Cutaneous Manifestations of Chemotherapeutic Agents

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Objectives

- Clearly define the most common reactions and toxicities of chemotheraputic agents
- Provide practical guidance for how to identify and manage these reactions
- Help keep patients on the medications that they need

Our #1 goal is always to keep patients on their cancer medicines!

Three Main Categories of Anti-Cancer Meds

Traditional Chemotherapy

- Alkylating agents: Busulfan, Cyclophosphamide, Etoposide, Dacarbazine...
- Antimetabolites: MTX, Capecitabine, Gemcitabine, Cytarabine...
- Topoisomerase interacting agents: Doxorubicin, Daunorubicin, Irinotecan...
- Anti-microtubule agents: Paclitaxel, Docetaxel, Vincristine...

Targeted Therapies

- EGFR inhibitors: Erlotinib, Gefitinib, Cetuximab...
- cKIT/PDGFR/BCR-ABL inh: Imatinib, Dasatinib, Nilotinib...
- Anti-angiogenic multikinase inh: Sorafenib, Sunitinib, Pazopanib, Regorafenib...
- mTOR inh: Everolimus, Temsirolimus
- BRAF inh: Vemurafenib, Dabrafenib
- MEK inh: Trametinib

Immunotherapy

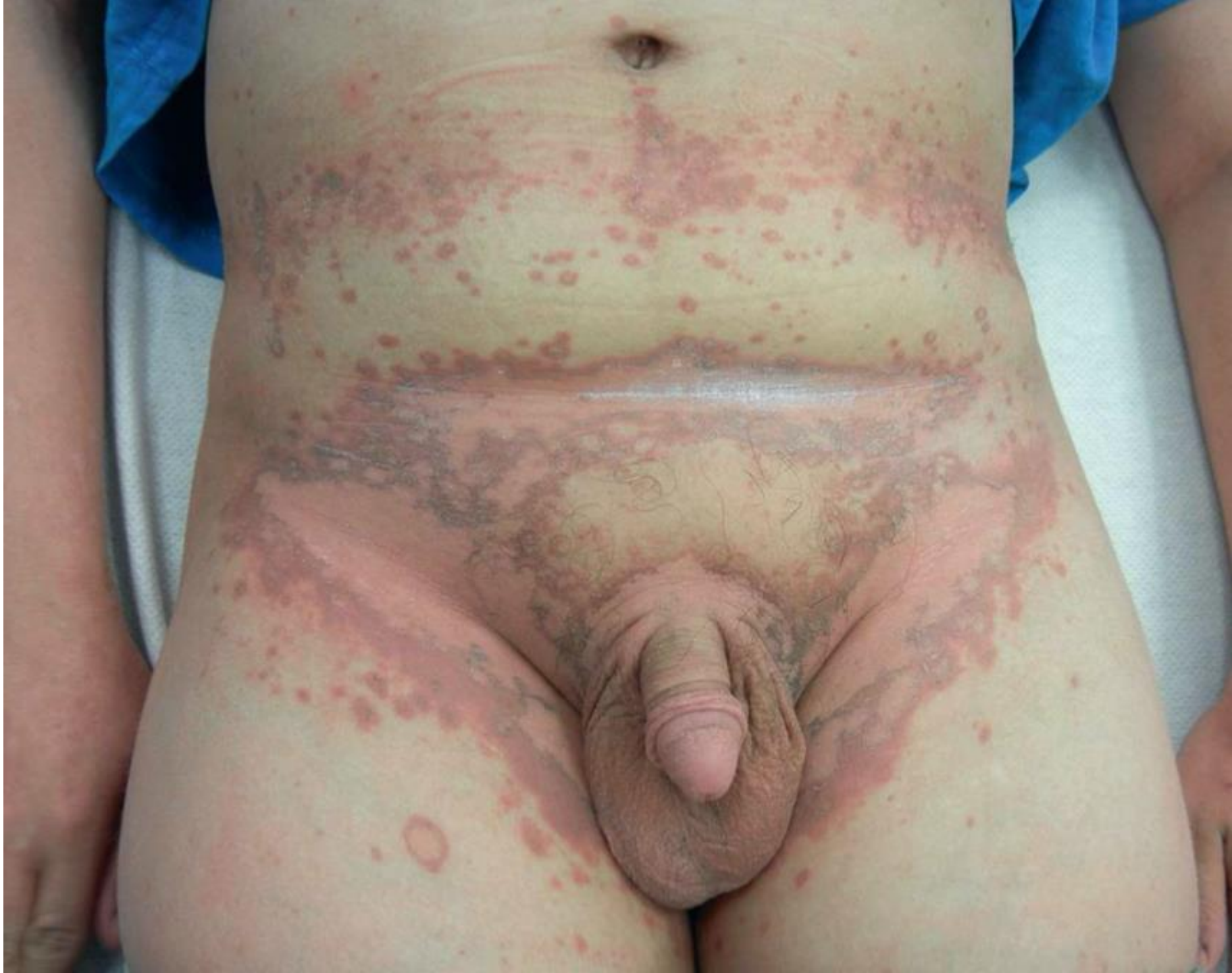
- Anti-CTLA4: Ipilimumab
- Anti-PD1: Nivolumab, Pembrolizumab

Conventional Chemotherapy

- **Toxic erythema of chemotherapy:**
  - Symmetric erythematous patches that can develop edema, erosions, desquamation and/or purpura (especially if low plts)
  - Can favor acral sites (**hand/foot syndrome**, Ara-C ears, scrotum), intertriginous zones or the elbows and knees

- Treat with topical steroids and cooling of hands/feet or other affected sites during infusion
  - the reaction is enhanced by heat/ vasodilatation →more drug delivered to the skin through the eccrine glands

Toxic Erythema of Chemotherapy



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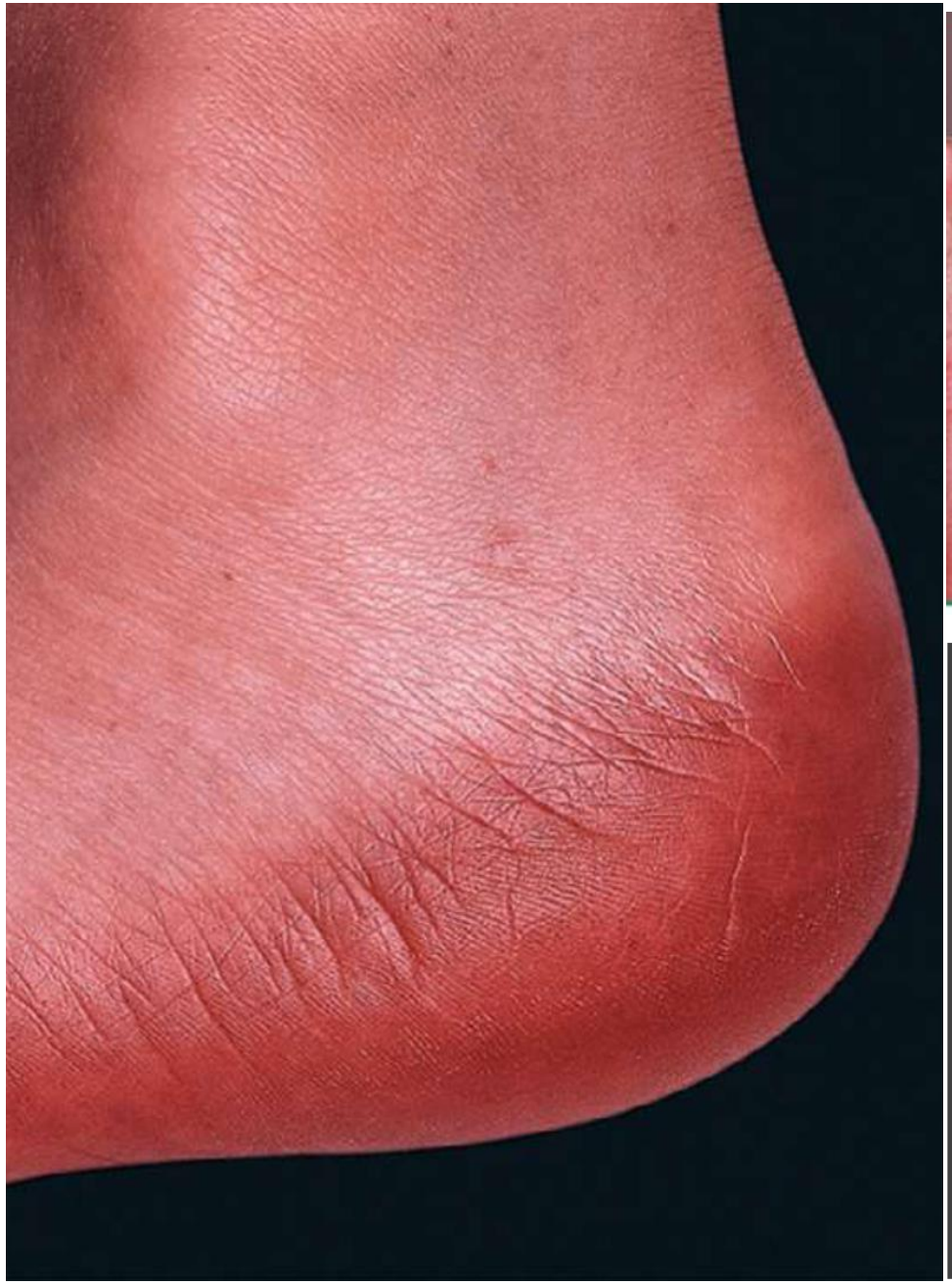
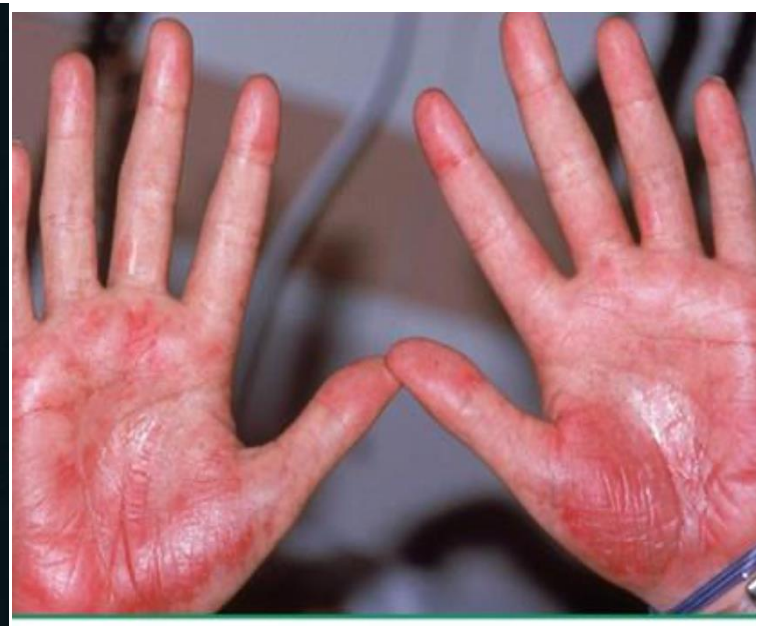
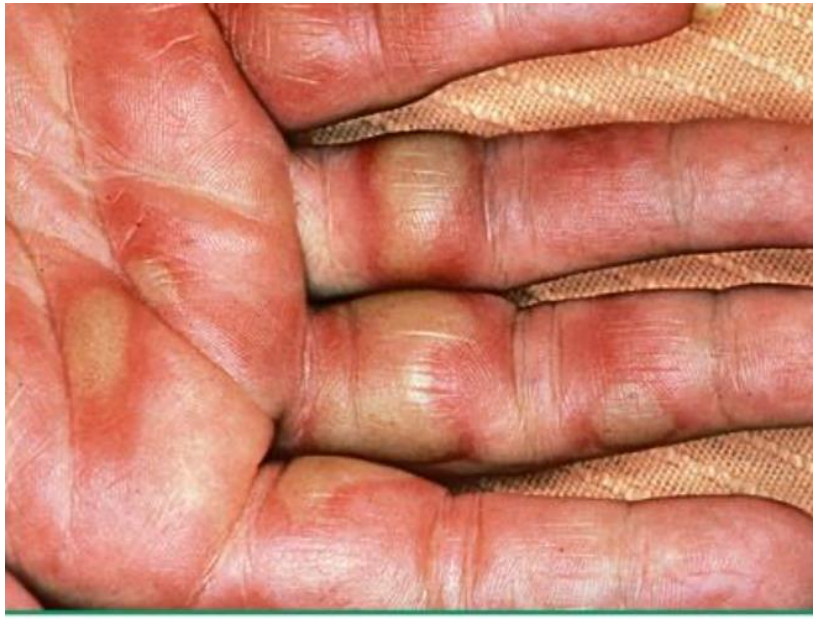


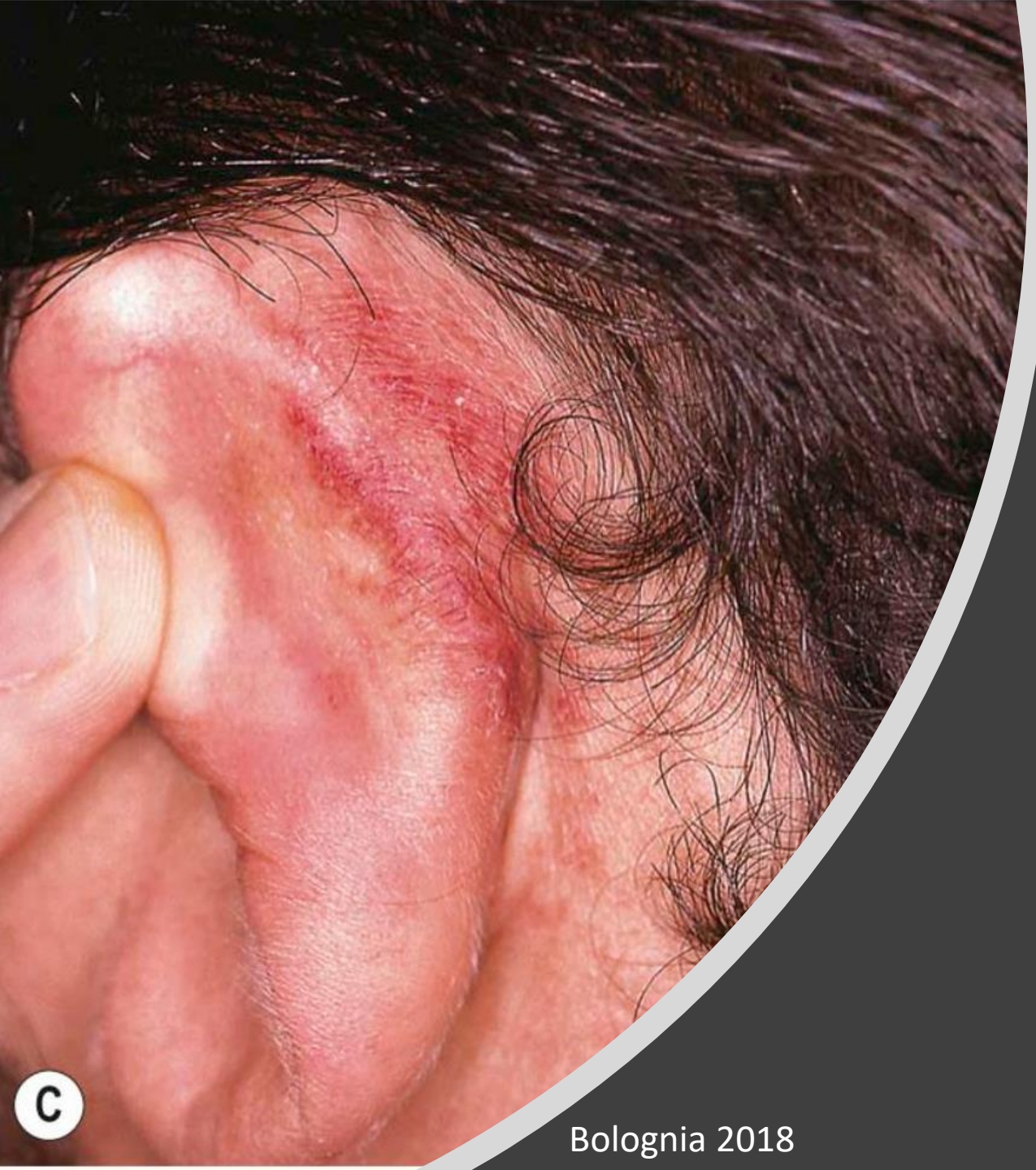




Conventional chemo: Hand-Foot Syndrome

(acral erythema, palmo-plantar erythrodysesthesia)

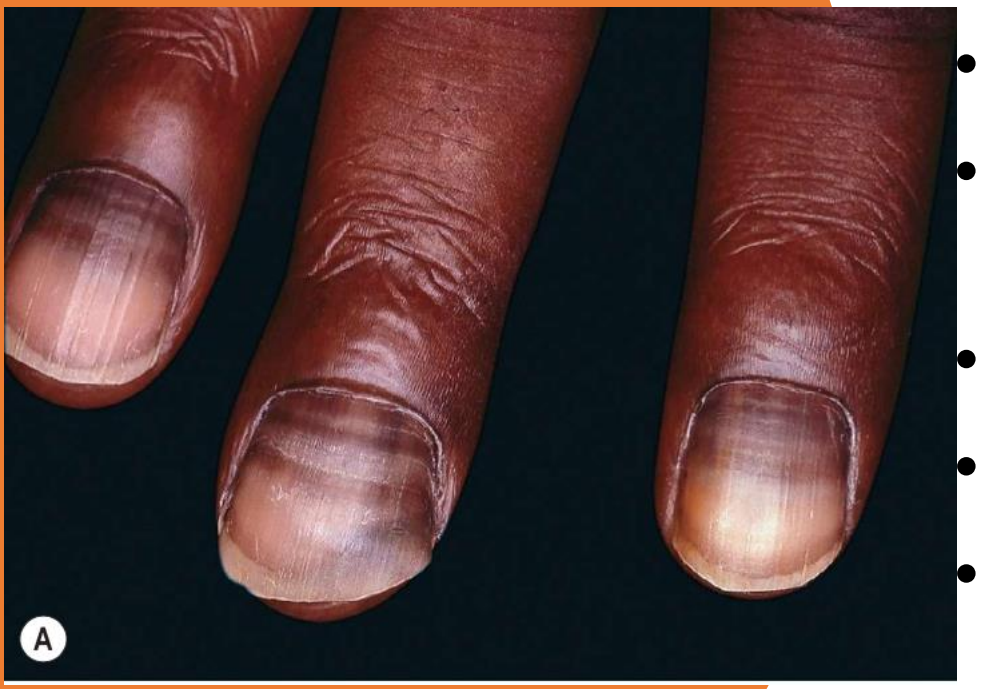
Images from Bolognia 2018 and uptodate.com



Conventional Chemo:

Ara-C ears

Other common cutaneous reactions:



- Alopecia – cooling cap, minoxidil
- **Mucositis** – oral hygiene, magic mouthwash, steroid swishes, nystatin, lidocaine ointment
- Extravasation reactions
- Hyperpigmentation of skin, mucosae, nails
- Radiation recall

Targeted Therapies

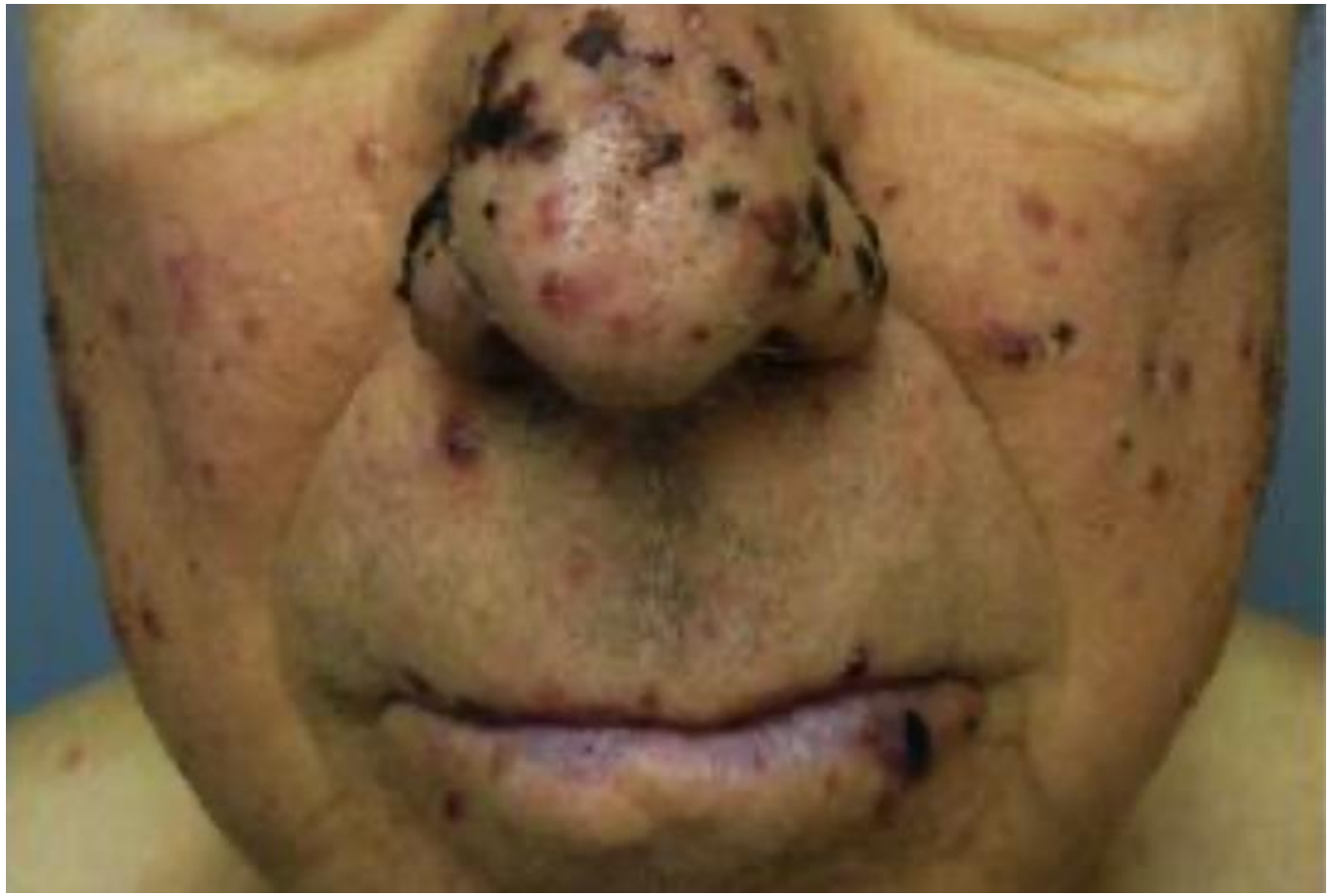
EGFR inhibitors:

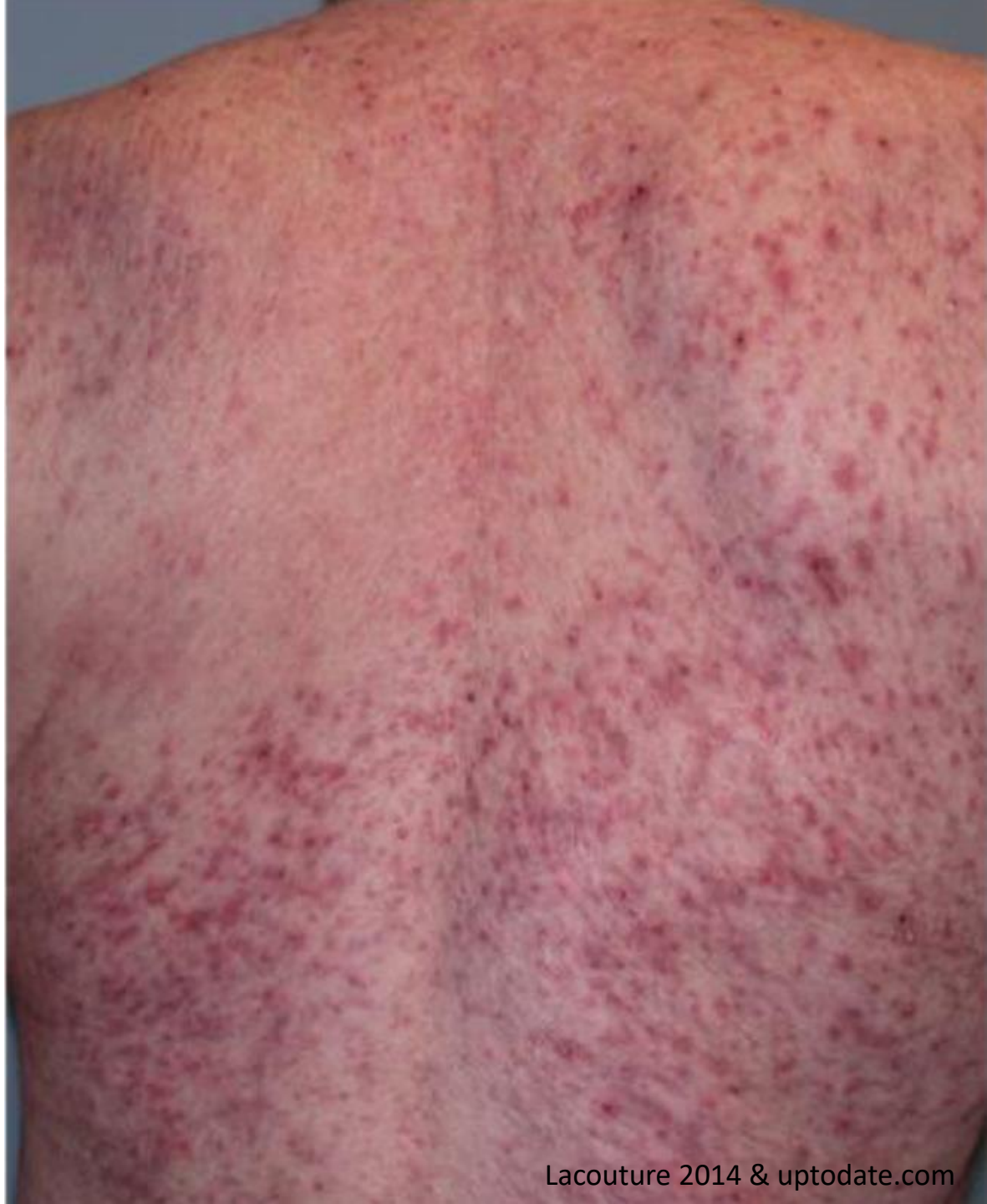
- **Papulopustular (acneiform) eruption**
  - Earliest and most common SE
  - Dose-dependent
    - Most targeted drug toxicities are dose dependent!
  - Head, neck, trunk and proximal upper extremities
  - Seborrheic distribution (most common)
  - Often associated with Staph superinfection

Targeted Therapies

EGFR inhibitors:

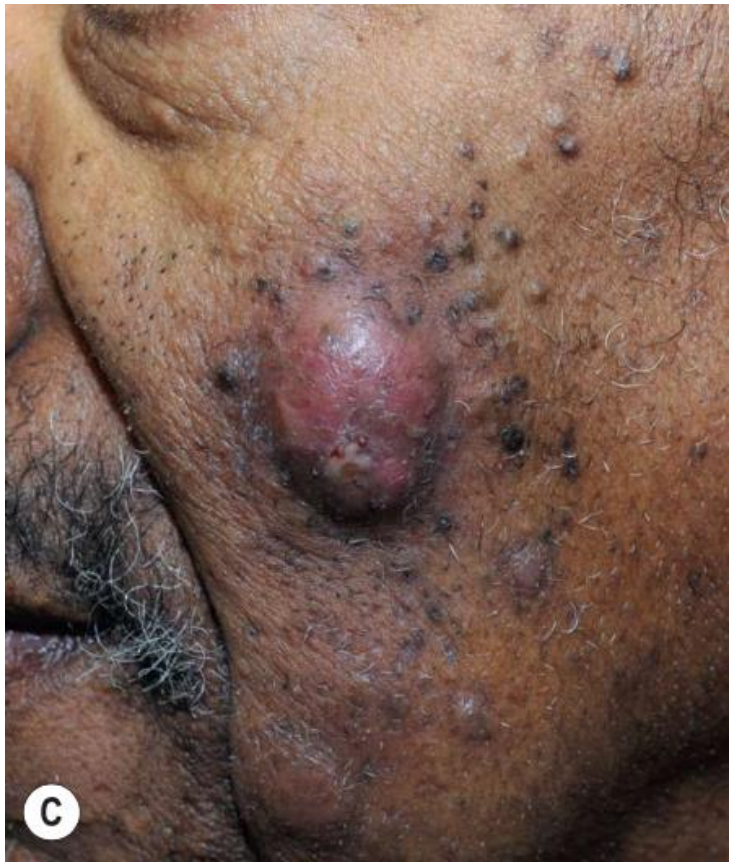
Papulopustular eruption

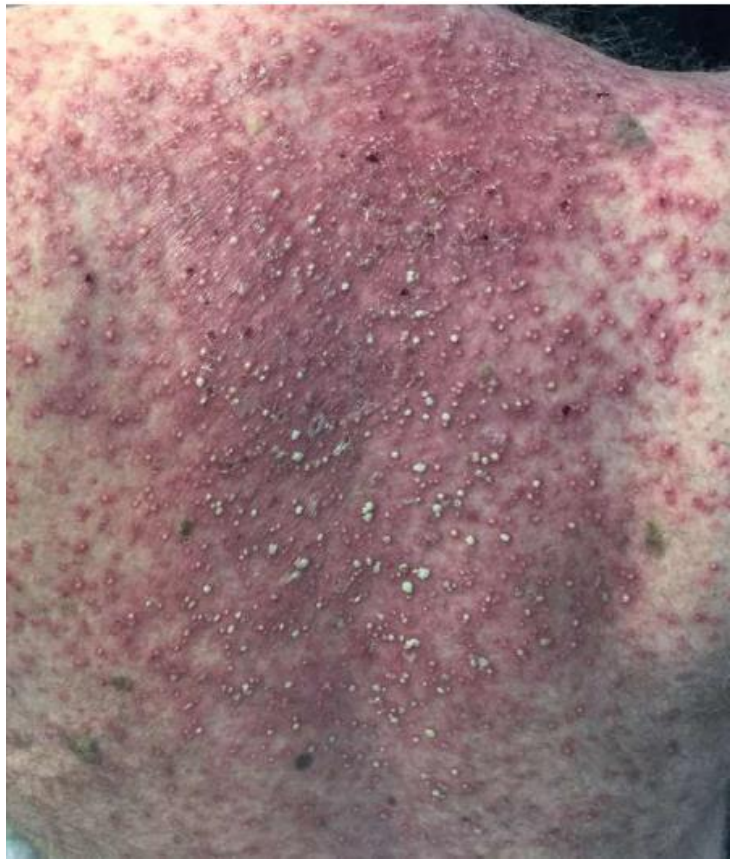




Lacouture 2014 & uptodate.com

EGFR inhibitors: Papulopustular eruption treatment

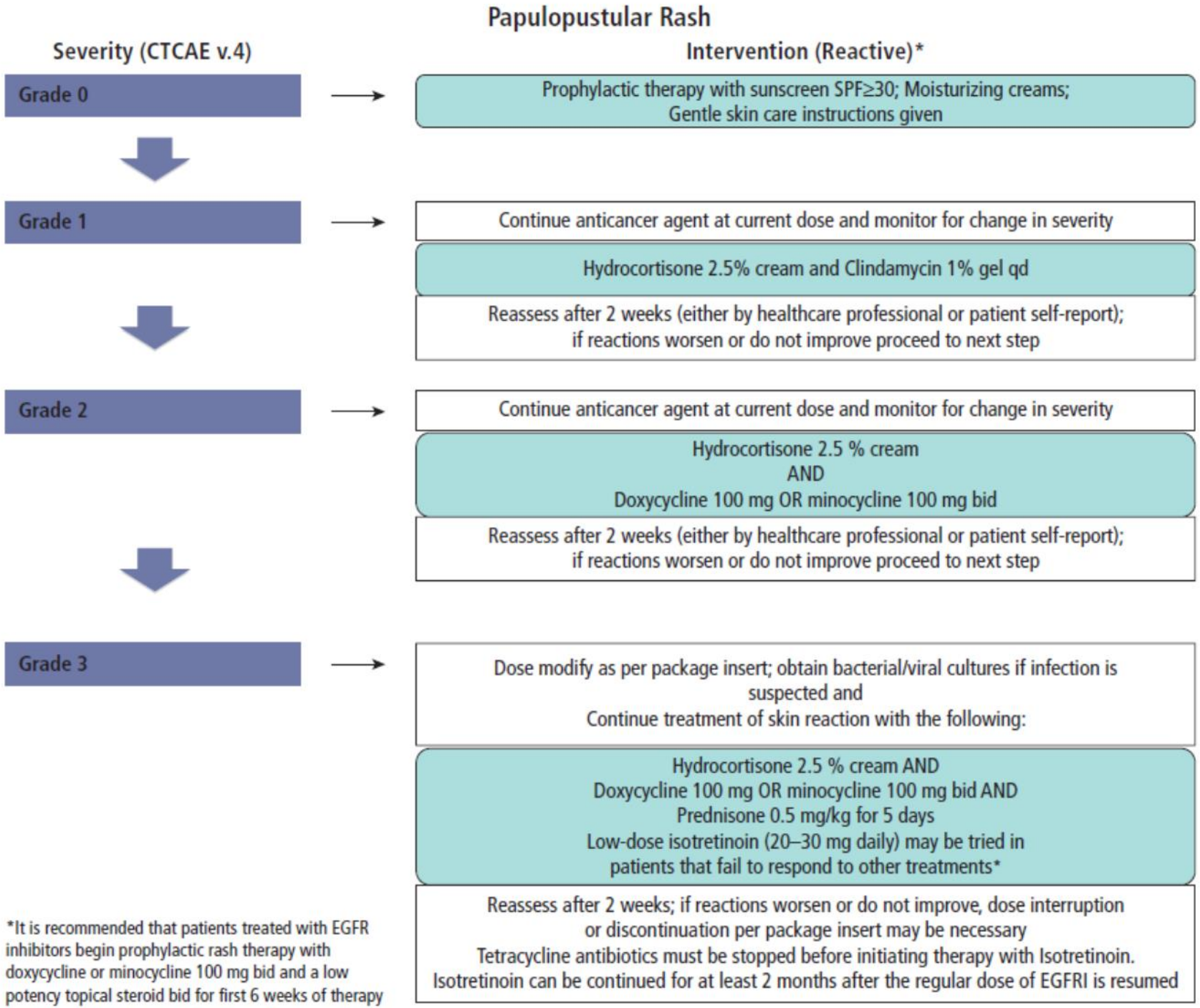




- Topical steroids
- Topical clindamycin
- Oral doxycycline or minocycline
- Bleach baths
- Prednisone
- Isotretinoin

Treatment algorithm for EGFR-inhib associated acneiform eruption

(Lacouture 2014)

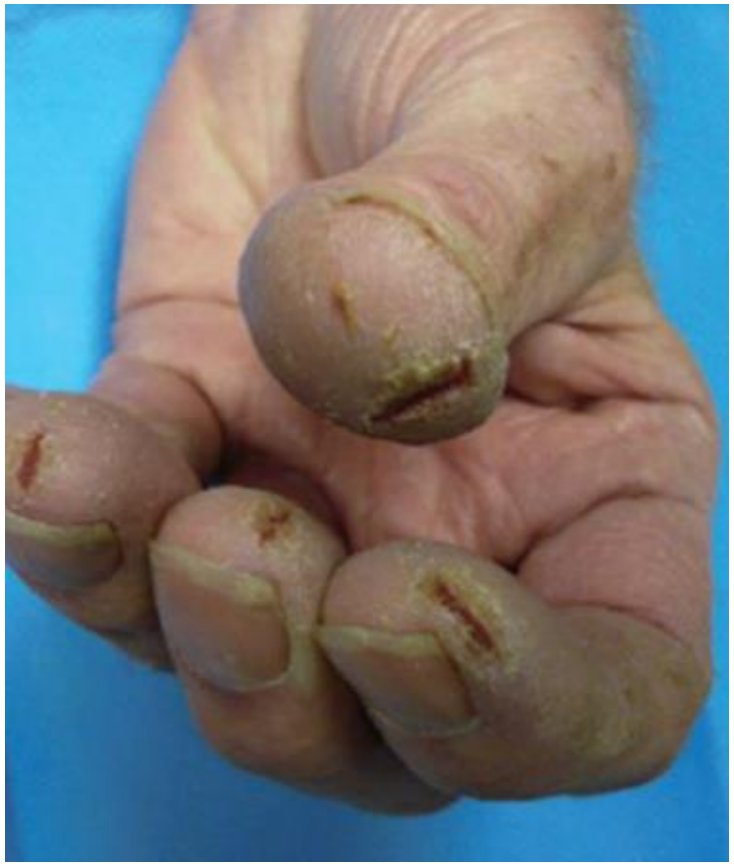


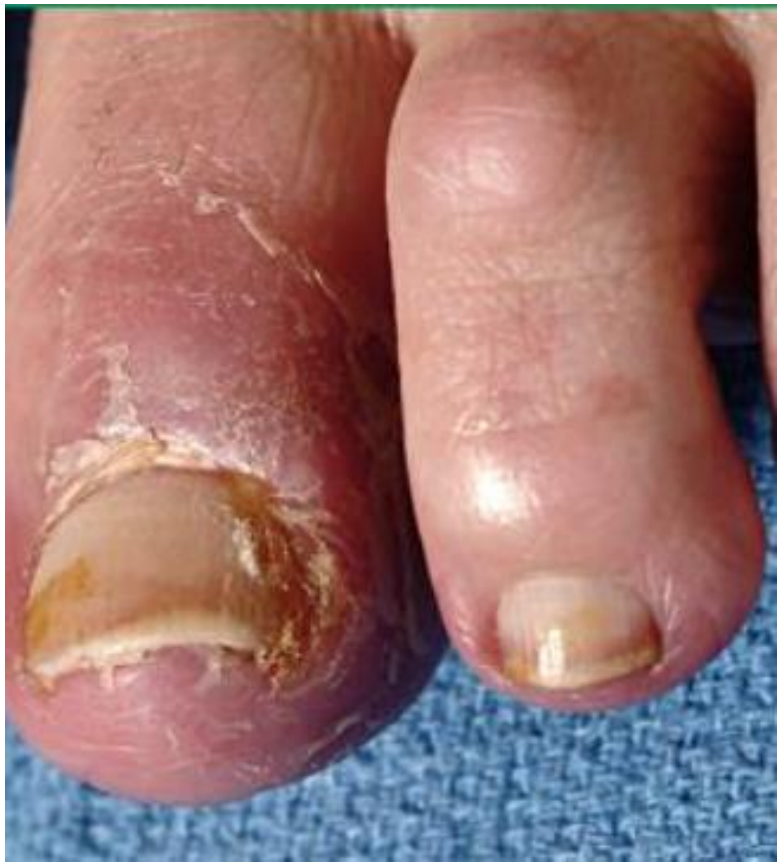
Targeted Therapies

- <u>EGFR inhibitors – other common toxicities:</u>

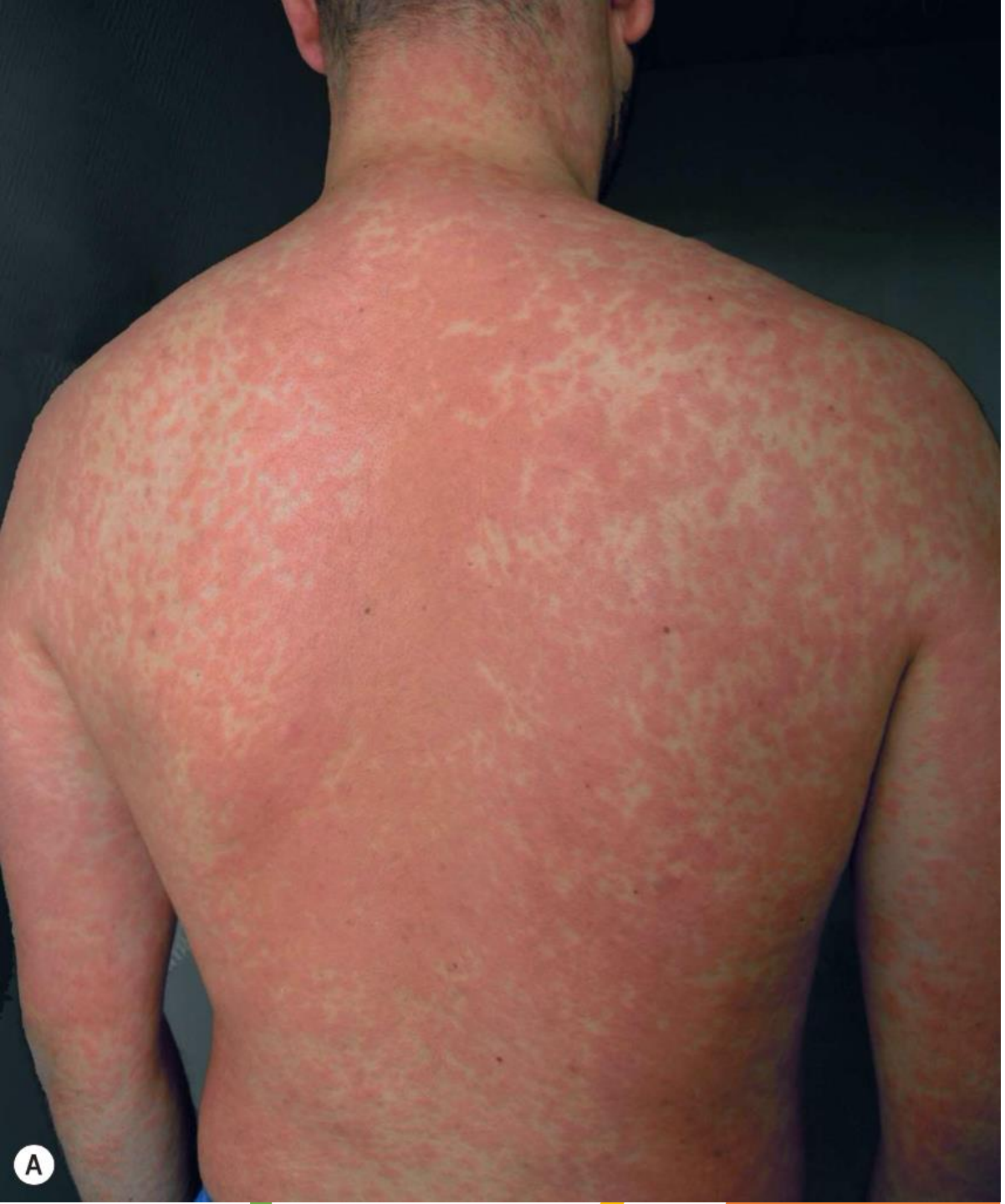
- Xerosis/ fissures
- Hair changes: kinking, trichomegaly, hirsutism, alopecia, poliosis
- Mucositis
- Nails: pyogenic granulomas, **paronychia**, onycholysis
- Photosensitivity

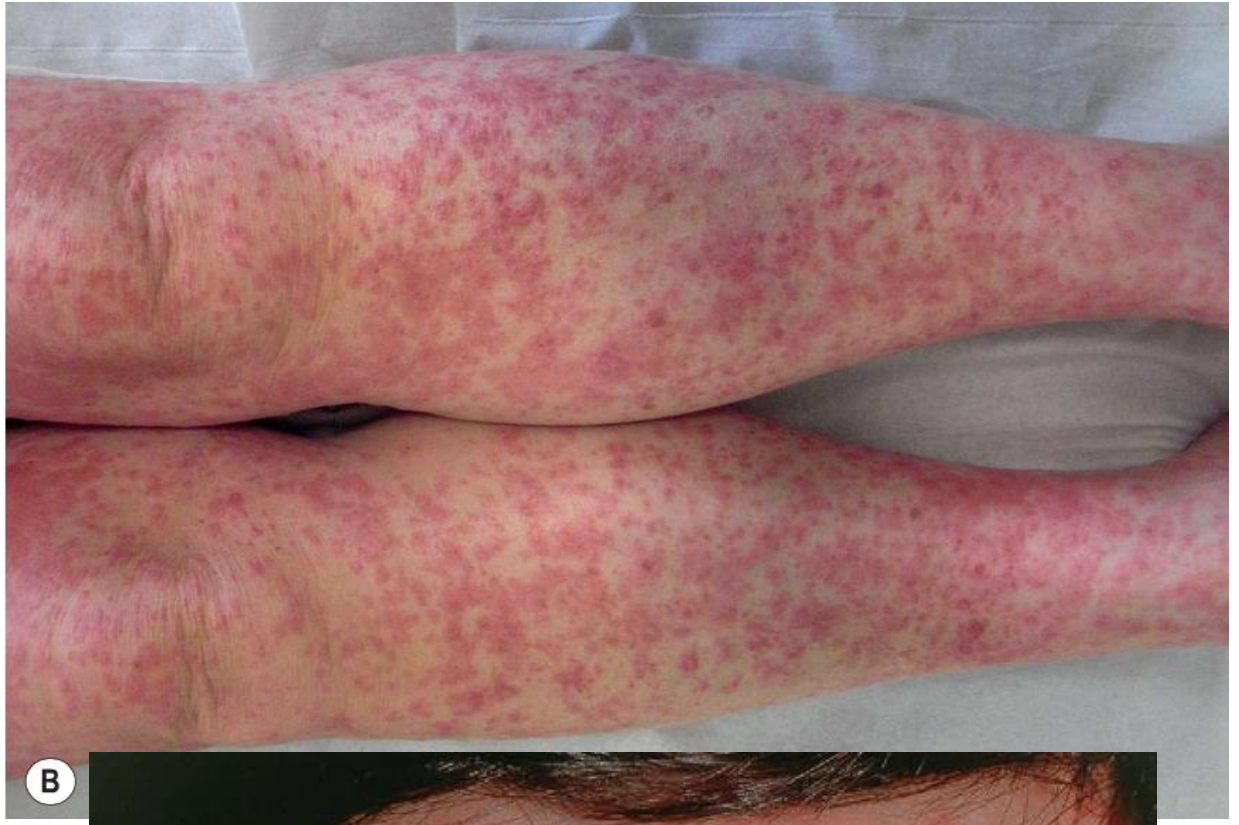
EGFR inhibitors – paronychia/fissures treatment:

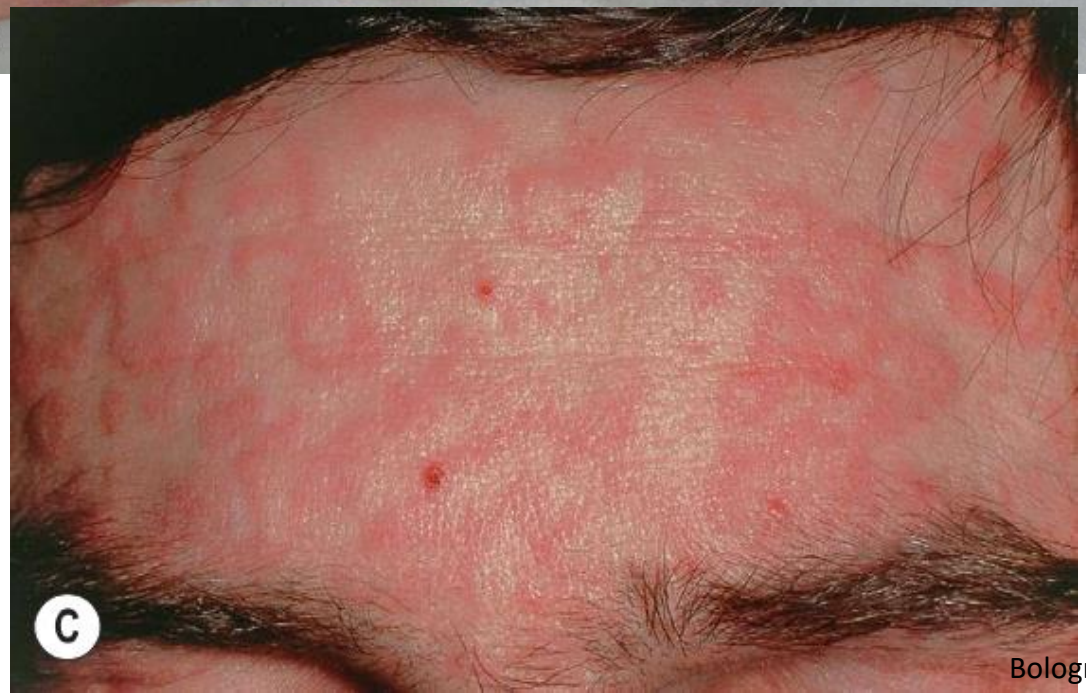




- Emollients
- Class 1 topical steroids
- Vinegar finger soaks (1:1 solution of white vinegar and warm water)
- CVS liquid bandage, Nexcare skin crack care or superglue for fissures
- Mix: Topical steroid, Clotrimazole 1%, Mupirocin 1% for fissures







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Targeted Therapies:

KIT and BCR-ABL inhibitors

- Papulosquamous
  - Psoriasis, psoriasis-like, lichenoid, PR-like
- **Pigmentary changes**
  - Depigmentation of hair or skin
  - More rarely, hyperpigmentation of skin or repigmentation of hair
  - reversible

Targeted Therapies:
KIT and BCR-ABL inhibitors

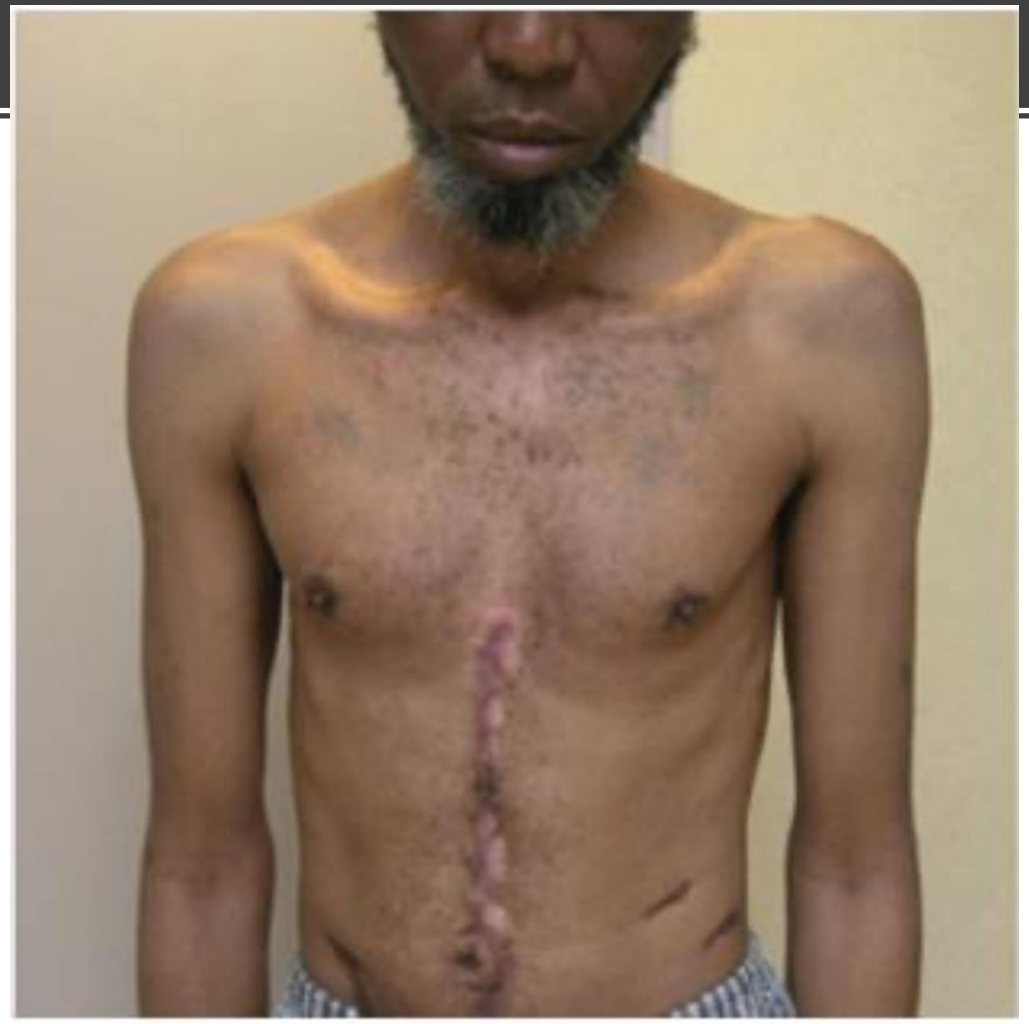


Figure 18.3 Imatinib-induced hypopigmentation.

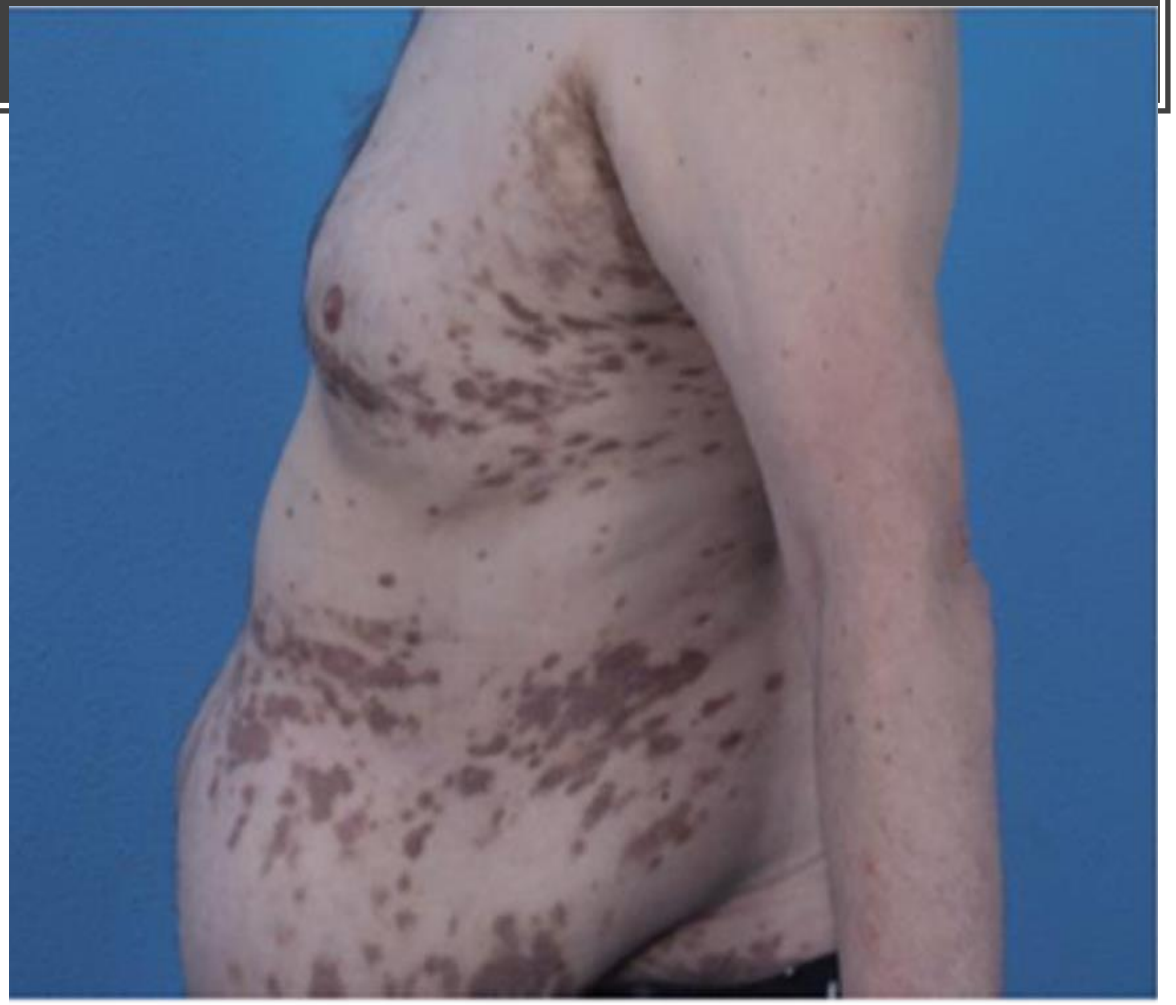


Figure 18.2 Imatinib-induced lichenoid rash.

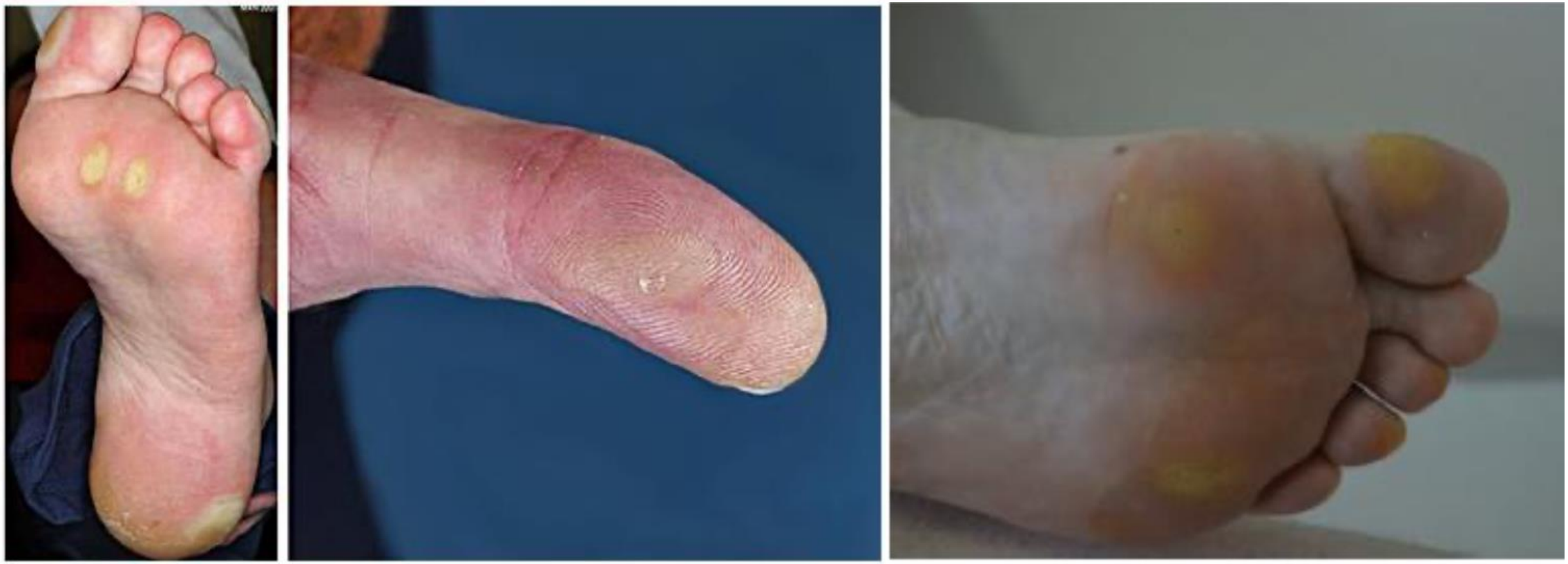
Targeted Therapies

<u>Antiangiogenic Multikinase Inhibitors:</u>

- **Hand foot skin reaction**
  - Painful hyperkeratotic plaques of sites of pressure and friction
  - Can be inflammatory, bullous
  - Pain can be debilitating – can be the reason for d/c of drug

Antiangiogenic Multikinase Inhibitors: Hand-Foot Skin Reaction

Hand-foot skin reaction in patients given sorafenib



Uptodate.com

Antiangiogenic Multikinase Inhibitors:

HFSR treatment

- Emollients
- Keratolytics (urea or salicylic acid creams/ointments)
- Orthopedic insoles / eval with a podiatrist (avoid any pressure points)
- Potent topical steroids
- Antiseptic soaks
- NSAIDS and other analgesics
- Topical retinoids
- Hold treatment and/or dose reduction
- Oral acitretin 10-25 mg QD

Treatment algorithm for HFSR to multikinase inhibitors

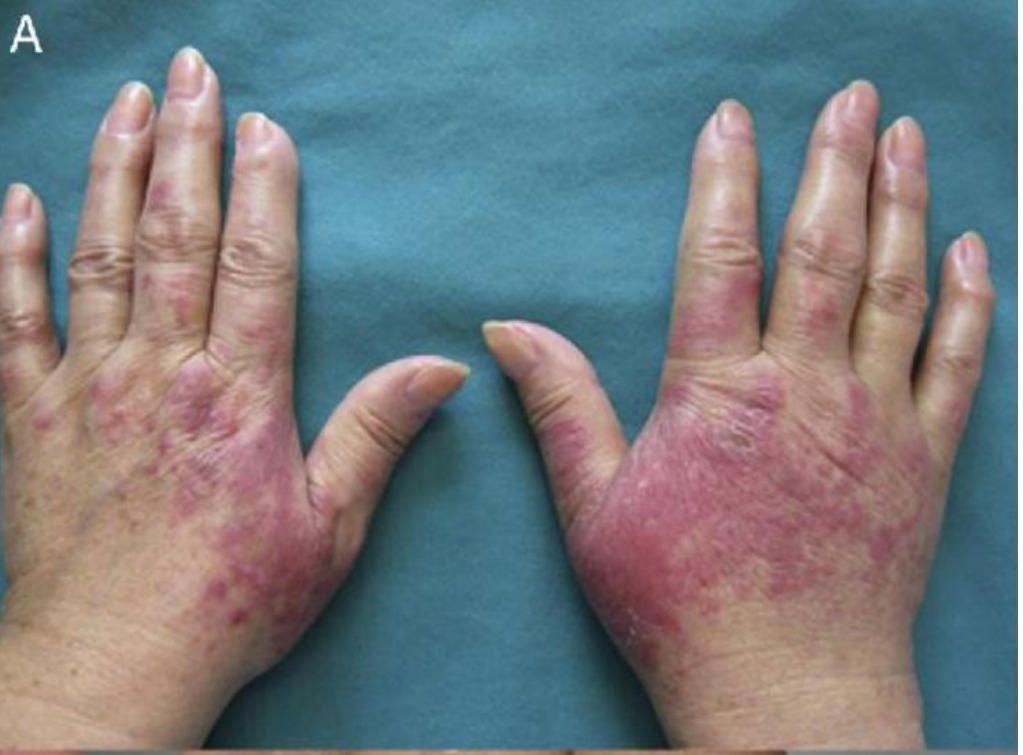
Severity (CTCAE v.4)	Intervention
Grade 0	Gentle skin care instructions given; Avoid irritation to the hands and feet; Urea 10% tid
Grade 1	Continue drug at current dose and monitor for change in severity
	Topical high-potency steroid bid AND urea 10% tid
	Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve proceed to next step
Grade 2	Continue drug at current dose and monitor for change in severity
	Topical high-potency steroid bid (may be combined concomitantly with topical moisturizer/keratolytic with occlusion) AND Pain control with NSAIDs/GABA agonists/Narcotics
	Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve proceed to next step
Grade ≥3	Interrupt treatment until severity decreases to grade 0–1; and continue treatment of skin reaction with the following:
Or intolerable grade 2	Topical high-potency steroid bid (may combine concomitantly with topical moisturizer/keratolytic with occlusion) AND Pain control with NSAIDs/GABA agonists/Narcotics
	Reassess after 2 weeks; if reactions worsen or do not improve, dose interruption or discontinuation per protocol may be necessary

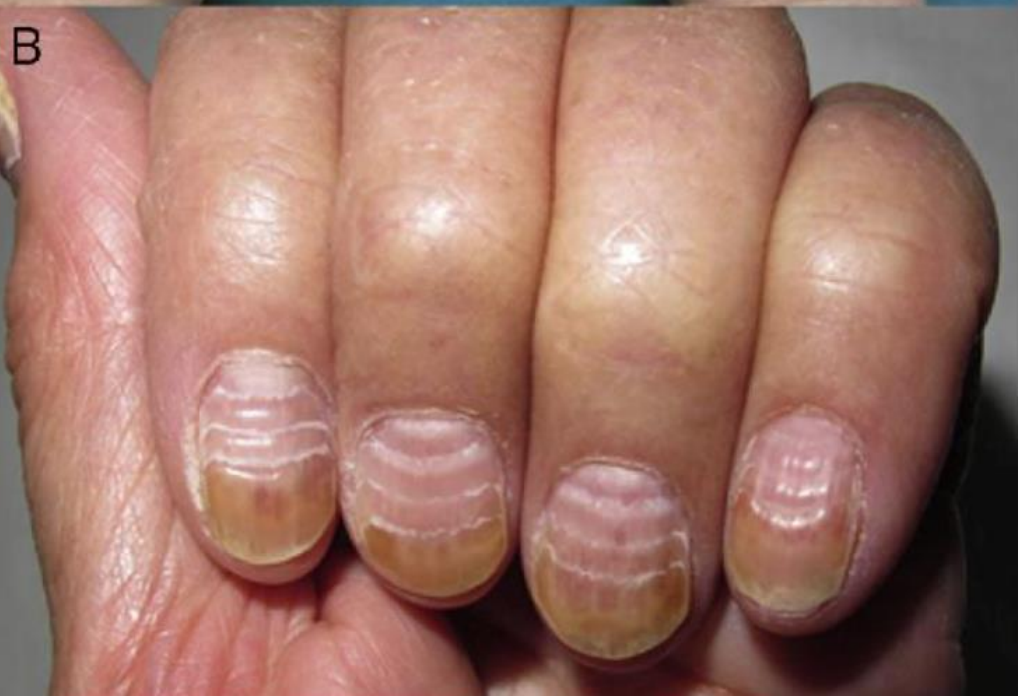
Antiangiogenic Multikinase Inhibitors – other toxicities:

- Subungual splinter hemorrhages
- Erythematous rashes – can predominate on the face, especially sorafenib
- Hair: alopecia, texture changes (drier/curlier)
- Xerosis
- Psoriasiform or lichenoid scrotal rashes
- Mucositis

Three Types of Hand / Foot Reactions

Hand Foot Syndrome	• Palmoplantar erythema, pain, dysesthesia • Conventional chemotherapy
Hand Foot Skin Reaction	• Painful hyperkeratotic plaques on pressure points • Targeted therapies, esp multikinase inhibitors
PATEO	• Periarticular thenar erythema and onycholysis • Taxanes





PATEO

Dorsal hands: tender/pruritic papules

Nails: subungual hemorrhage, onycholysis, Beau's lines, onychomelanosis, onychomadesis

Etiology: Taxanes

Treatment:

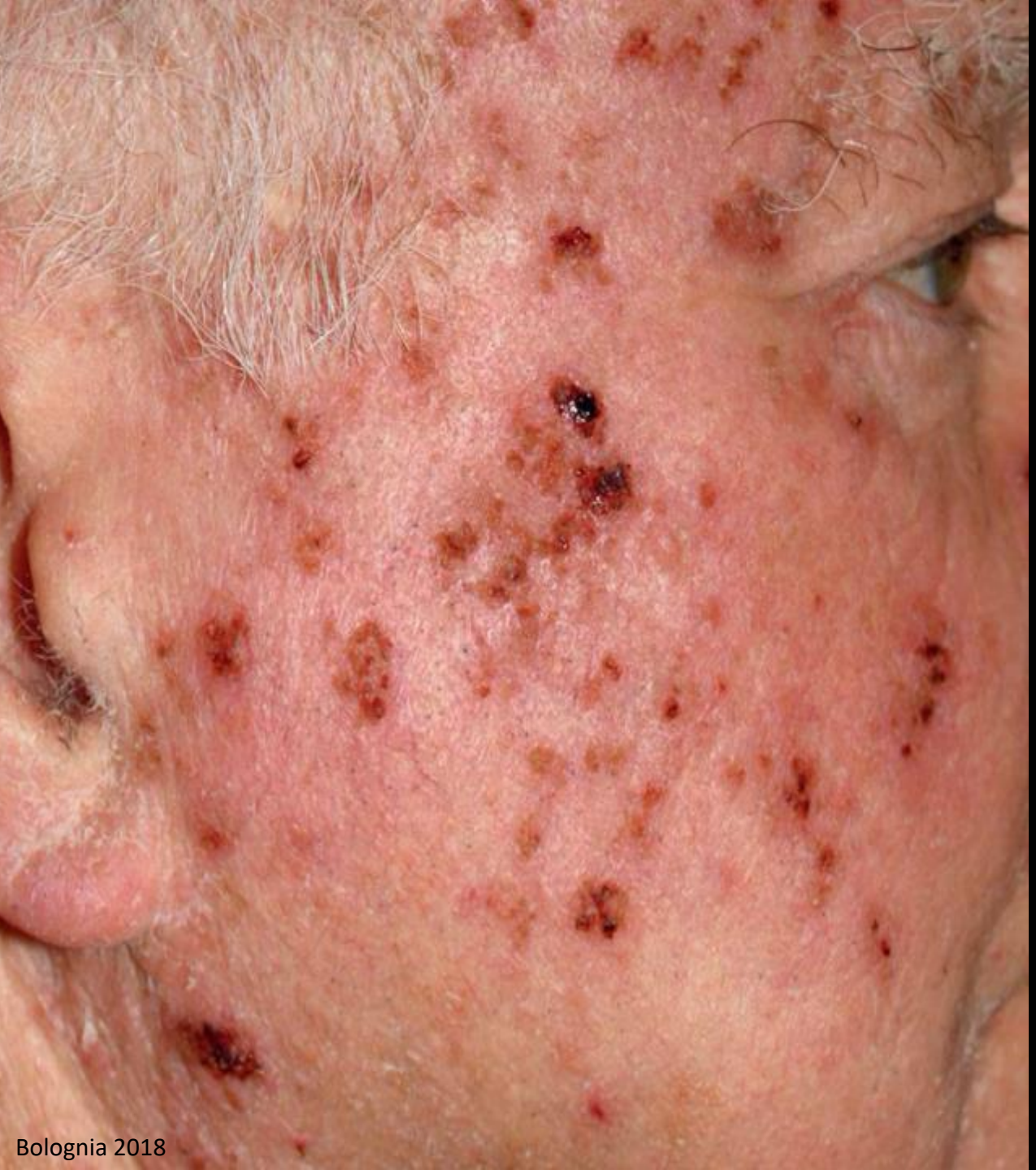
- Frozen gloves during docetaxel infusion to decrease nail side toxicities
- High potency topical steroids for skin

Rodríguez-Lomba, Enrique et al. "Periarticular Thenar Erythema and Onycholysis Syndrome: A Manifestation of Taxane-Induced Cutaneous Toxicity." Actas dermo-sifiliograficas 108 6 (2017): 595-597.

Targeted Therapies

BRAF inhibitors:

- Folliculocentric erythematous rash of smooth papules that coalesce into broad morbilliform or toxic erythema-like plaques
  - Topical steroids or short course of prednisone
- Verrucal keratoses
  - Benign squamoproliferative lesions
  - Cryotherapy, efudex, imiquimod, PDT...
- Keratoacanthomas, Squamous cell carcinomas
  - Surgery



BRAF inhibitors:

- Verrucal keratoses
- Keratoacanthomas, SCCs

Combining an anti-BRAF with an anti-MEK blocks the paradoxal activation of the MAPK pathway by BRAFi and results in less epidermal neoplasms

BRAF inhibitors (continued):

- Eruptive nevi, melanoma
  - Require frequent monitoring of pigmented lesions while on therapy
- Keratosis pilaris-like rash
- Seb derm-like rash
- Hand foot skin reaction
- Photosensitivity
- Panniculitis
- Alopecia

Targeted Therapies

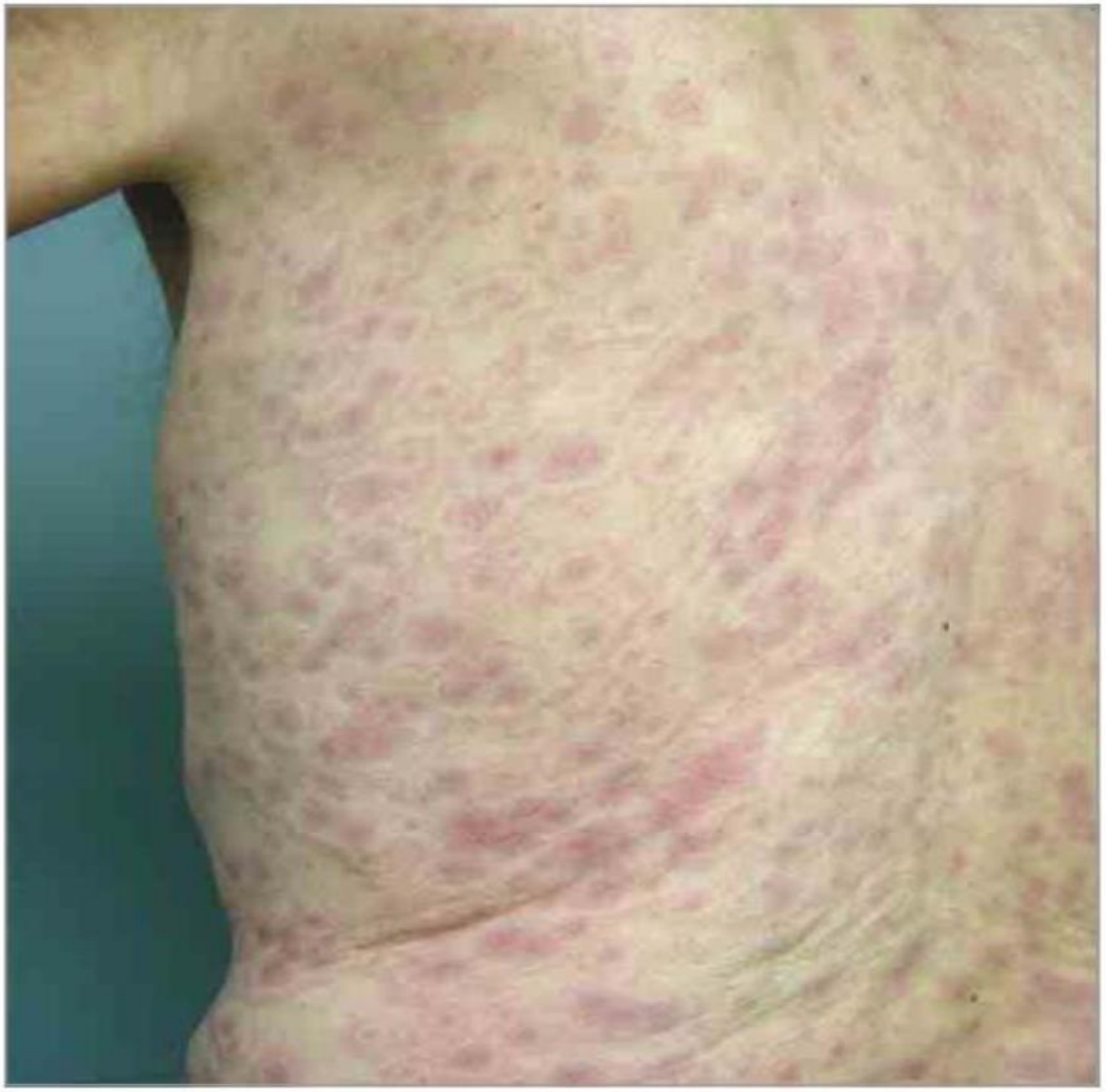
MEK inhibitors:

- EGFRi-like papulopustular eruption
- Morbilliform rash
  - Can have dusky erythematous rashes
- Xerosis
- Paronychia

Targeted Therapies

- <u>MEK inhibitors – dusky erythema:</u>

Figure 1. Skin Eruption in Patient 1 During Selumetinib Therapy



Targetoid patches with central duskiness.

Uptodate.com

Immune Checkpoint Inhibitors:

CTLA-4 and PD1/PDL1 inhibitors:

- Immune activation leads to autoimmune and autoreactive dermatoses
- Can cause just about anything...

Immune Checkpoint Inhibitors:

CTLA-4 and PD1/PDL1 inhibitors:

- The more commonly encountered reactions:
  - Vitiligo
  - Lichenoid skin reactions
  - Morbilliform rashes
  - Eczematous dermatitis
  - Pruritus

Immune Checkpoint Inhibitors:

<u>CTLA-4 and PD1/PDL1 inhibitors:</u>

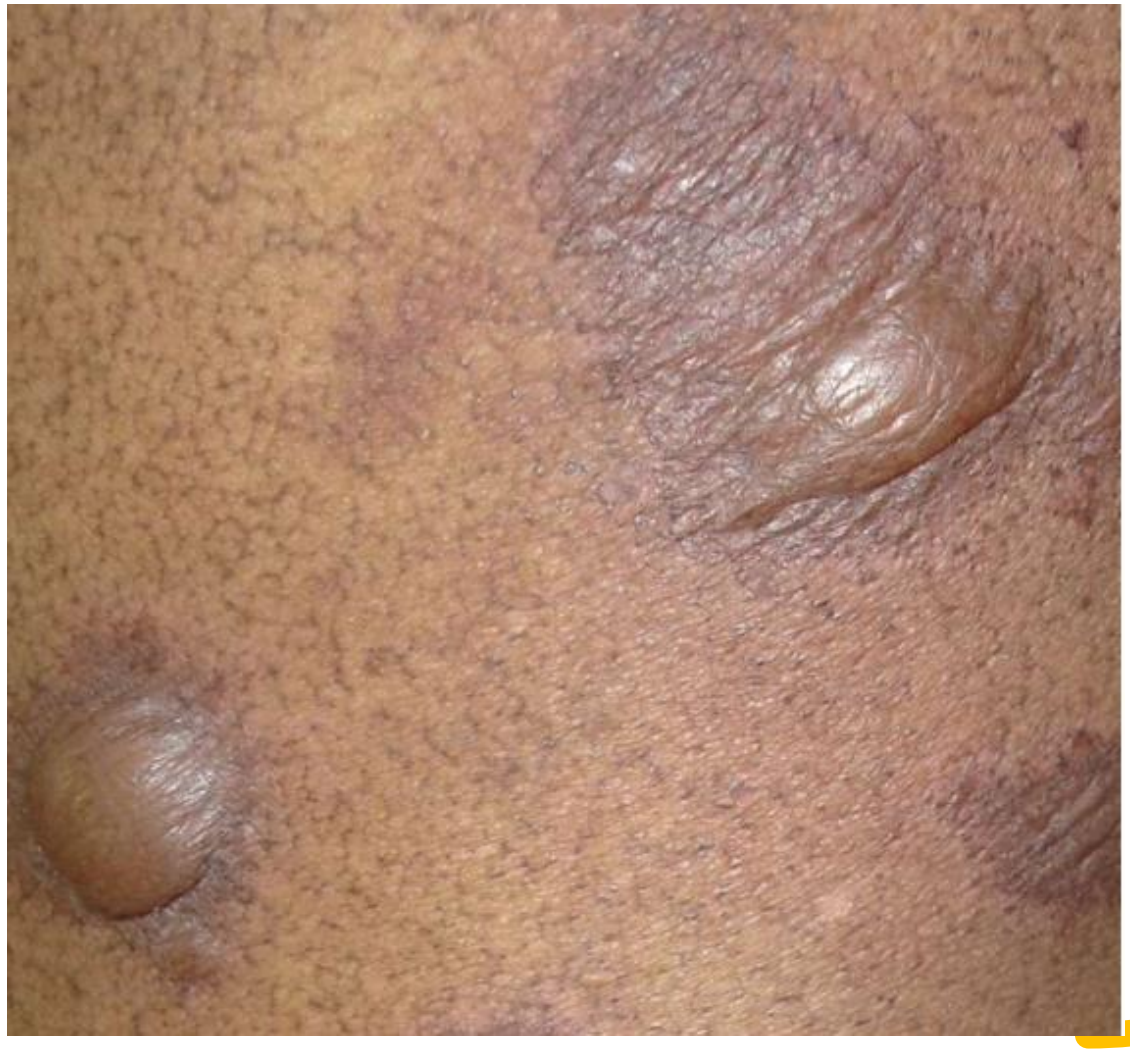
Others:

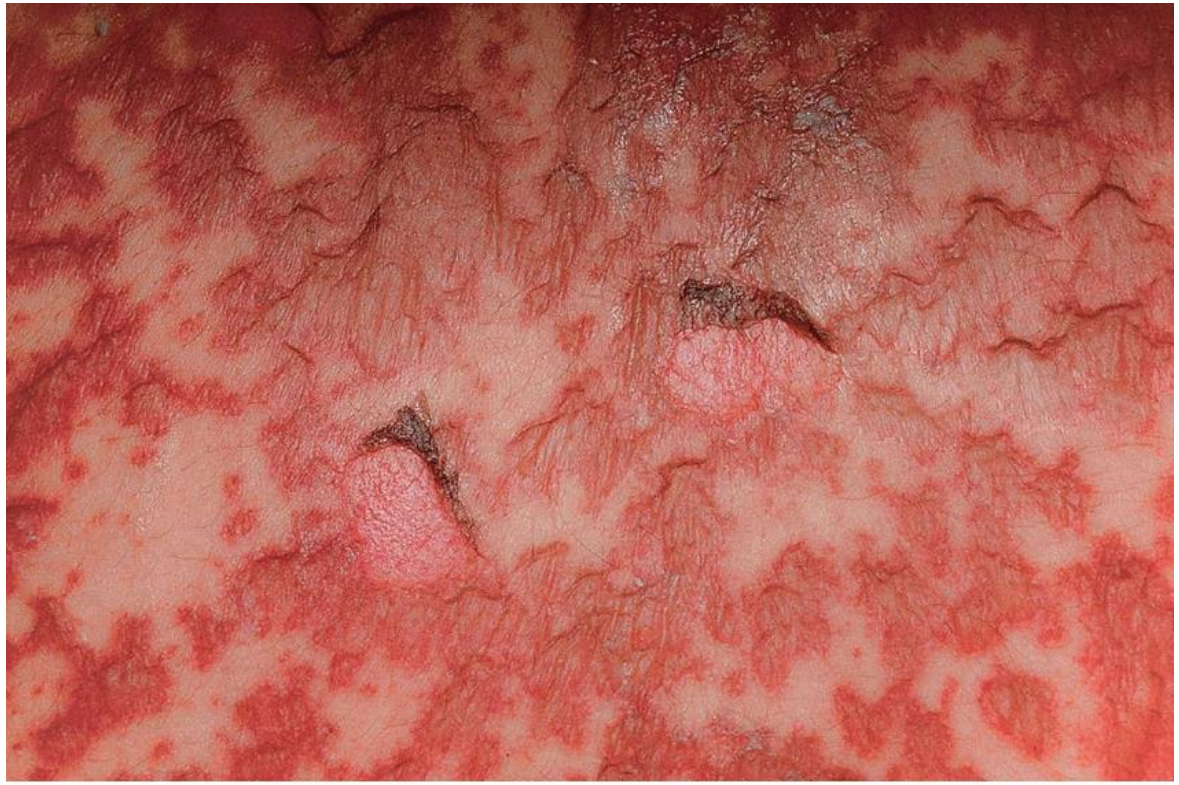
- Bullous pemphigoid
- Papulopustular eruptions
- Pyoderma gangrenosum-like ulcers
- Photosensitivity
- Radiation recall
- Prurigo nodularis
- SLE
- DRESS
- SJS/TEN* -- most often these are not true SJS, we refer to them instead as severe mucocutaneous reactions

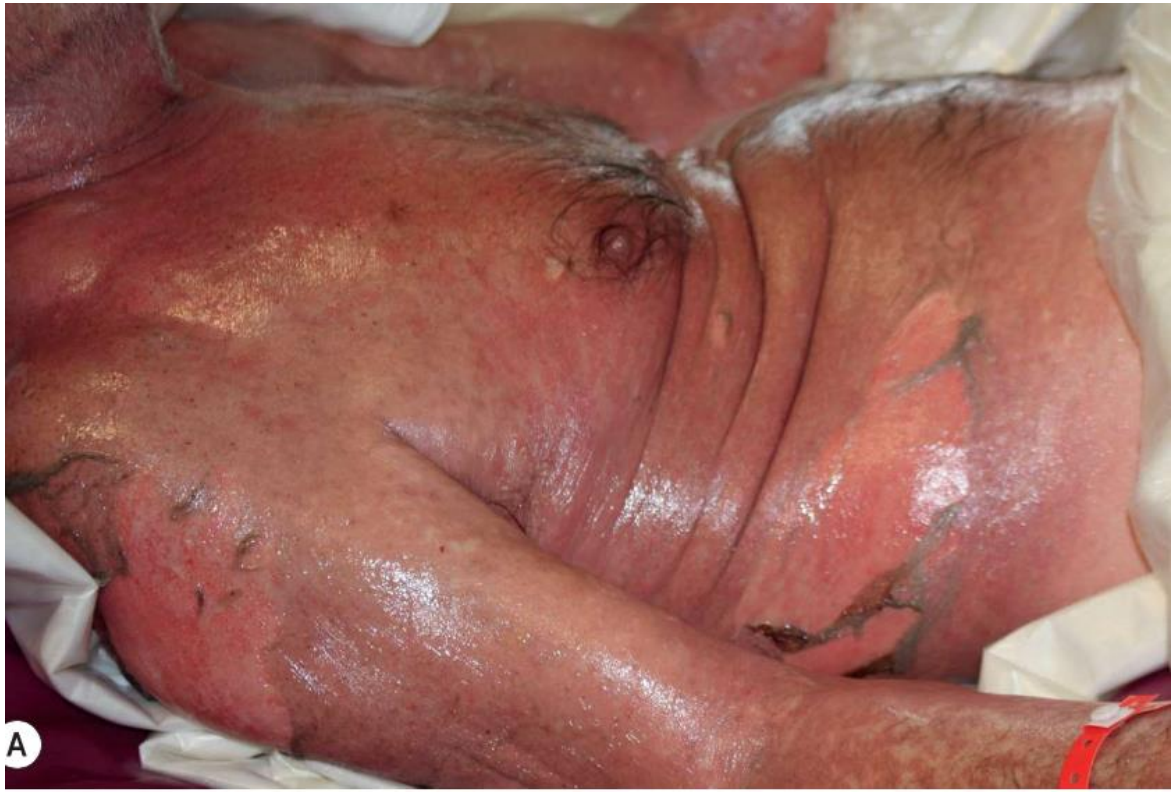
Immune Checkpoint Inhibitors:

CTLA-4 and PD1/PDL1 inhibitors:

- Bullous pemphigoid







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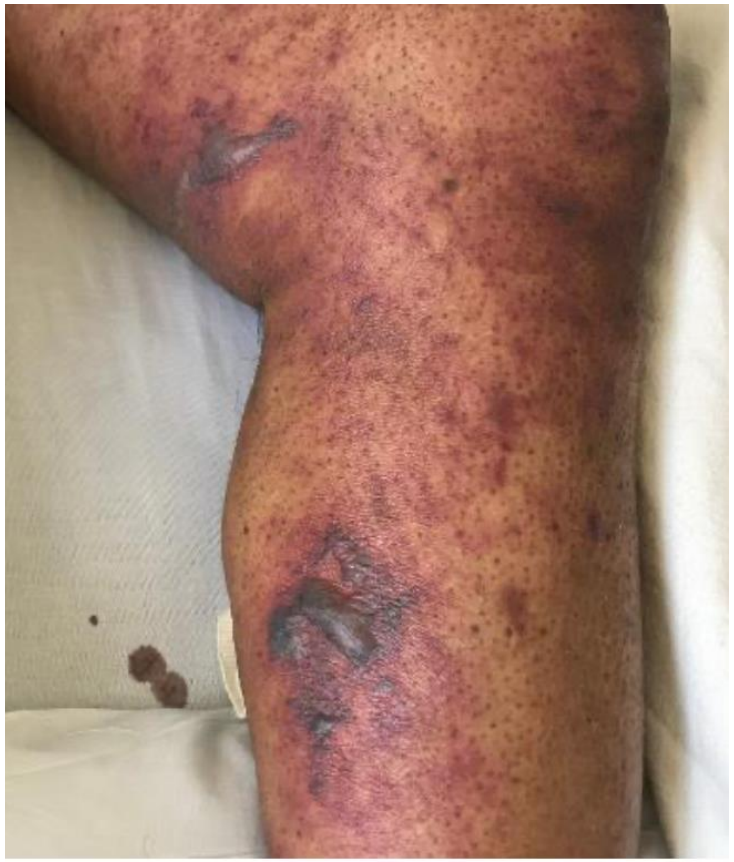
CTLA-4 and PD1/PDL1 inhibitors:

- Severe mucocutaneous reaction to ipilimumab

Immune Checkpoint Inhibitors:



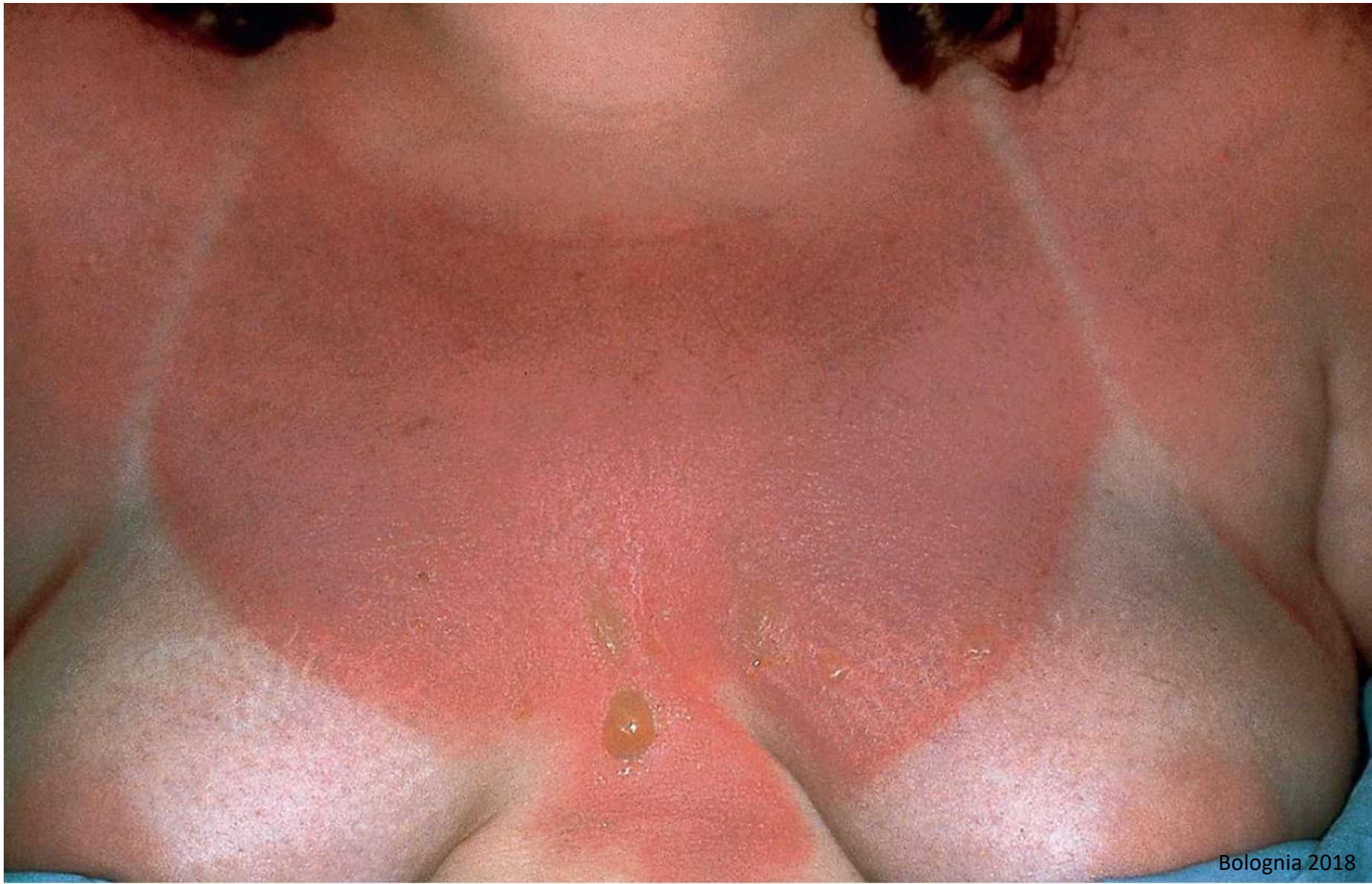
<u>CTLA-4 and PD1/PDL1 inhibitors:</u>

- Severe mucocutaneous reaction to PD1i

BWH Inpatient Service

CTLA-4 and PD1/PDL1 inhibitors

- Photosensitivity
- Radiation recall



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Immune Checkpoint Inhibitors:

CTLA-4 and PD1/PDL1 inhibitors:

- Typically occur within days to weeks of starting, but may be delayed/occur several months after starting
- May persist after d/c the medication
  - Immune activation persists
  - Long half-life
- Triggers:
  - UV exposure, infections, local dermatitis (ex: a contact dermatitis), vaccines..
  - Anything that would call inflammatory cells into the skin can result in a skin toxicity

CTLA-4 and PD1/PDL1 inhibitors—

Treatment

- Treatment varies by reaction
- General measures: emollients, topical steroids, topical tacrolimus, antihistamines, photoprotection
- Chronic maintenance with daily emollients and topical steroids 3x a week can help some patients stay on treatment

- **Patients can often be re-challenged**
  - *Skin toxicities are not an automatic contraindication to re-starting the medication*

Immune Checkpoint Inhibitors

CTLA-4 and PD1/PDL1 inhibitors:

- **Avoid oral prednisone whenever possible**
  - *Systemic steroids are okay for targeted therapy toxicities (where they do not interfere with mechanism of action) but should be avoided in immune checkpoint inhibitor toxicities if possible since they likely decrease the immune response against the tumor*

- Use disease specific non-prednisone treatment options when possible.
  - *example: doxycycline/nicotinamide or rituximab for BP*

References

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  - Toxicities associated with checkpoint inhibitor immunotherapy
- Rodríguez-Lomba, Enrique et al. “Periarticular Thenar Erythema and Onycholysis Syndrome: A Manifestation of Taxane-Induced Cutaneous Toxicity.” Actas dermo-sifiliograficas 108 6 (2017): 595-597.