromboembolic pulmonary HTN
  - Thromboembolic disease
  - Bronchospasm

Malignant Pleural Effusion

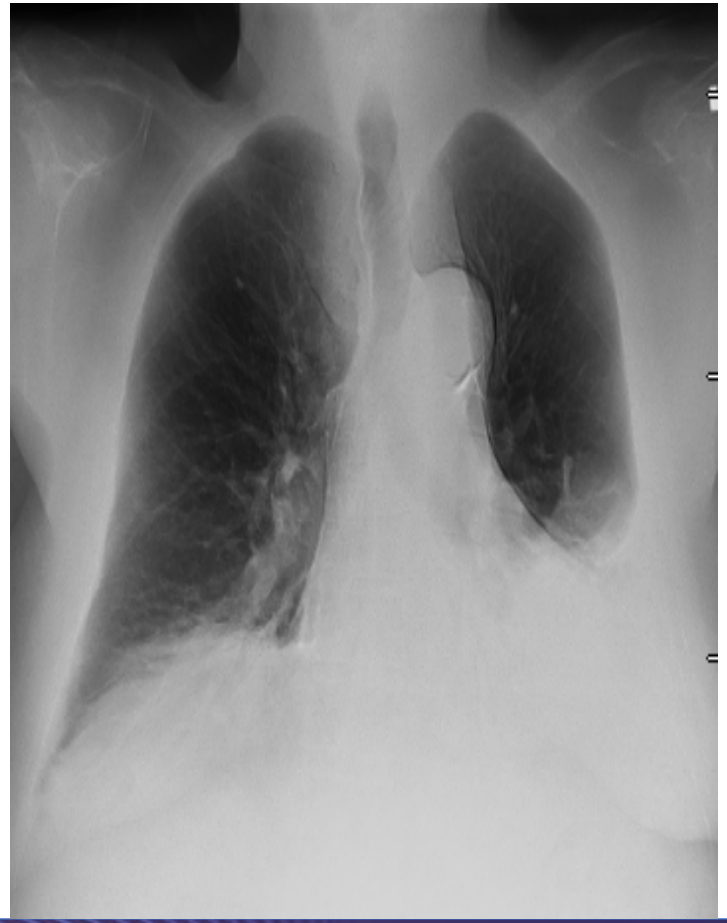
Etiology	Pathogenesis
Cancer: 15% of patients develop • Most common in lung, breast cancers (50-65%) • Mesothelioma (affects 90%), lymphomas, metastatic cancer to the pleura BCR-ABL TKIs • *Dasatinib*: Incidence 10-35%, higher risk with twice daily dosing (70 mg), change to daily dose (100 mg) PDGFR-inhibitors MET inhibitors * Poor prognostic indicator (in most cases) *	Invasion of malignant cells into pleural tissue, confirmation by pleural biopsy or cytology of pleural fluid Paramalignant effusion: indirect tumor effects on pleural space (bronchial obstruction, mediastinal lymph node infiltration, thromboembolism, SVC syndrome

Malignant Pleural Effusion

Clinical presentation

Dependent upon extent of involvement

- Most common: Dyspnea/SOB
- Cough
- Chest pain
- Orthopnea
- May asymptomatic



Management

Palliative– dependent upon symptoms, size of effusion

- Asymptomatic may resolve with cancer therapy

Therapeutic thoracentesis

- Volume up to 1.5 L
- ½ of MPE's recur, 2/3 of these within one month

Recurring effusions

- Repeat thoracentesis
- Indwelling pleural catheter (IPC)
- Pleurodesis with sclerosing agent (talc)

Complications

- Non-expandable lung: from tumor, loculations, septations, or scar tissue
- May require additional procedures

Interstitial Lung Disease (pneumonitis)

Drugs		Incidence
<u>Chemotherapy</u> • Bortezomib, thalidomide, lenalidomide • Anthracyclines (and like agents) • Fludarabine, gemcitabine, ifosfamide • Irinotecan, oxaliplatin, vinca alkaloids <u>Targeted therapies</u> • EGFR inhibitors • ALK inhibitors • BRAF inhibitors • PI 3K inhibitors • mTOR inhibitors • Sotarasib • Trametinib • Trastuzumab • FLT-3 inhibitors • MET inhibitors	<u>ADCs</u> • Enfortumab vedotin • Tisotumab vedotin • Fam trastuzumab deruxitecan • Ado-trastuzumab emtansine Monoclonal Ab: • Rituximab	Immune Checkpoint inhibitors • Overall 5% • Anti PD-1 & PD-L1 monotherapy: 3% • Combined anti CTLA-4 + anti-PD-1 or anti PD-L1: 10%

Interstitial Lung Disease (pneumonitis)

Pathogenesis	
• Direct injury to pneumocytes or the alveolar capillary endothelium→ **release of cytokines** and recruitment of **inflammatory cells** • Systemic release of cytokines→ **endothelial dysfunction**, **capillary leak syndrome, noncardiogenic pulmonary edema** (gemcitabine) • **Oxidative injury** from free oxygen radicals (bleomycin) • Unintended **dysregulation** of the immune system and **T-cell activation** by immune checkpoint blockade	• Cell-mediated lung injury due to **activation of lymphocytes** and **alveolar macrophages** • **Impairment** of alveolar repair mechanisms (EGFR inhibitors) • Subclinical parenchymal **radiation-induced injury** that becomes apparent with another pulmonary insult (cytotoxic chemotherapy)

Interstitial Lung Disease (pneumonitis)

Clinical presentation

Onset:
Typically within weeks to few months after start of therapy
ICI: Median 2.8 months
Delayed fibrotic changes: Bleomycin

Non-specific

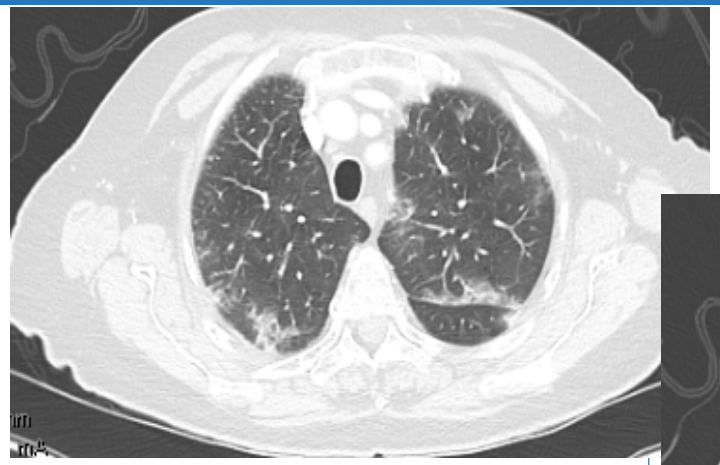
- Cough
- Dyspnea
- Low-grade fever
- Hypoxemia
- May be asymptomatic

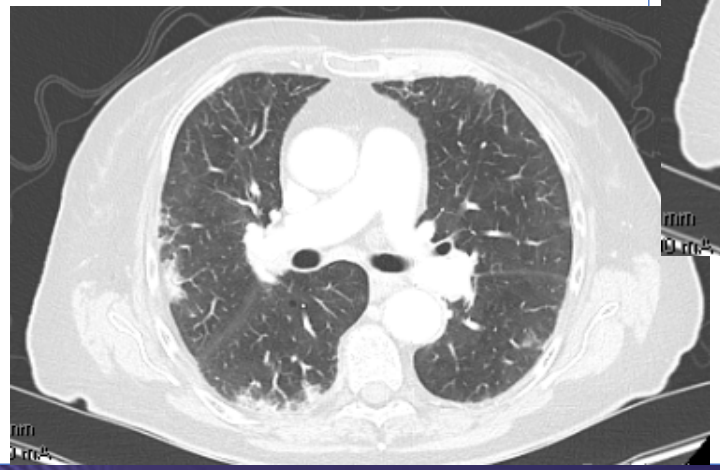
RARE: chills, sputum production

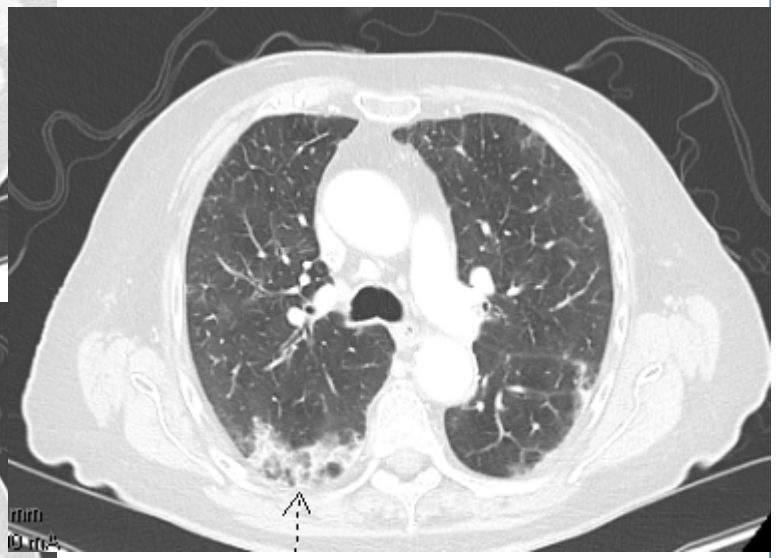
ICI: May present with another irAE (>50%)

Exam:
Auscultate bibasilar crackles, often is normal
Wheezing suggests hypersensitivity reaction, bronchoconstriction

Evaluation







CT: *ground glass opacities, consolidation, interlobular septal thickening, centrilobular nodules*

Interstitial Lung Disease (pneumonitis)

Evaluation/Diagnosis		Management
Pulmonary Function Tests (PFTs) • Decrease in DLCO • Advanced cases: Restrictive changes- decreased TLC, reduced FVC Imaging • Bleomycin: Findings c/w early pulmonary fibrosis- bibasilar subpleural reticular and ground glass opacification with volume loss, blunting costophrenic angles • Radiation recall: Opacities in same distribution as prior radiation • Direct involvement by tumor 6 Minute Walk Test • Documents degree of desaturation with exertion, need for O2.	Cardiac workup/Differential: • Heart failure • Pulmonary hypertension • Pulmonary Veno-Occlusive disease • Obtain ECG, Echo, BNP/N-Terminal proBNP Routine testing • CBC, Coagulation panel, blood cx, sputum cx, viral serology Bronchoscopy/BAL • Exclude other causes- infection, diffuse aleveolar hemmorhage, lymphangitic spread * Consider ER evaluation*	Grade 1/asymptomatic: Withhold drug for 2-4 weeks with close follow up Grade >2: Stop offending agent **Steroids**: Dependent upon severity and escalation of worsening side effects • Severe: Oral prednisone 40-60 mg • Intravenous steroids for impending respiratory failure • Taper: 1-2 months (dependent on response) **Supportive Care** • Oxygen (avoid high concentrations in bleomycin induced injury) • Bronchodilators if indicated

Other clinical syndromes

Syndrome	Clinical presentation	Associated agents
Acute bronchoconstriction	Airflow limitation (wheezing, prolonged expiratory phase, reduced FEV1)	Carboplatin, cyclophosphamide, etoposide, paclitaxel, rituximab, vinorelbine
Infusion reaction	Acute onset (ex. angioedema, flushing, urticaria, bronchoconstriction, dyspnea, hypoxemia, back pain, nausea) during or shortly after infusion	Platinum drugs, taxanes, rituximab, L-asparaginase, carfilzomib, cytarabine, etoposide
Alveolar hemorrhage	Dyspnea, sometimes hemoptysis, diffuse radiographic opacities, hypoxemia, BAL + hemorrhage	All-trans retinoic acid, bevacizumab, crizotinib, gefitinib, docetaxel, erlotinib, etoposide, fludarabine, gemcitabine, irinotecan, lenalidomide, sorafenib, Sunitinib
Eosinophilic pneumonia	Dyspnea, diffuse pulmonary opacities, hypoxemia, BAL fluid >20% eosinophils	Bleomycin, lenalidomide, fludarabine, gemcitabine
Hypersensitivity pneumonitis	Dyspnea and radiographic opacities developing within hours to days of treatment; may have pulmonary eosinophilia	Bleomycin, methotrexate, cytarabine, dactinomycin
Radiation recall	Radiographic opacities and areas of prior radiation and response to treatment with a cytotoxic agent, cough, dyspnea	Carmustine, doxorubicin, etoposide, gefitinib, gemcitabine, paclitaxel, trastuzumab
Noncardiogenic pulmonary edema	Pulmonary edema without evidence of heart failure or increase in left atrial pressure	Mitomycin, cytarabine, gemcitabine, interleukin-2
Capillary leak syndrome	Noncardiogenic pulmonary edema associated with diffuse peripheral edema and sometimes intravascular hypovolemia	Docetaxel, interleukin-2
ARDS	Noncardiogenic pulmonary edema plus evidence of acute inflammation (fever, elevated neutrophils in BAL fluid)	Dactinomycin, bleomycin, cytarabine, gemcitabine, mitomycin
Pulmonary veno-occlusive disease	Form of pulmonary HTN with capillary occlusion; CT: Diffuse or mosaic groundglass opacities, septal lines, pulmonary artery enlargement and mediastinal adenopathy	Bleomycin, carmustine, cisplatin, cyclophosphamide, gemcitabine, mitomycin

Maldonado, et al. 2023

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Questions?

Thank you!

mkholloway@mdanderson.org