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Recent Advances in Dermatology for the Allergist

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Disclosures

Consultant: *Arcutis*

Speaker: *Arcutis and Sanofi-Regeneron*

Goals

- Discuss a new take on an old allergen: meet the 2024 Contact Allergen of the Year
- Describe new innovations in topical therapy for Atopic Dermatitis
- Review more recently reported potential adverse effects of Dupilumab
- Discuss classification of immune related cutaneous adverse events (irAER) to immune checkpoint inhibitors (ICI) and newer concepts on therapy

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Contact Allergen of the Year 2024: Sulfites

- Multiple uses:
  - Industrial
  - Personal care products
  - Food and beverage

- Act as preservative and anti-oxidant
  - Prevent microbial growth
  - Prevent oxidation to preserve shelf life of food/beverage

Contact Allergen of the Year 2024: Sulfites

- Multiple uses:
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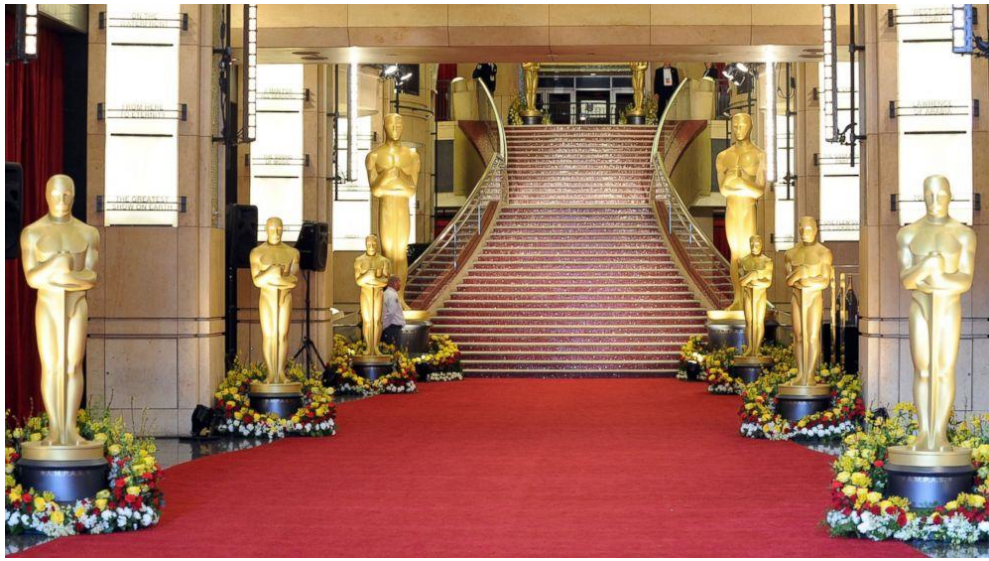

- Act as preservative and anti-oxidant
  - Prevent microbial growth
  - Prevent oxidation to preserve shelf life of food/beverage

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TABLE 4. Commercially Available Sulfites Used in Food and Cosmetics

Compound	Chemical Formula	CAS Number	E Number	Food	Cosmetics
Sodium sulfite	Na_2SO_3	7757-83-7	E221	Yes	Yes
Sodium bisulfite	$NaHSO_3$	7631-90-5	E222	Yes	Yes
Sodium metabisulfite	$Na_2S_2O_5$	7681-57-4	E223	Yes	Yes
Potassium sulfite	K_2SO_3	10117-38-1	E225	Yes	Yes
Potassium bisulfite	$KHSO_3$	7773-03-7	E228	Yes	Yes
Potassium metabisulfite	$K_2S_2O_5$	16731-55-8	E224	Yes	Yes
Calcium sulfite	$CaSO_3$	10257-55-3	E226	Yes	No
Calcium bisulfite	$Ca(HSO_3)_2$	13780-03-5	E227	Yes	No
Ammonium bisulfite	NH_4HSO_3	10192-30-0	—	No	Yes
Ammonium sulfite	$(NH_4)_2SO_3$	7026-44-7	—	No	Yes

Sulfites: Allergen of the Year 2024. Dermatitis®: ahead of print

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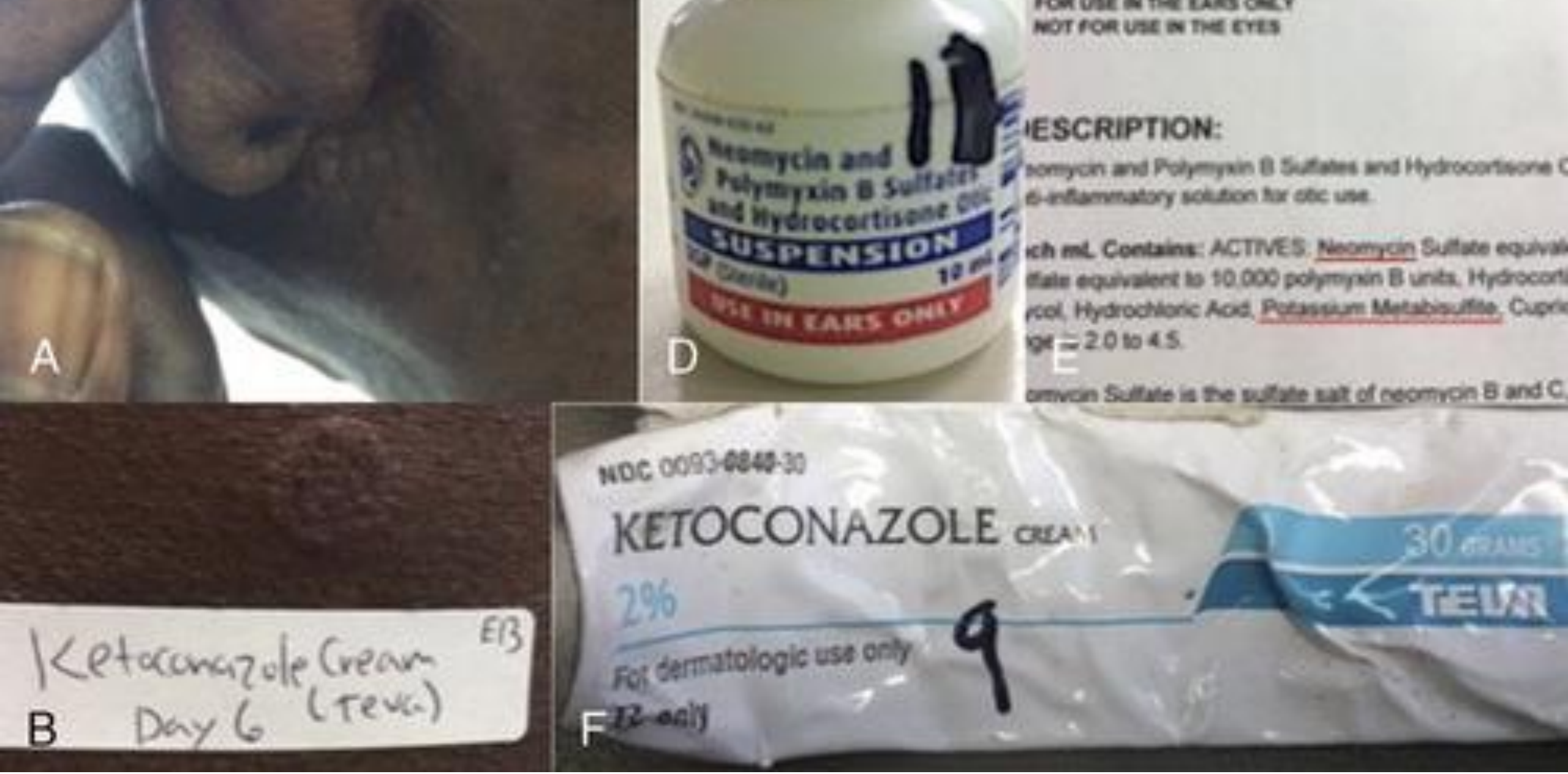
Sulfites

- Not included in routine patch testing: contact dermatitis to sulfites likely under-reported
  - Prevalence hard to estimate, likely exceeds 1% of tested populations
  - Included in NACDG but not ACDS Core Series or TRUE test
  - Clinical relevance: 50-65.2% in various studies
- When tested, 28.8% of reactors had facial dermatitis and/or hand dermatitis (20.5%)
- Rare association with Type I reactions including anaphylaxis and urticaria
  - Led to FDA ban on use of sulfites on fresh fruit

Sulfites: Allergen of the Year 2024.Dermatitis®: ahead of print

Common Medications Containing Sulfites

- Antifungal creams/ shampoo
- Topical steroids
- Hemorrhoidal creams
- Ophthalmologic solutions
- Epinephrine



Sulfites: No Longer a Zebra? Dermatitis.Dec 2017.28(6) 364-366.

Personal Care Products with Sulfites

- Shampoos
- Hair coloring agents (Dyes and bleaches)
- Hair sprays
- Tanning lotions
- Facial cleansers and body washes
- Sunscreens
- Eye creams and antiaging products
- Deodorants

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Occupational Exposures

- Brewing and wine making
- Photographic chemicals
- Leather manufacturing
- Food preparation
- Pharmaceutical production
- Rubber manufacturing

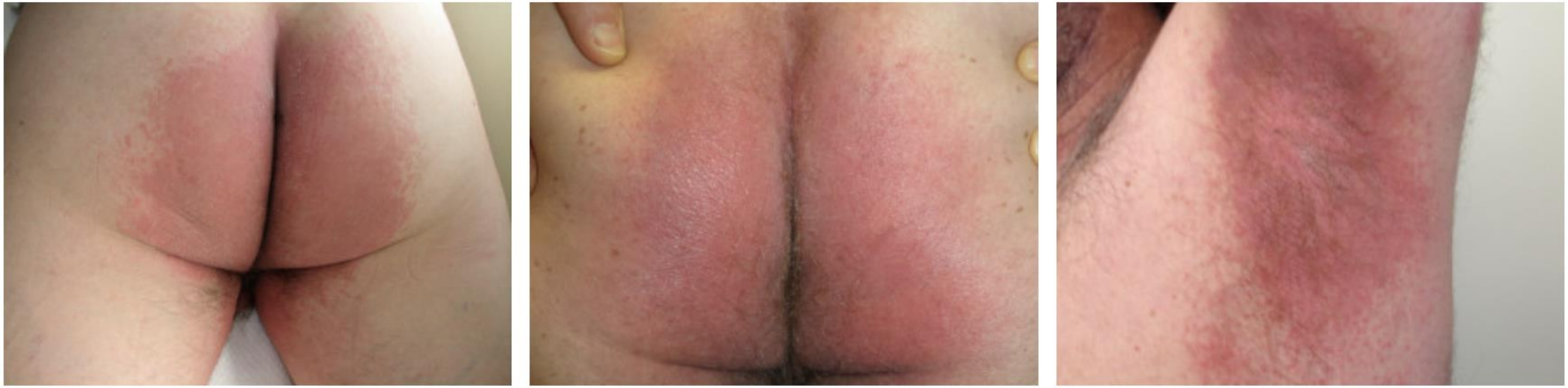
Dietary Exposures

- Apricots and avocados
- Jams and Jellies
- Beer
- Wine (sulfites added during fermentation)

- High dietary exposure can predispose patients to systemic contact dermatitis

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) or ‘Baboon Syndrome'

Clinical presentation of SDRIFE



https://dermnetnz.org/topics/symmetrical-drug-related-intertriginous-and-flexural-exanthema

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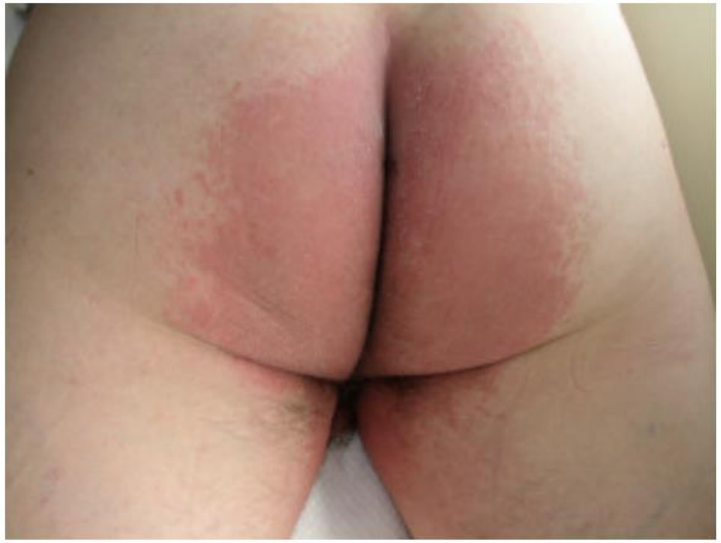
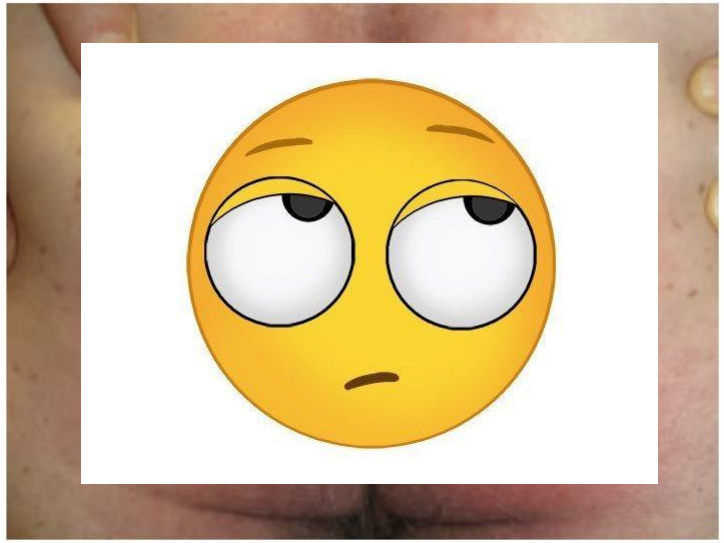
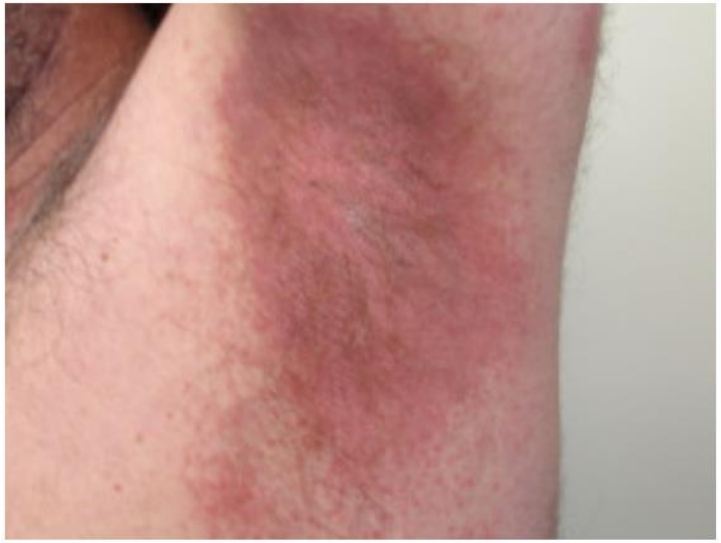
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)

Clinical presentation of SDRIFE







https://dermnetnz.org/topics/symmetrical-drug-related-intertriginous-and-flexural-exanthema

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ONE OF THE
MOST BIZARRE
FORMS OF LIFE
LIVING
FOSSIL
Lichens, like the ones you see here, are one of the most bizarre forms of life because each lichen is actually composed of two, possibly even three, distinct species of organisms! Lichens are a partnership between fungus and algae that grow on rocks, tree branches and the bare ground. Lichens are considered living fossil plants, since they are directly linked to the original plant life that first inhabited the Earth.

New Topical Therapies for the Treatment of Atopic Dermatitis

- Steroid overuse: cutaneous atrophy, steroid withdrawal, and steroid addiction. Patients and parents of children with AD may have 'steroid phobia’
- Older non-steroid options include topical calcineurin inhibitors and crisaborole ointment
    - Potency issues
    - Can cause burning and stinging on application
- New Tools for the toolbox are needed!

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New Topical Therapies for the Treatment of Atopic Dermatitis

- More than twenty new topical therapies are in development for the treatment of Atopic Dermatitis
- Approved: ruxolitinib 1.5% cream
- Others are in various stages of development for treatment of atopic dermatitis
  - Tapinarof
  - Difamilast and roflumilast
  - Delgocitinib

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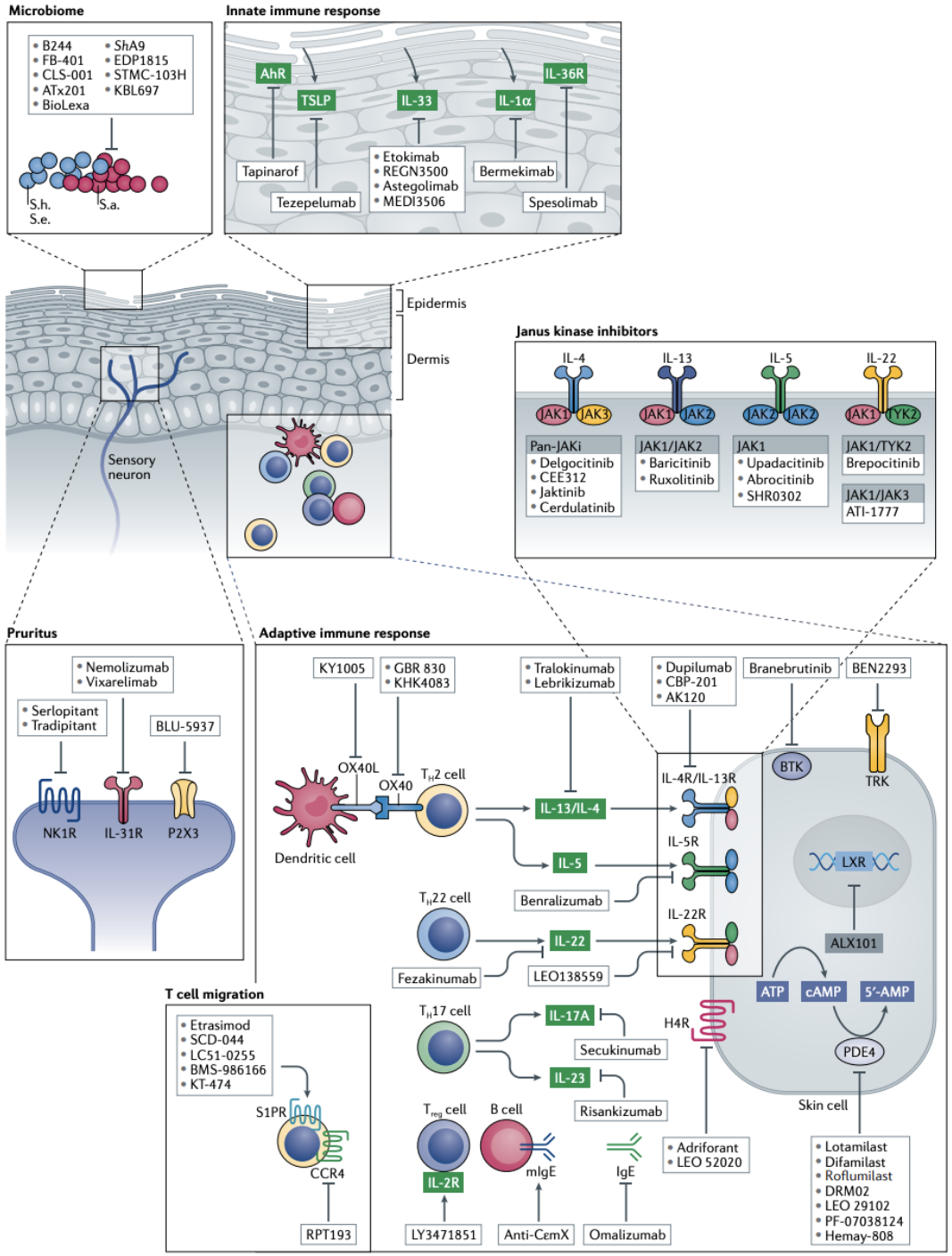
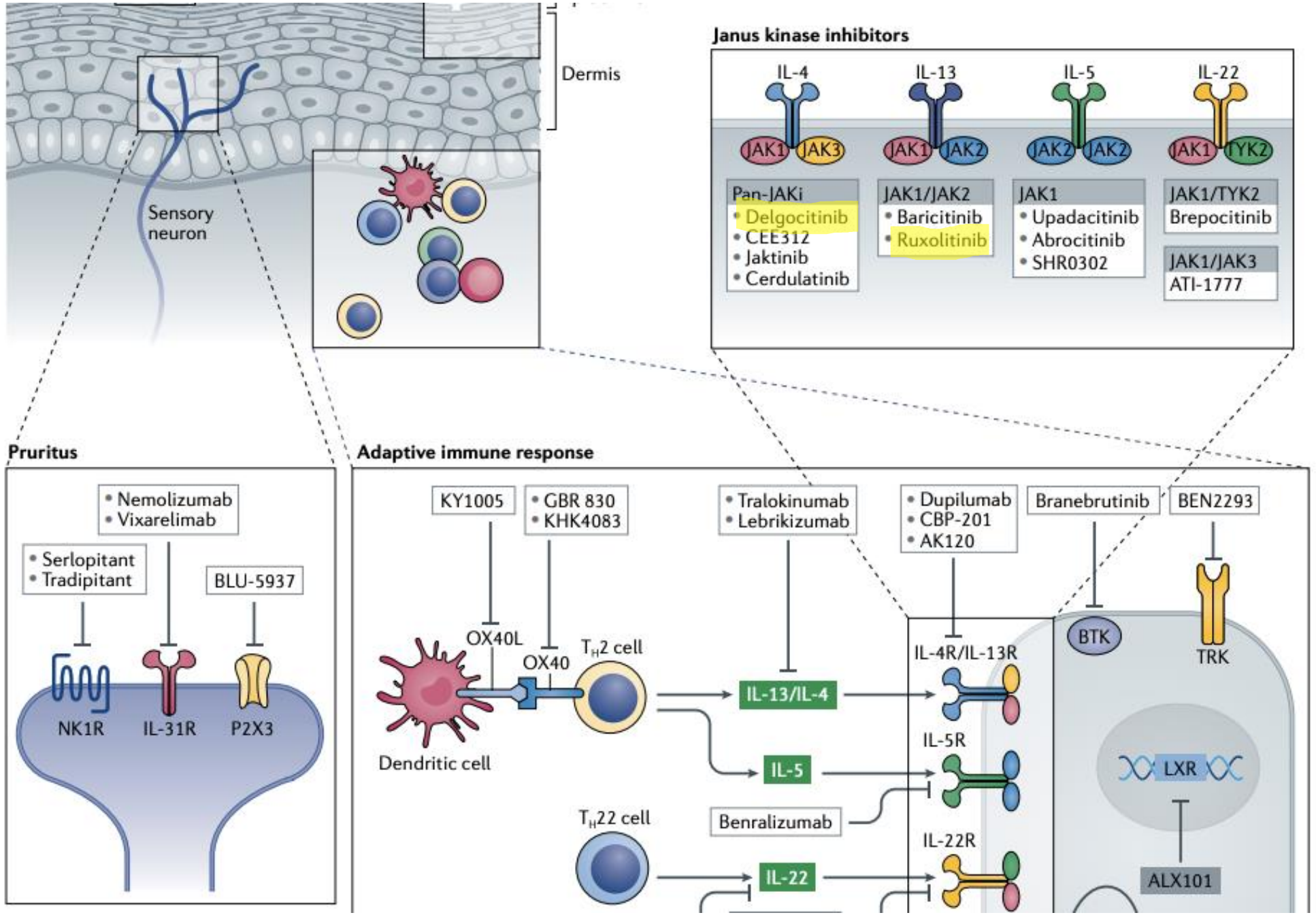
Drugs. 2022 Jun;82(8):843-853

TOPICAL MOLECULES

APPROVED AGENTS		
Delgocitinib	Pan- JAK	Approved in Japan (2020)
Ruxolitinib	JAK1/JAK3	FDA Approval (2021)
Difamilast	PDE4	Approved in Japan (2021)
IN DEVELOPMENT		
Tapinarof	AHR	Phase 3
Roflumilast	PDE4	Phase 3
Ivarmacitinib	JAK1	Phase 3


Microbiome
B244
FB-401
CLS-001
ATx201
BioLexa
ShA9
EDP1815
STMC-103H
KBL697
S.h.
S.e.
S.a.
Innate immune response
AhR
TSLP
IL-33
IL-1α
IL-36R
Tapinarof
Tezepelumab
Etokimab
REGN3500
Astegolimab
MEDI3506
Bermekimab
Spesolimab
Epidermis
Dermis
Sensory neuron
Janus kinase inhibitors
IL-4
IL-13
IL-5
IL-22
JAK1
JAK3
JAK2
TYK2
Pan-JAKi
Delgocitinib
CEE312
Jaktinib
Cerdulatinib
JAK1/JAK2
Baricitinib
Ruxolitinib
JAK1
Upadacitinib
Abrocitinib
SHR0302
JAK1/TYK2
Brepocitinib
JAK1/JAK3
ATI-1777
Pruritus
Nemolizumab
Vixarelimab
Serlopitant
Tradipitant
BLU-5937
NK1R
IL-31R
P2X3
Adaptive immune response
KY1005
GBR 830
KHK4083
Tralokinumab
Lebrikizumab
Dupilumab
CBP-201
AK120
Branebrutinib
BEN2293
OX40L
OX40
TH2 cell
Dendritic cell
IL-13/IL-4
IL-5
IL-4R/IL-13R
IL-5R
IL-22R
BTK
TRK
LXR
ALX101
Benralizumab
TH22 cell
IL-22
Fezakinumab
LEO138559
ATP
cAMP
5′-AMP
PDE4
Skin cell
T cell migration
Etrasimod
SCD-044
LC51-0255
BMS-986166
KT-474
S1PR
CCR4
RPT193
TH17 cell
IL-17A
Secukinumab
IL-23
Risankizumab
H4R
Treg cell
B cell
IL-2R
mIgE
IgE
LY3471851
Anti-CemX
Omalizumab
Adriforant
LEO 52020
Lotamilast
Difamilast
Roflumilast
DRM02
LEO 29102
PF-07038124
Hemay-808


Dermis
Sensory neuron
Janus kinase inhibitors
IL-4
IL-13
IL-5
IL-22
JAK1
JAK3
JAK1
JAK2
JAK2
JAK2
JAK1
TYK2
Pan-JAKi
• Delgocitinib
• CEE312
• Jaktinib
• Cerdulatinib
JAK1/JAK2
• Baricitinib
• Ruxolitinib
JAK1
• Upadacitinib
• Abrocitinib
• SHR0302
JAK1/TYK2
Brepocitinib
JAK1/JAK3
ATI-1777
Pruritus
• Nemolizumab
• Vixarelimab
• Serlopitant
• Tradipitant
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NK1R
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Adaptive immune response
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• GBR 830
• KHK4083
• Tralokinumab
• Lebrikizumab
• Dupilumab
• CBP-201
• AK120
Branebrutinib
BEN2293
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OX40
TH2 cell
Dendritic cell
IL-13/IL-4
IL-4R/IL-13R
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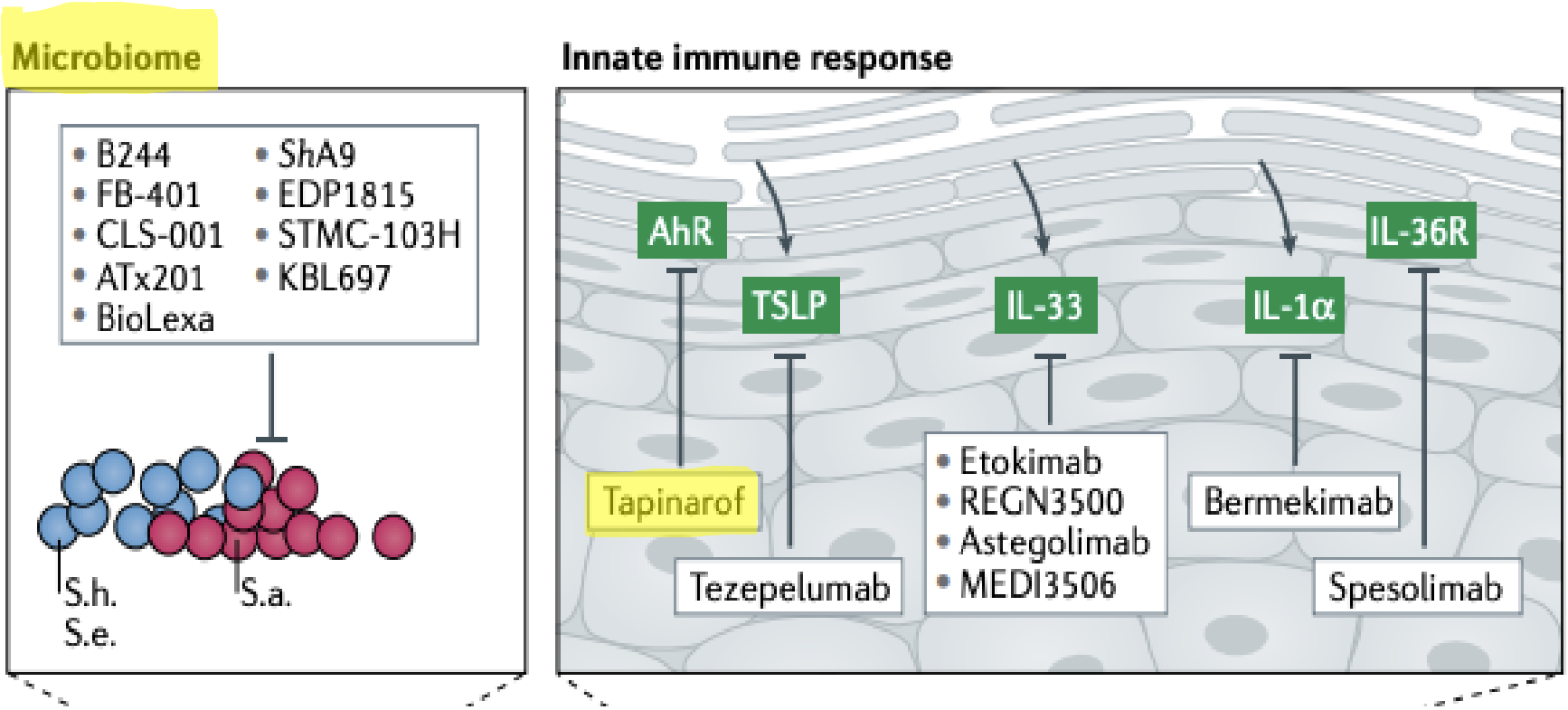
TRK
IL-5
IL-5R
Benralizumab
LXR
TH22 cell
IL-22
IL-22R
ALX101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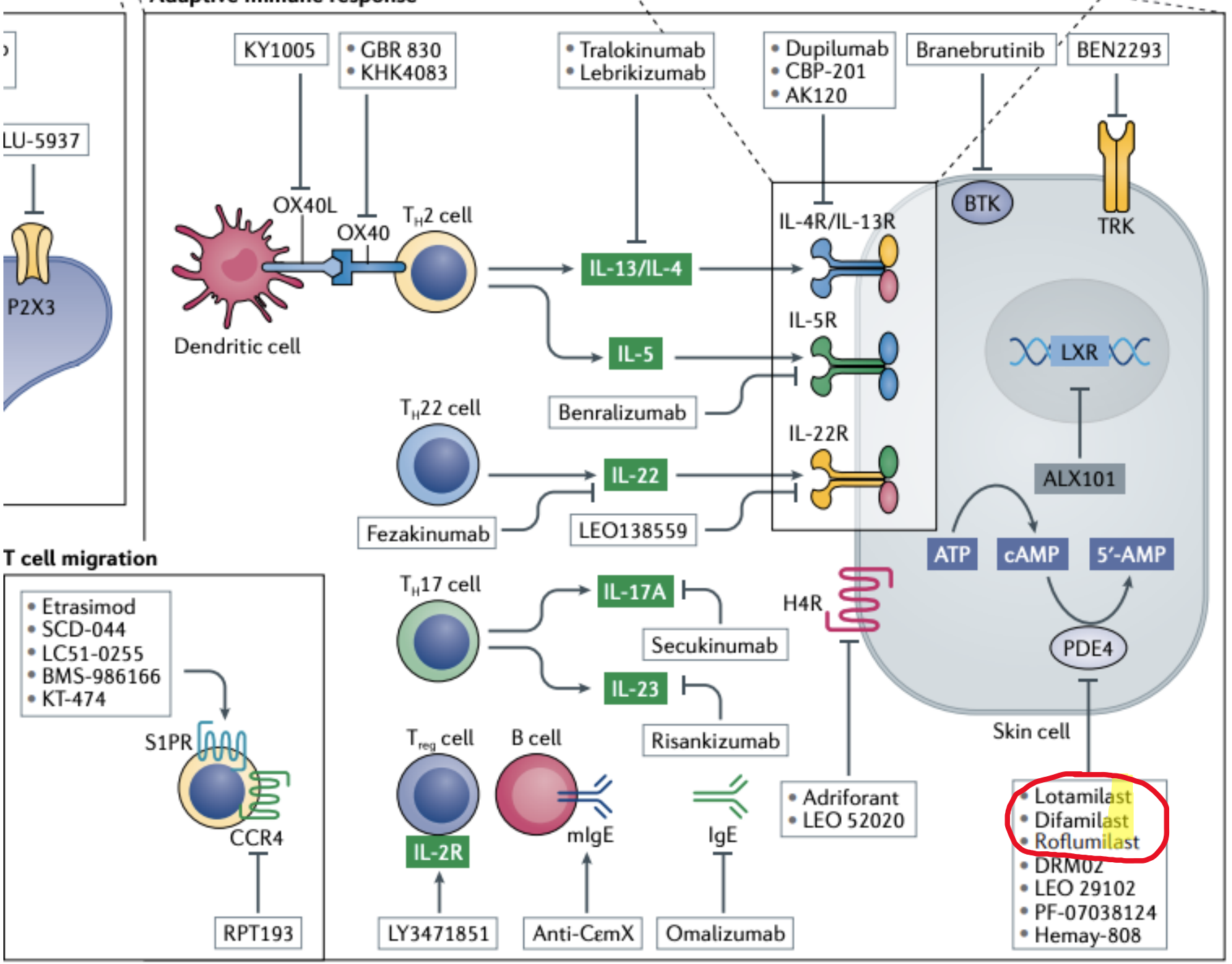
• REGN3500
• Astegolimab
• MEDI3506
Bermekimab
Spesolimab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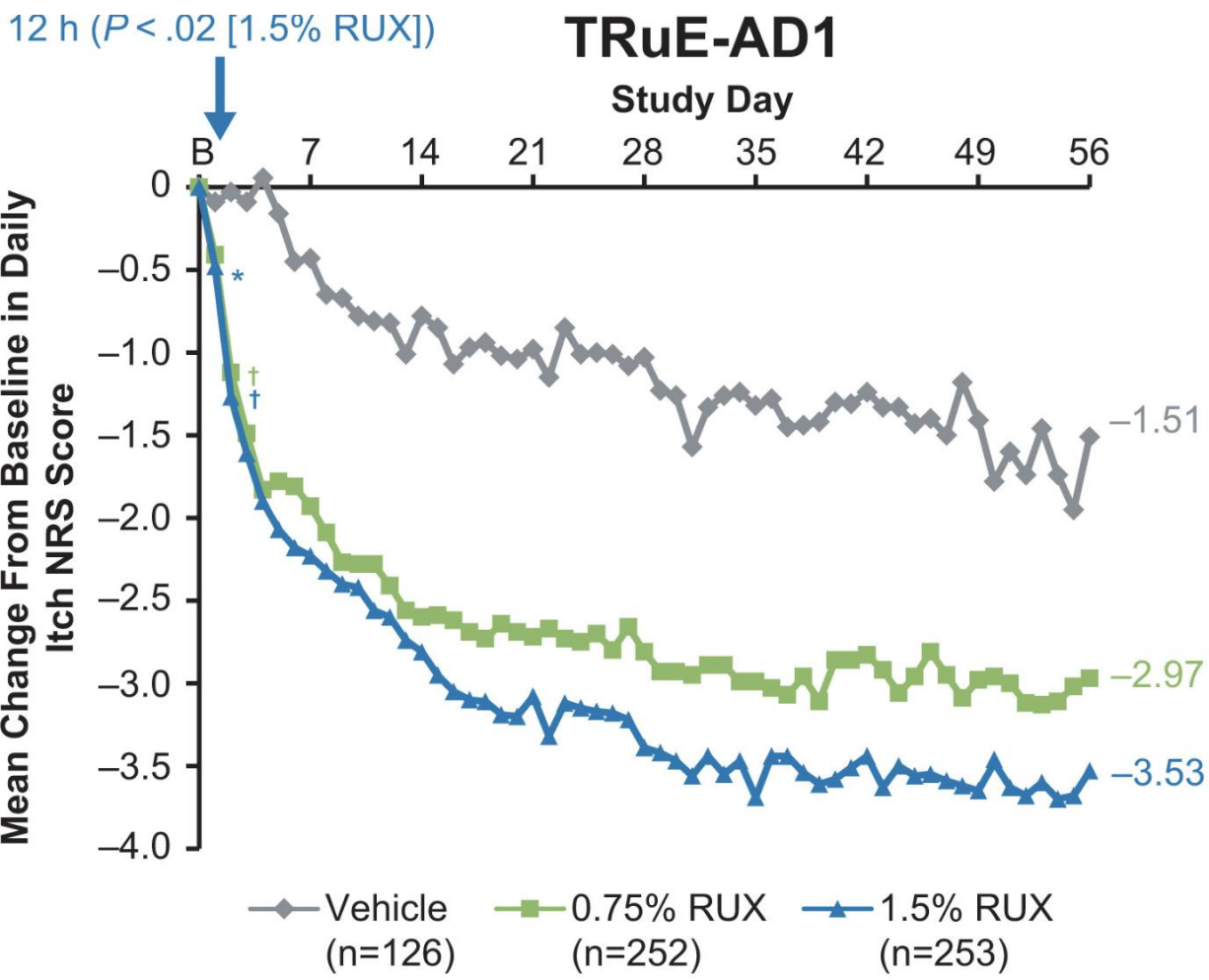
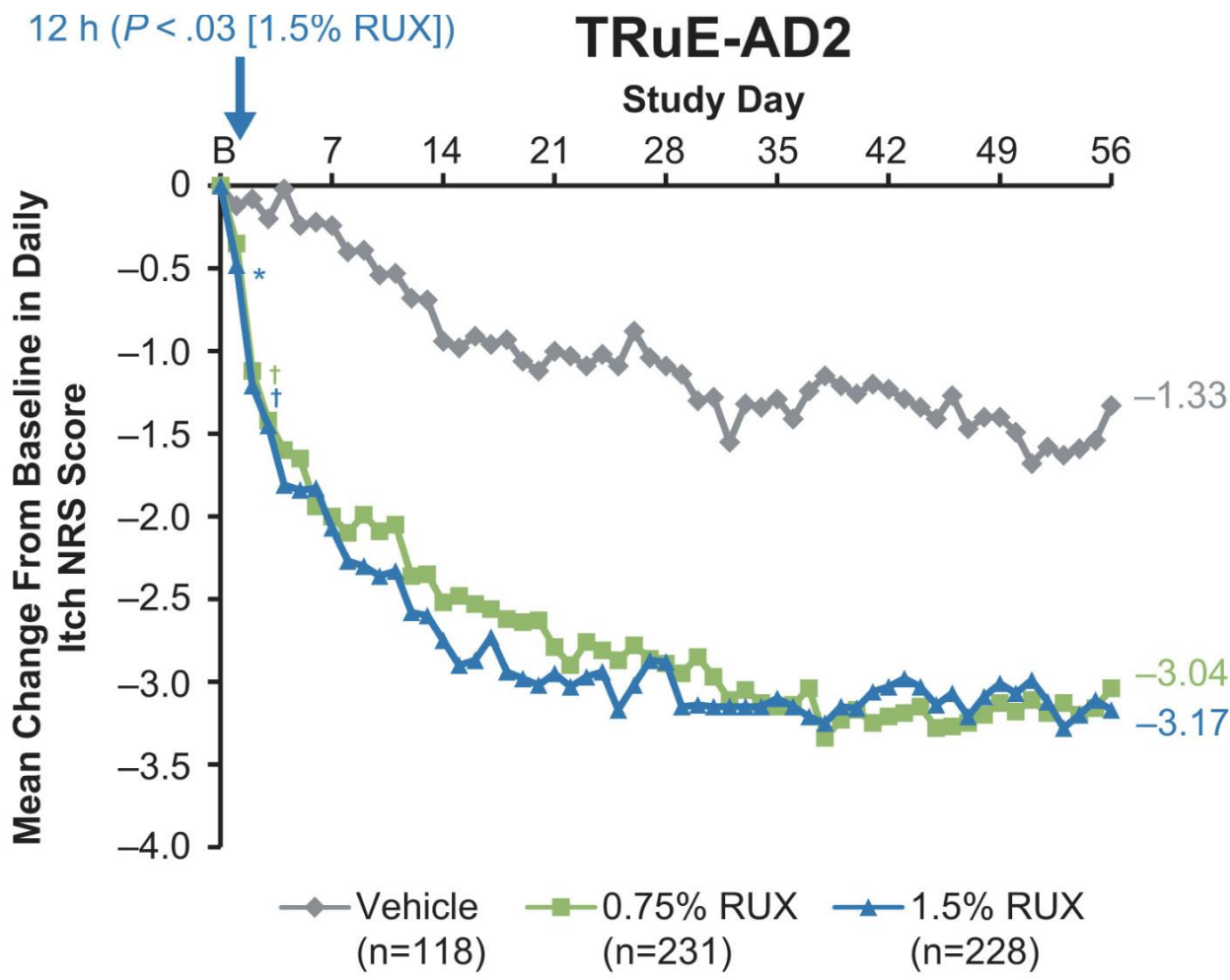
IL-5
Benralizumab
IL-4R/IL-13R
IL-5R
IL-22R
BTK
TRK
LXR
ALX101
T_H22 cell
IL-22
Fezakinumab
LEO138559
ATP
cAMP
5'-AMP
PDE4
Skin cell
T cell migration
Etrasimod
SCD-044
LC51-0255
BMS-986166
KT-474
S1PR
CCR4
RPT193
T_H17 cell
IL-17A
Secukinumab
IL-23
Risankizumab
H4R
Adriforant
LEO 52020
T_{reg} cell
IL-2R
LY3471851
B cell
mIgE
Anti-CεmX
IgE
Omalizumab
Lotamilast
Difamilast
Roflumilast
DRM02
LEO 29102
PF-07038124
Hemay-808

New Topical Therapies for the Treatment of Atopic Dermatitis

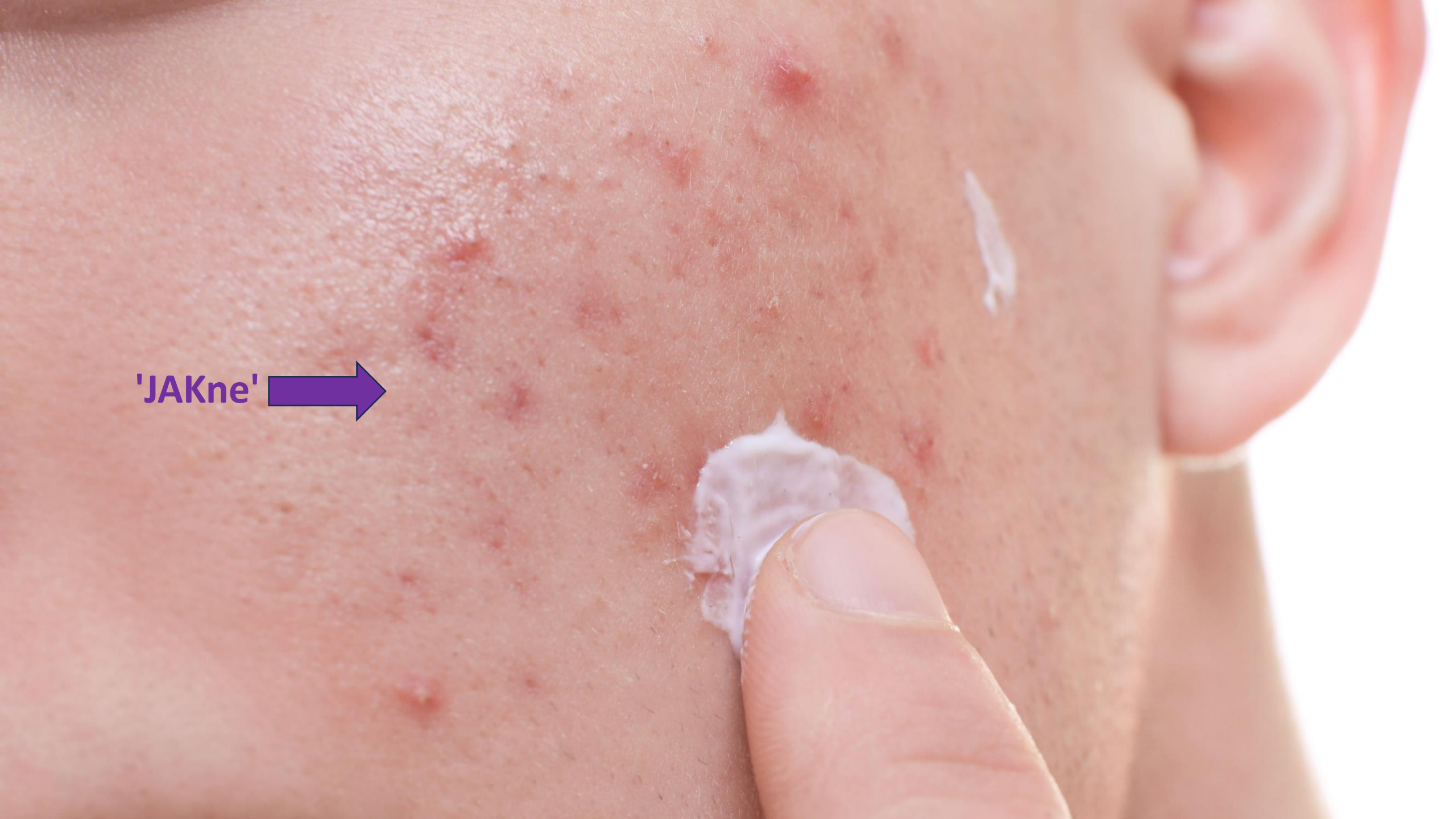
- Ruxolitinib 1.5% cream received FDA approval for treatment of AD in 2021
  - Dual JAK1/2 inhibitor
  - Approved for non-continuous treatment of mild to moderate AD for age ≥12
  - Limit use to no greater than 20% TBSA or 1 tube per week to avoid systemic absorption
- Pooled analysis of TRuE-AD1/TRuE-AD2 trials demonstrate that ruxolitinib significantly improves AD lesions and pruritus as early as Week 2 with steady improvement to week 8
  - EASI-75 at week 8 was achieved by 62.1% and 61.8% on 1.5% cream vs. 24.6% and 14.4% on vehicle ($p<0.05$)
- Rare application site irritation and acneiform eruptions ('Jakne') can occur
  - 15/17 patients (88.2%) with a reported location had facial involvement
  - Mild to moderate in severity



Number of Patients	Day 14	Day 28	Day 56
Vehicle	105	94	59
0.75% RUX	208	199	146
1.5% RUX	218	220	158



Number of Patients	Day 14	Day 28	Day 56
Vehicle	99	96	64
0.75% RUX	190	86	129
1.5% RUX	190	184	149


'JAKne'

Guidelines of care for the management of atopic dermatitis in adults with topical therapies

- Strong Evidence Supports use of:
  - Topical corticosteroids
  - Topical calcineurin inhibitors
    - Pimecrolimus 1%
    - Tacrolimus 0.1 and 0.03%
  - Topical PDE4i
    - Crisaborole 2% ointment
    - (Roflumilast/Difamilast)?
  - Topical JAKi
    - Ruxolitinib 1.5% cream
    - (Delgocitinib)?

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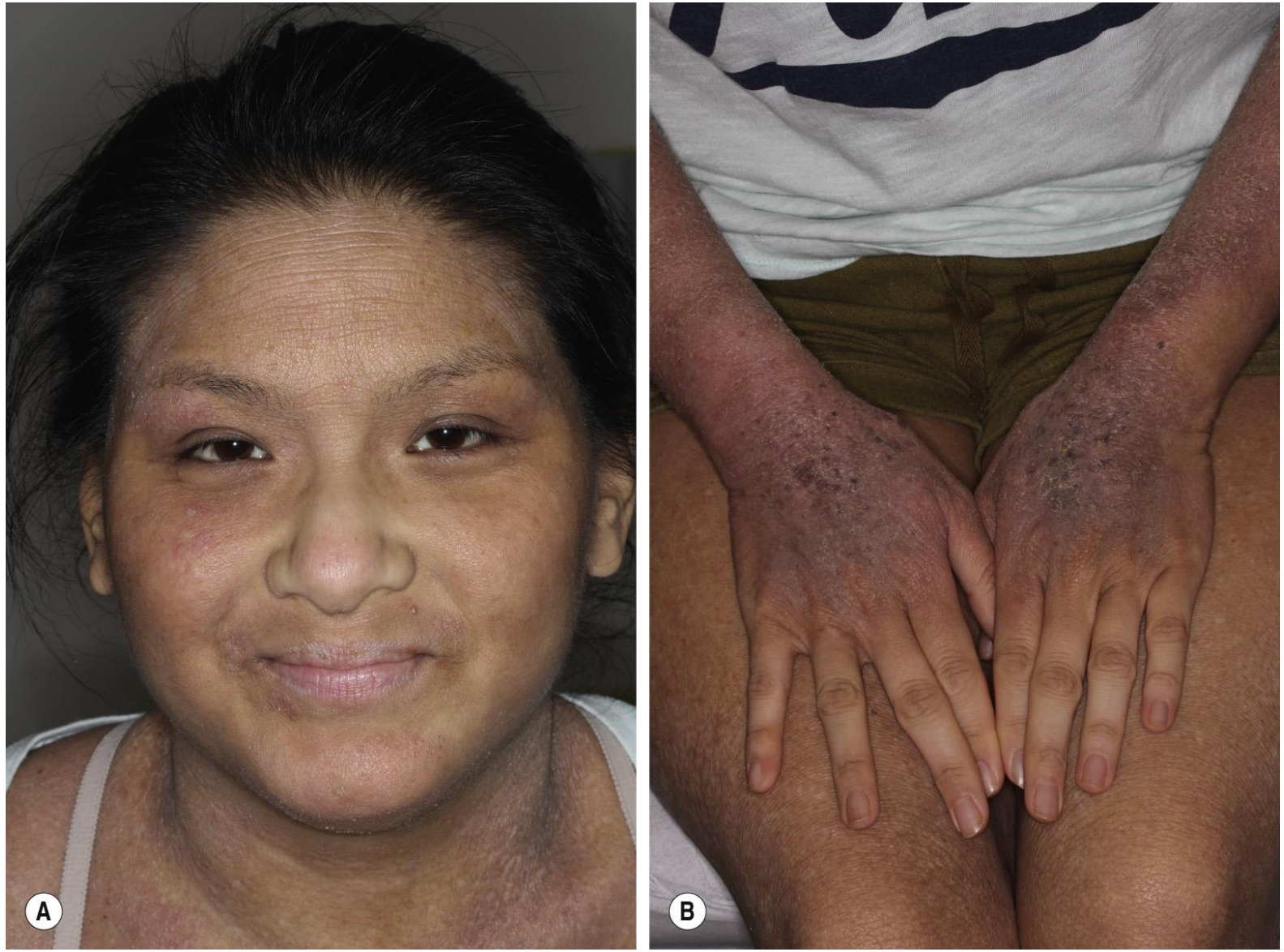
J Am Acad Dermatol. 2023 Jul 89(1):e1-e20.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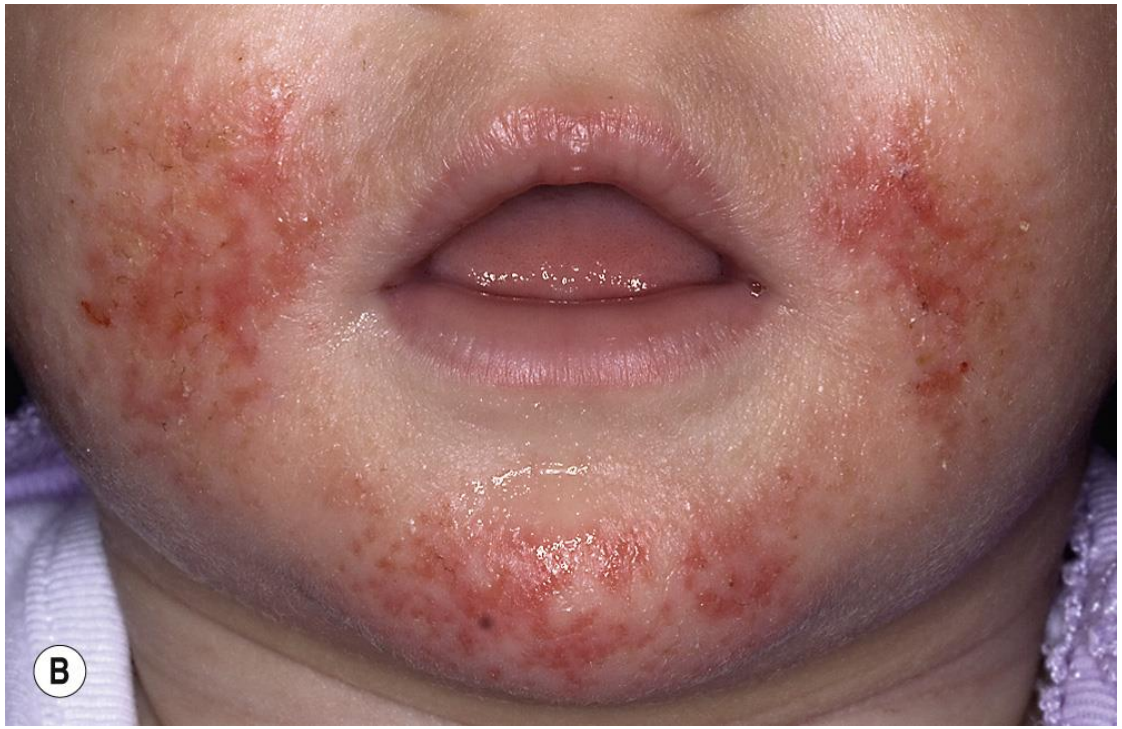
B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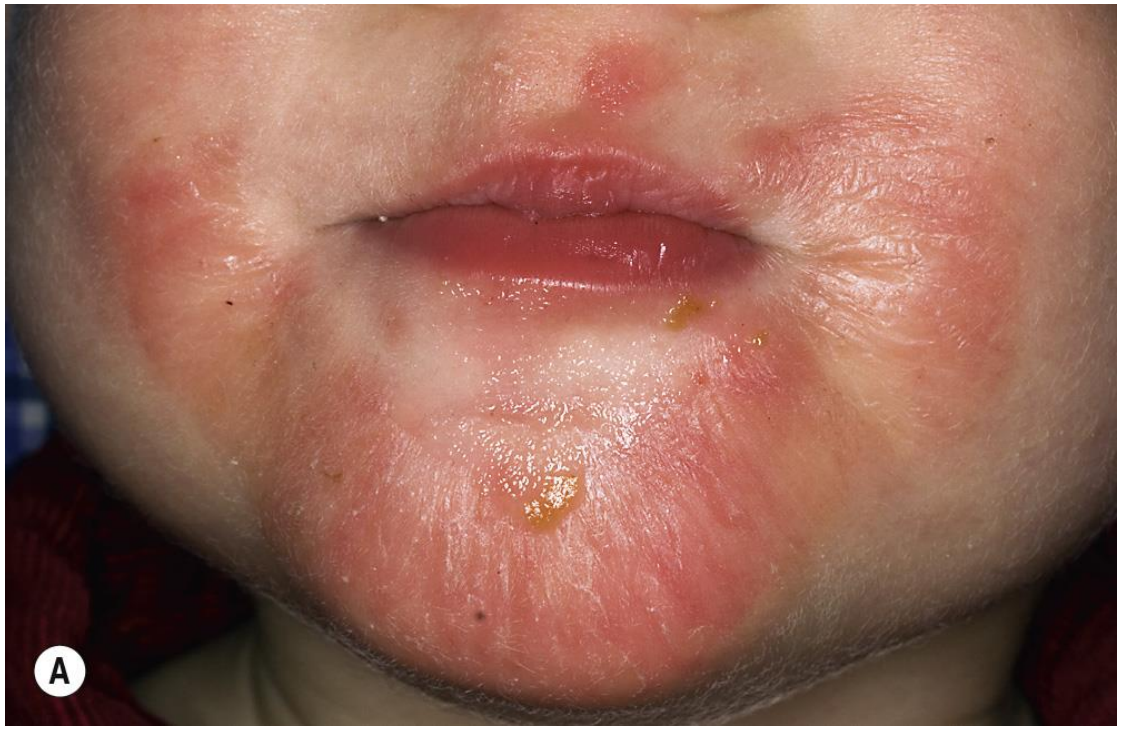
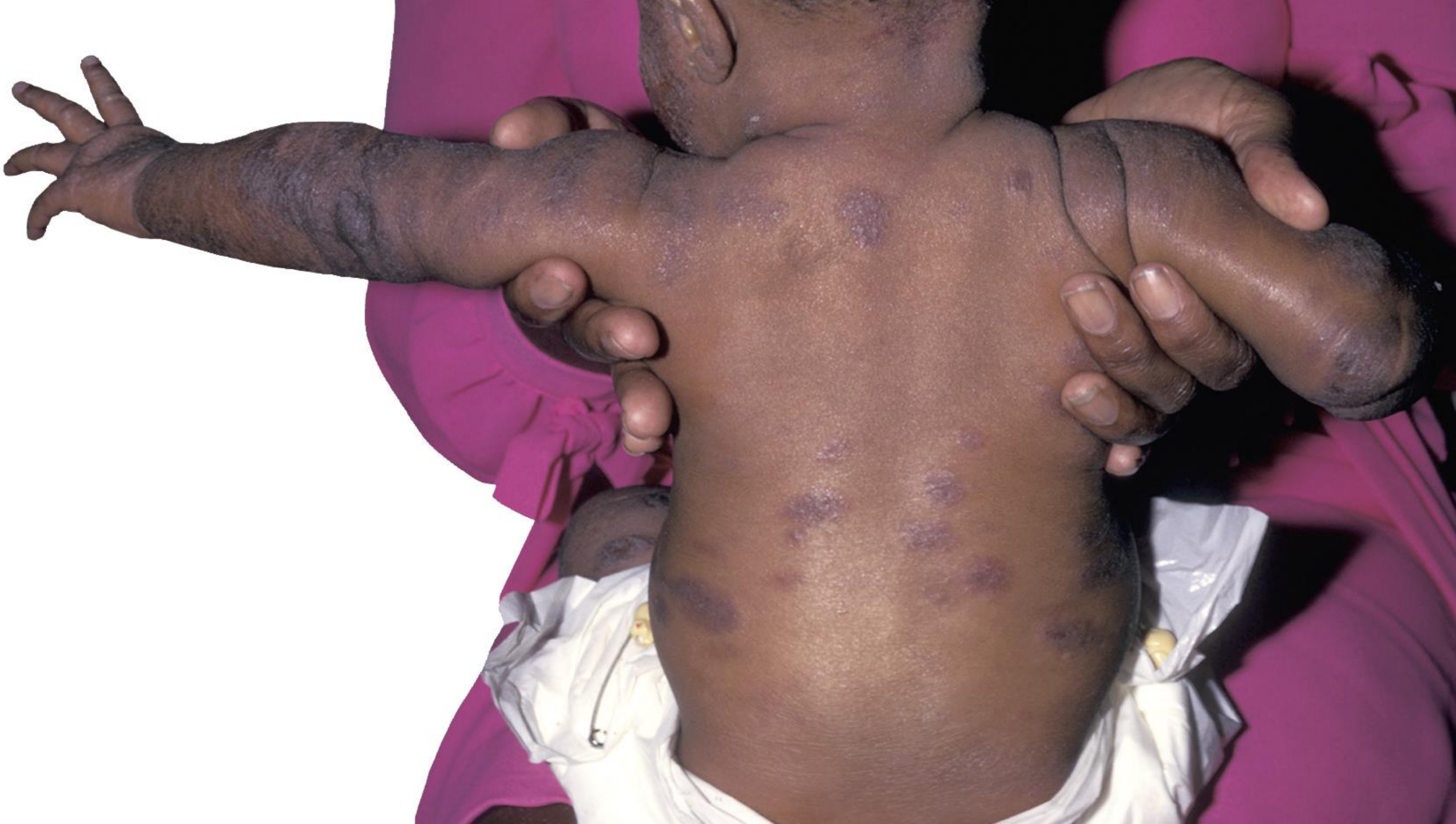
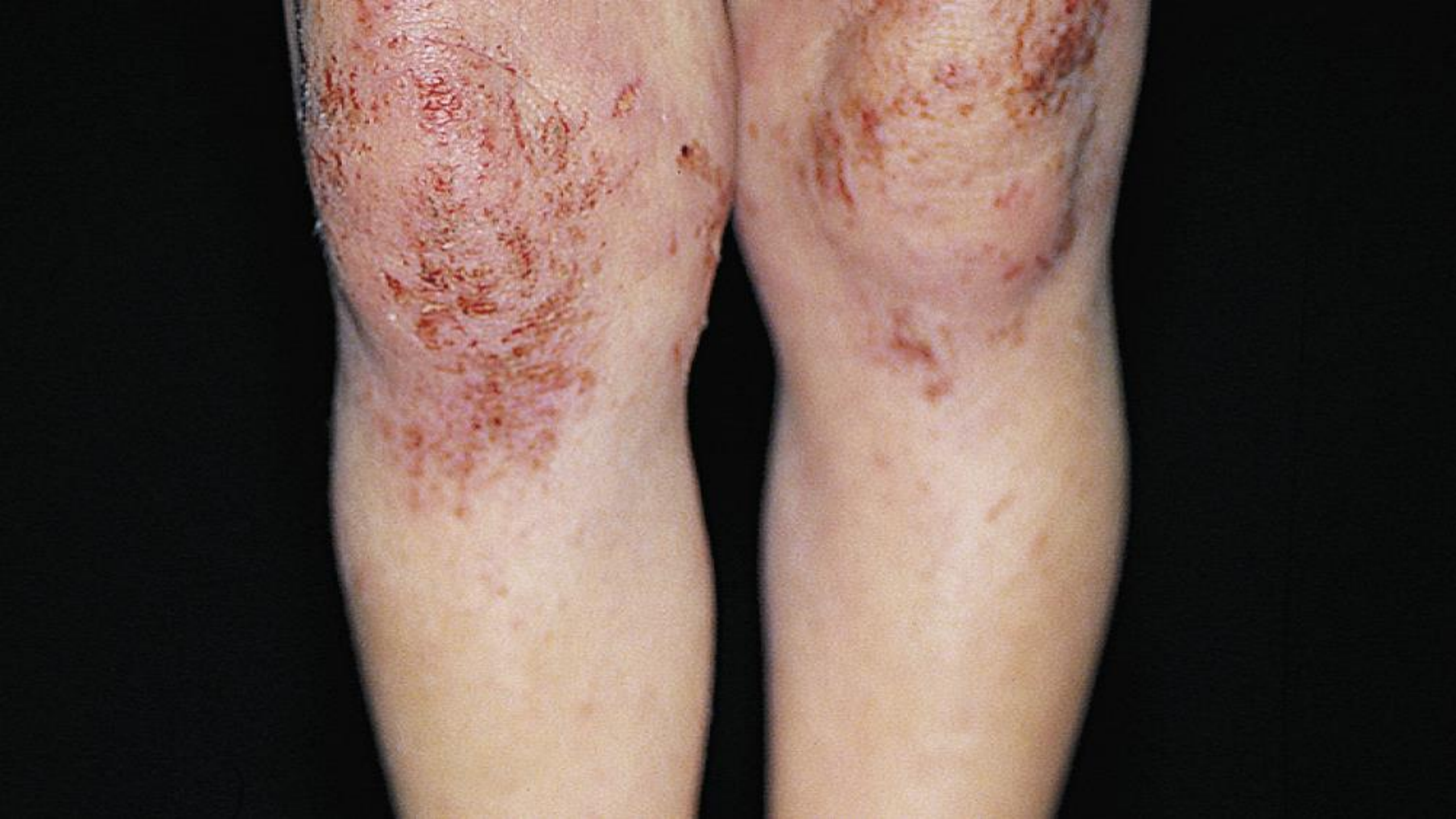
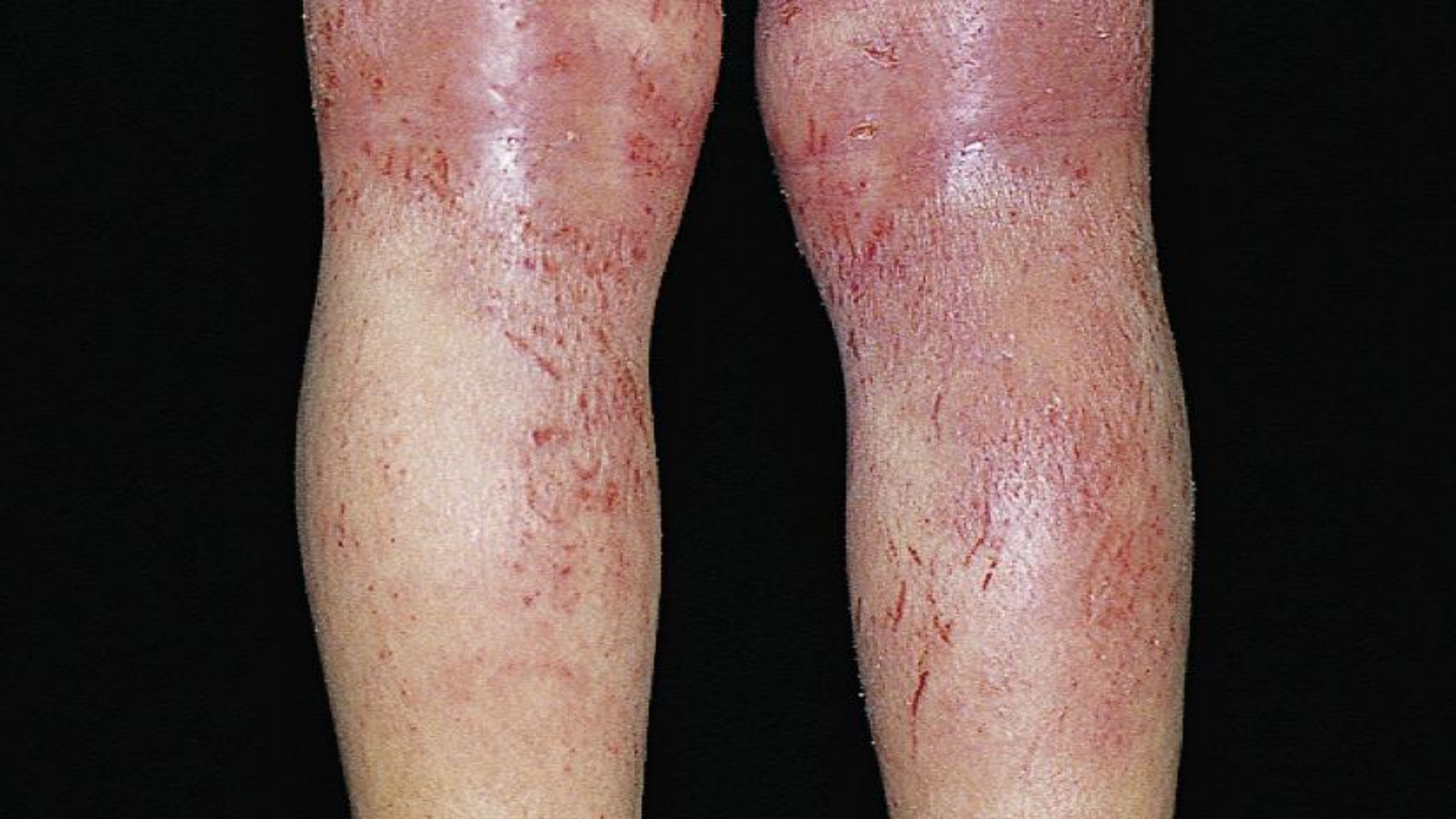
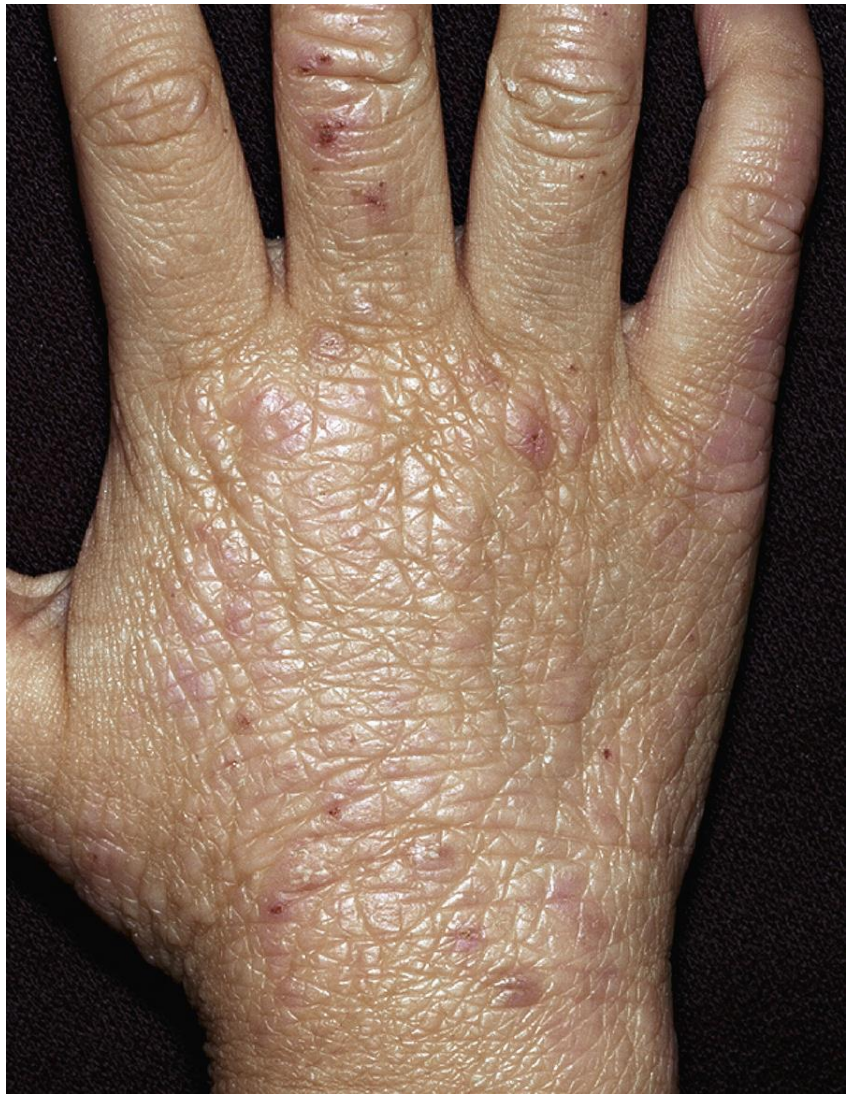
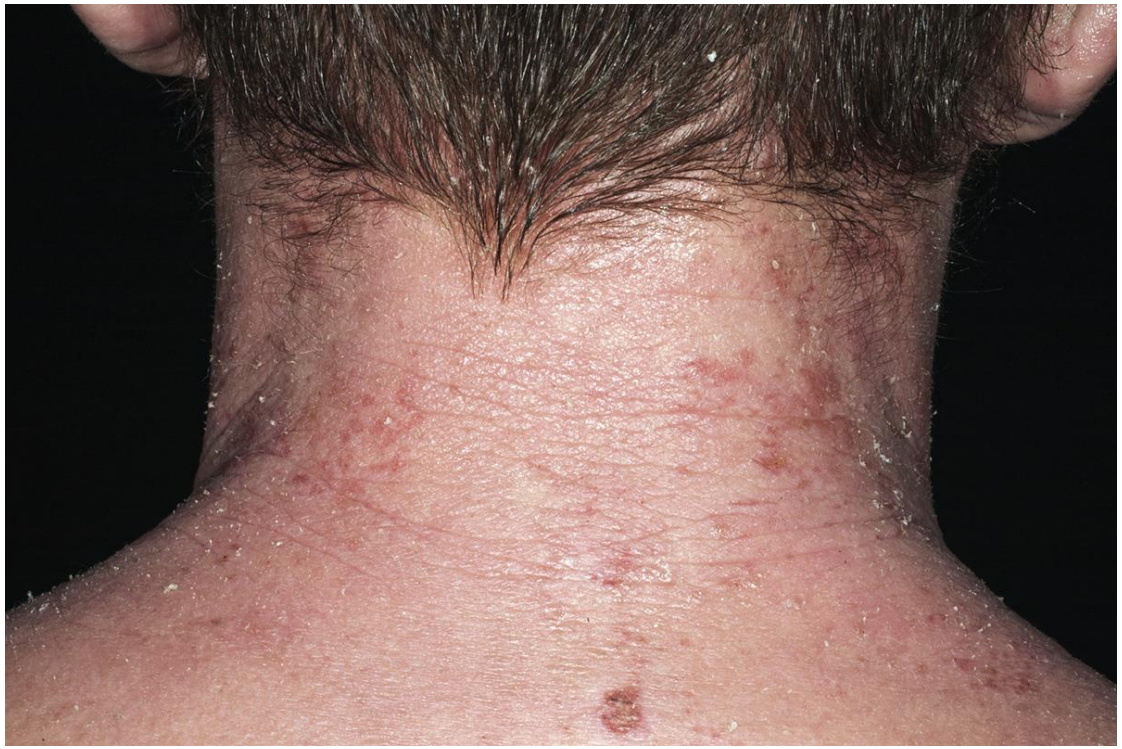

A

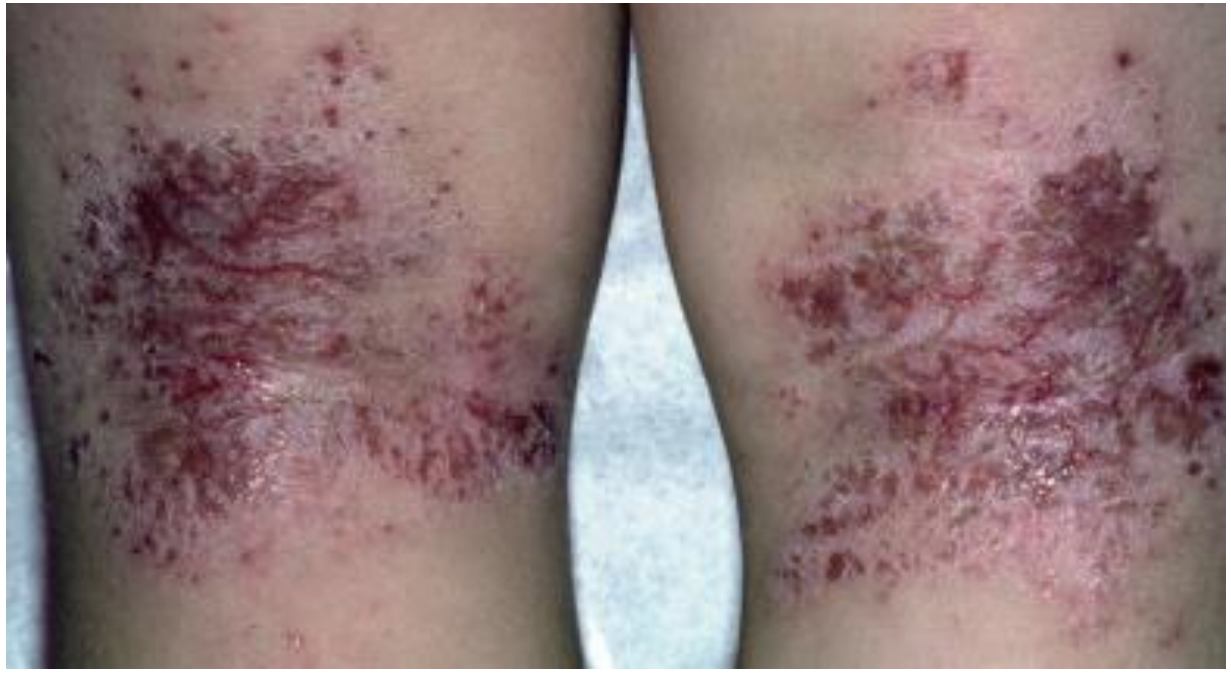


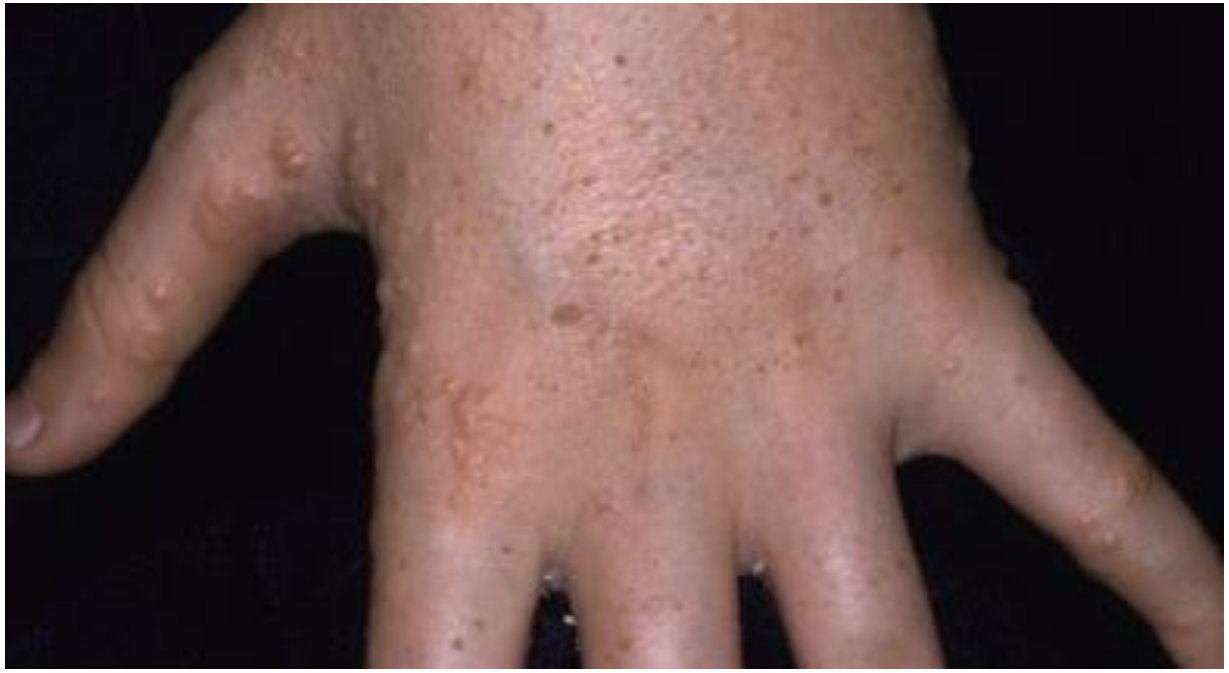


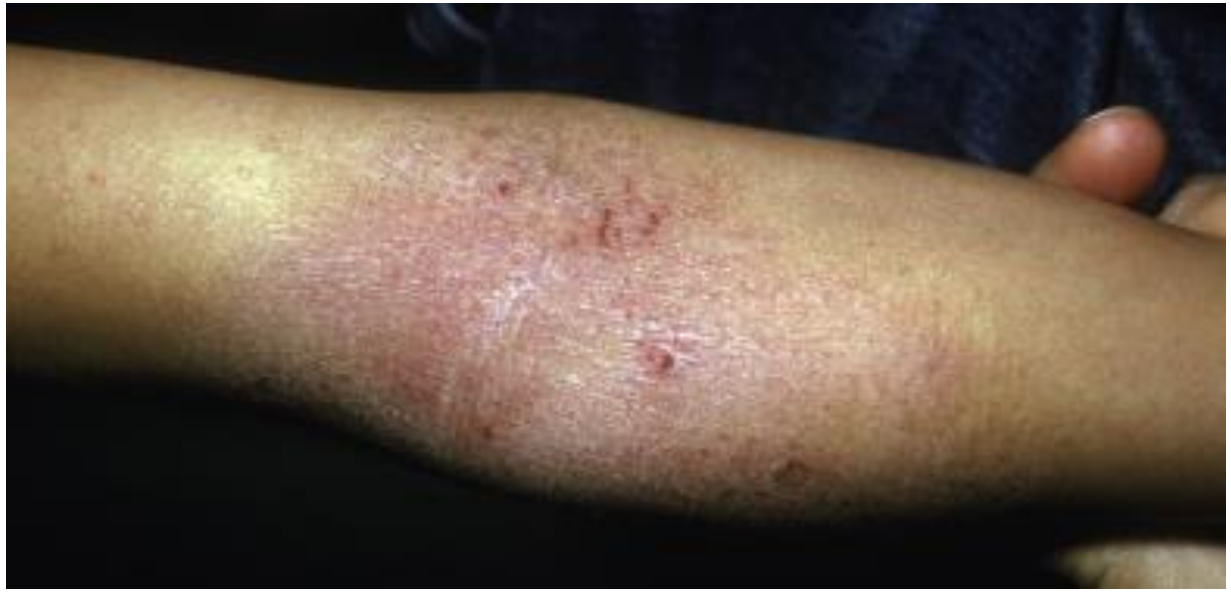


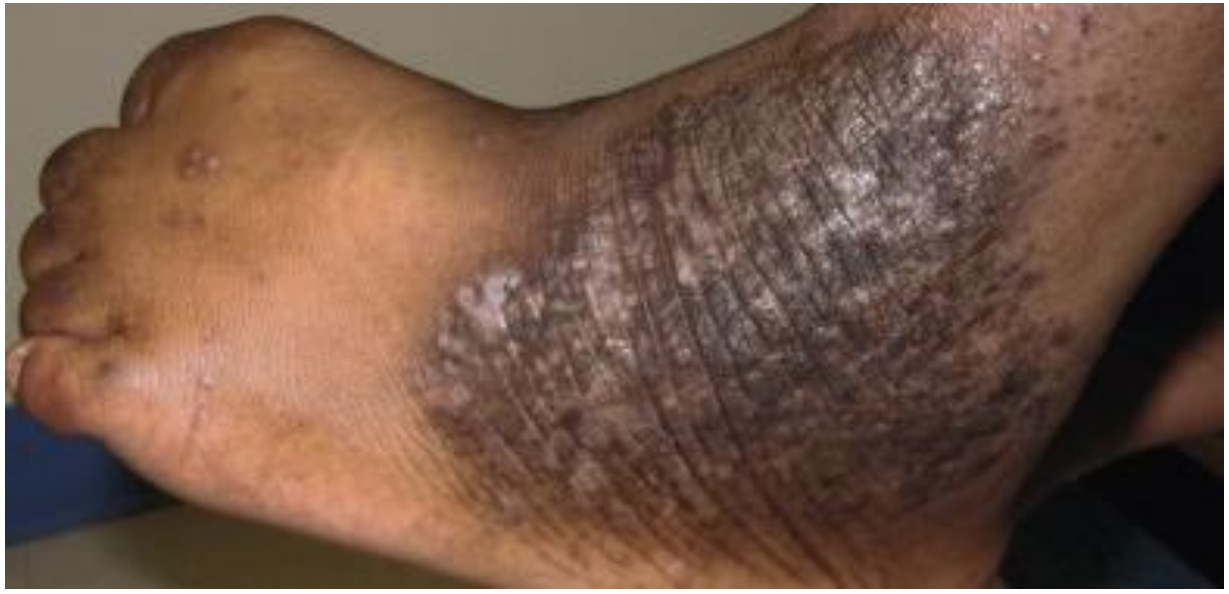


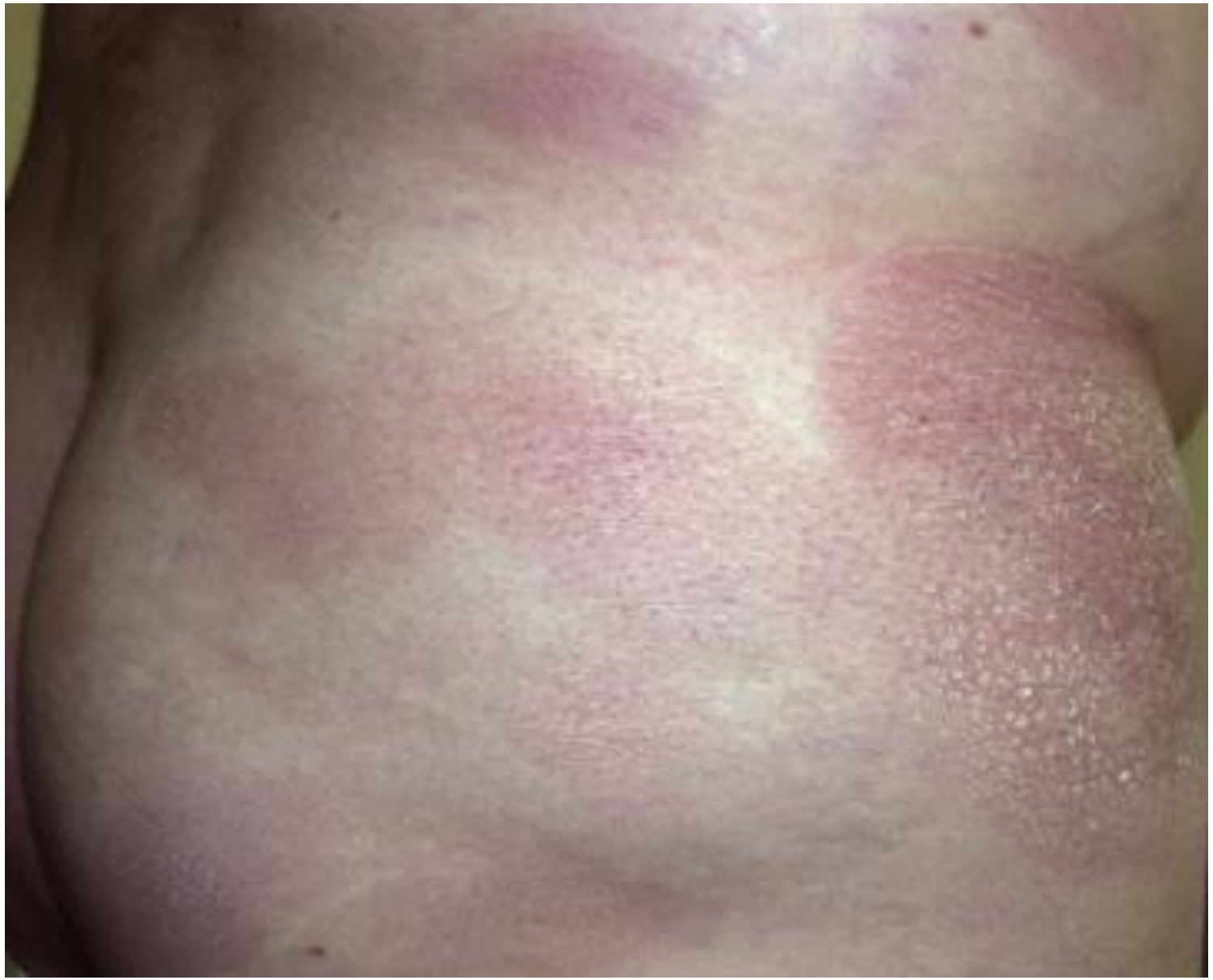


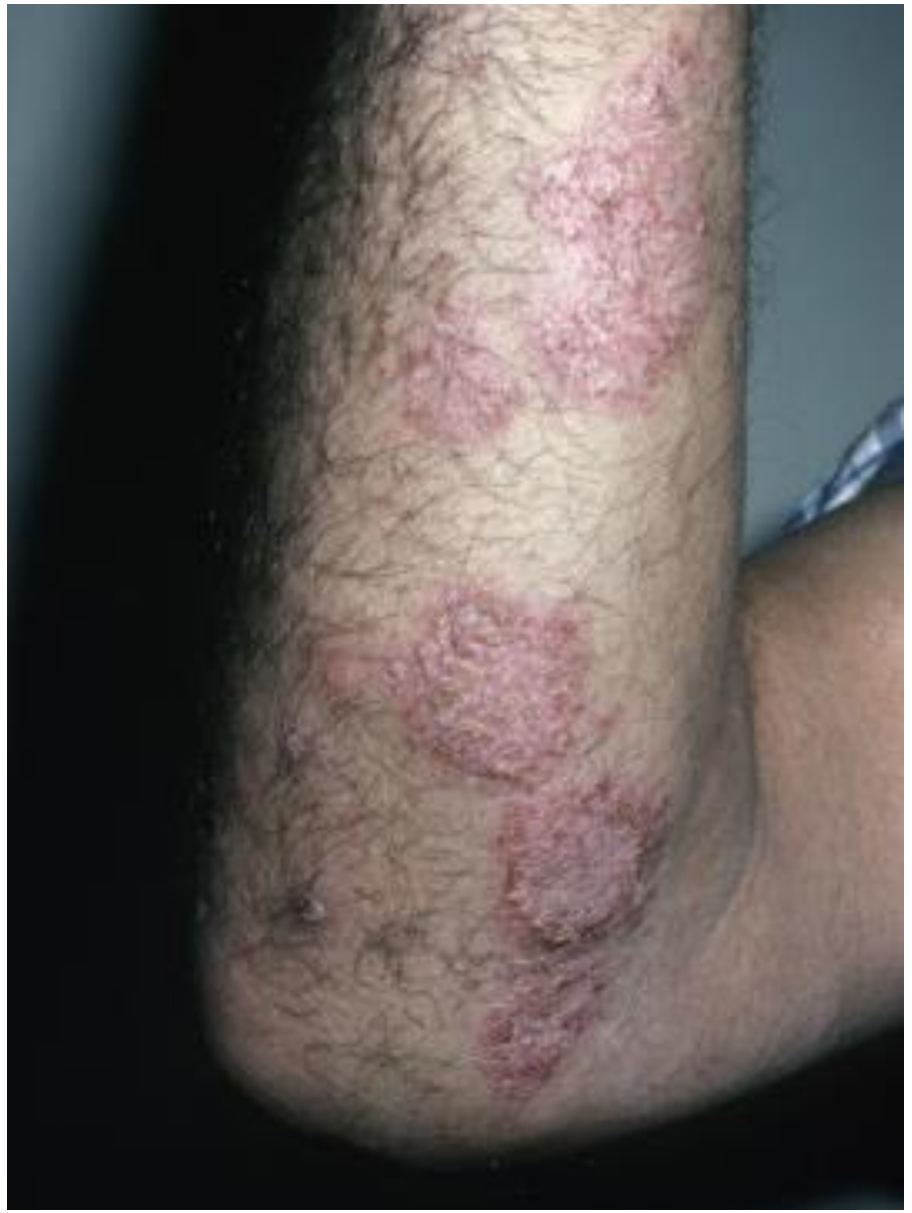


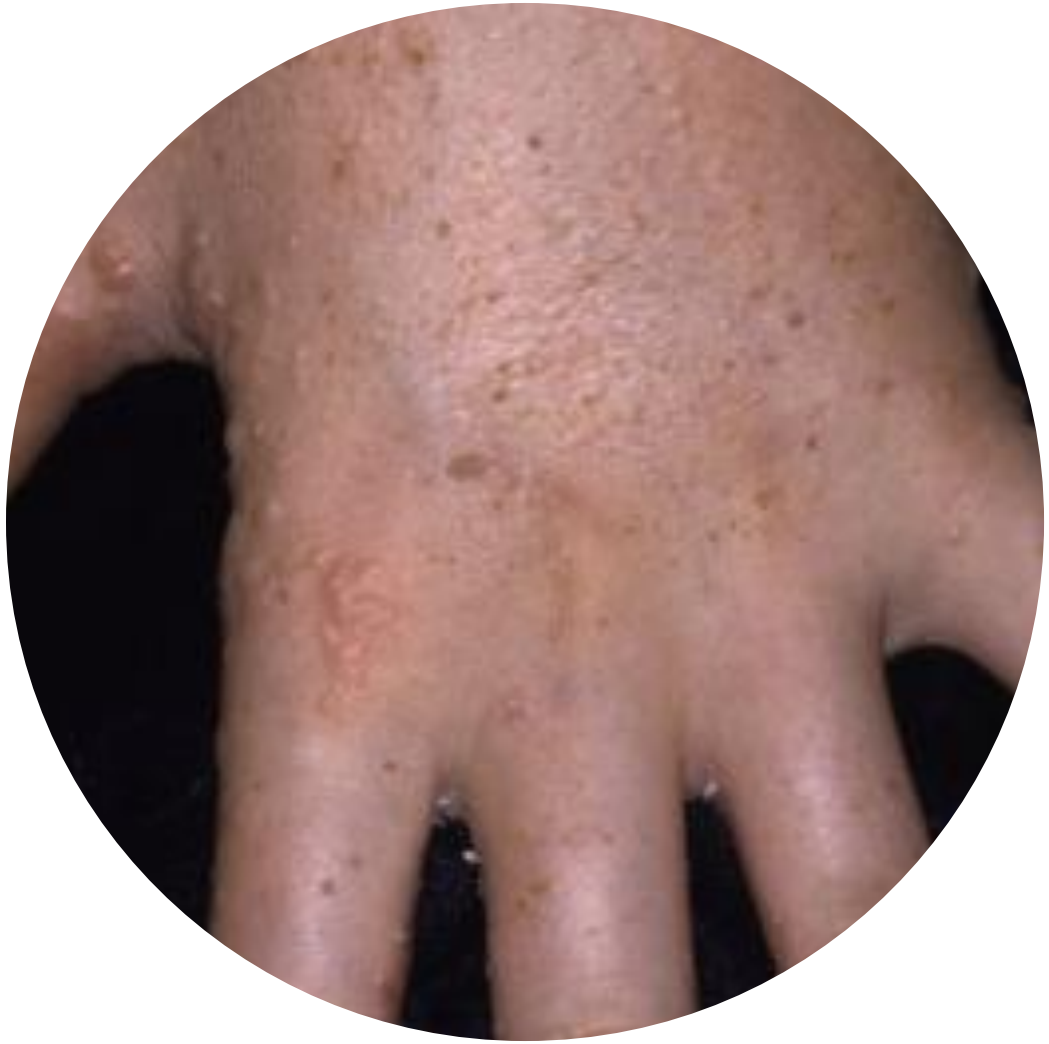


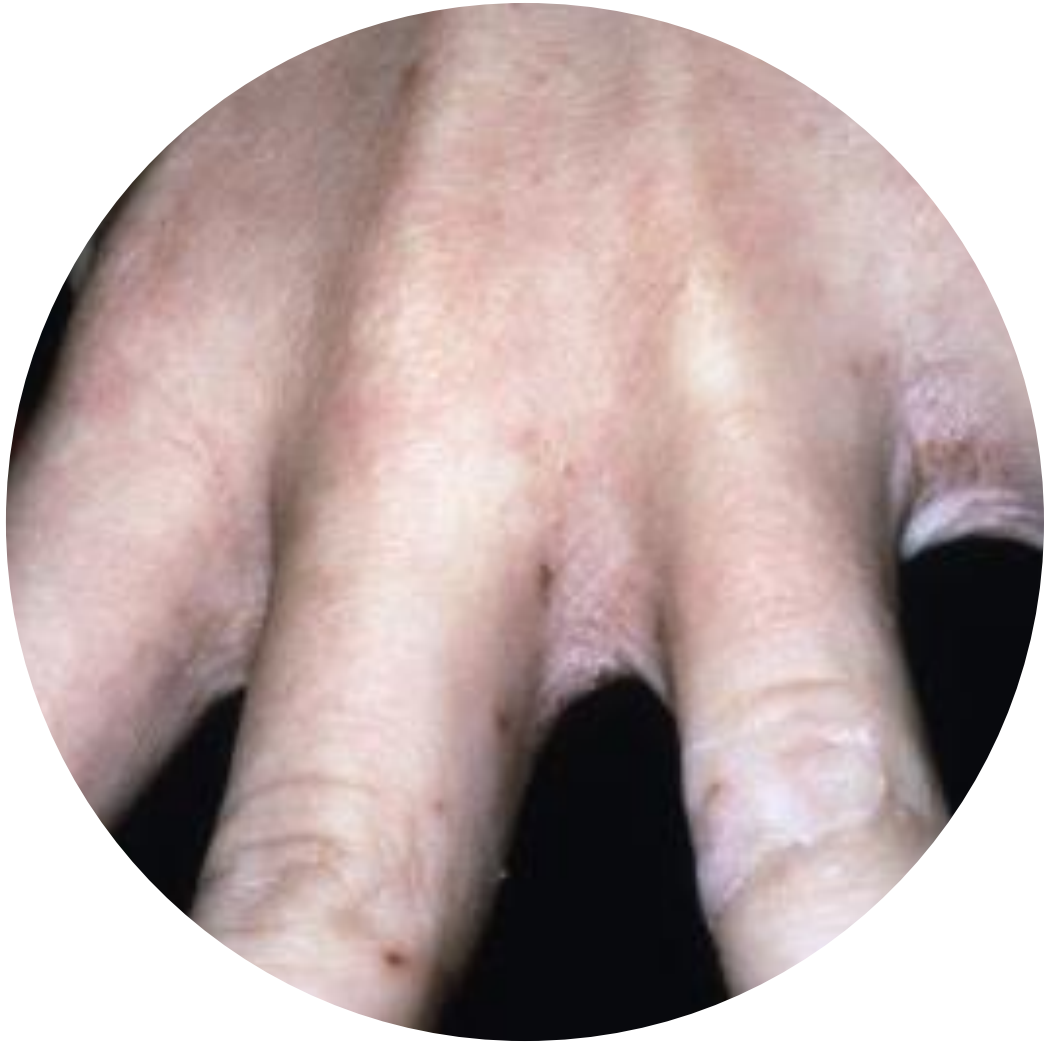




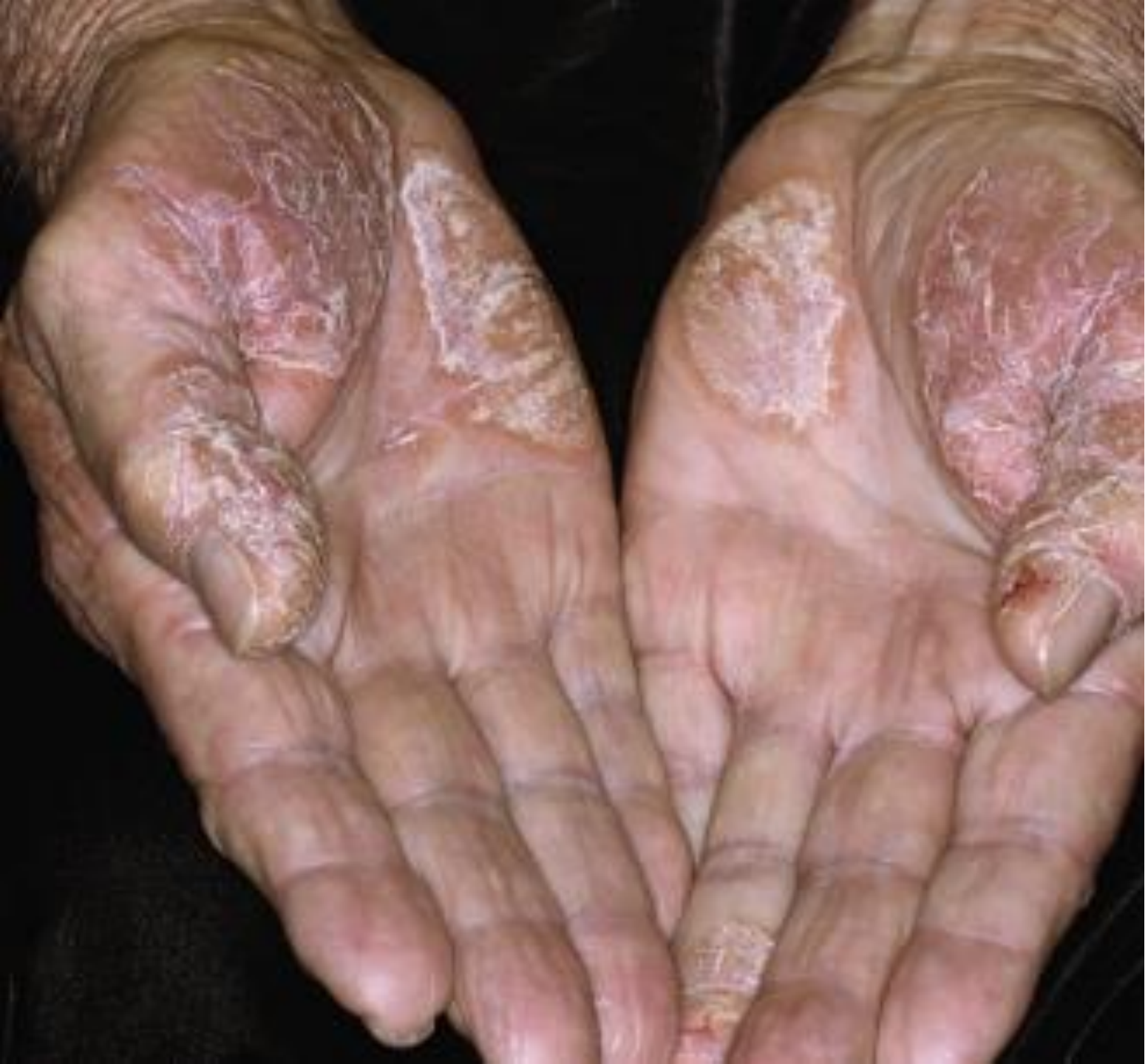


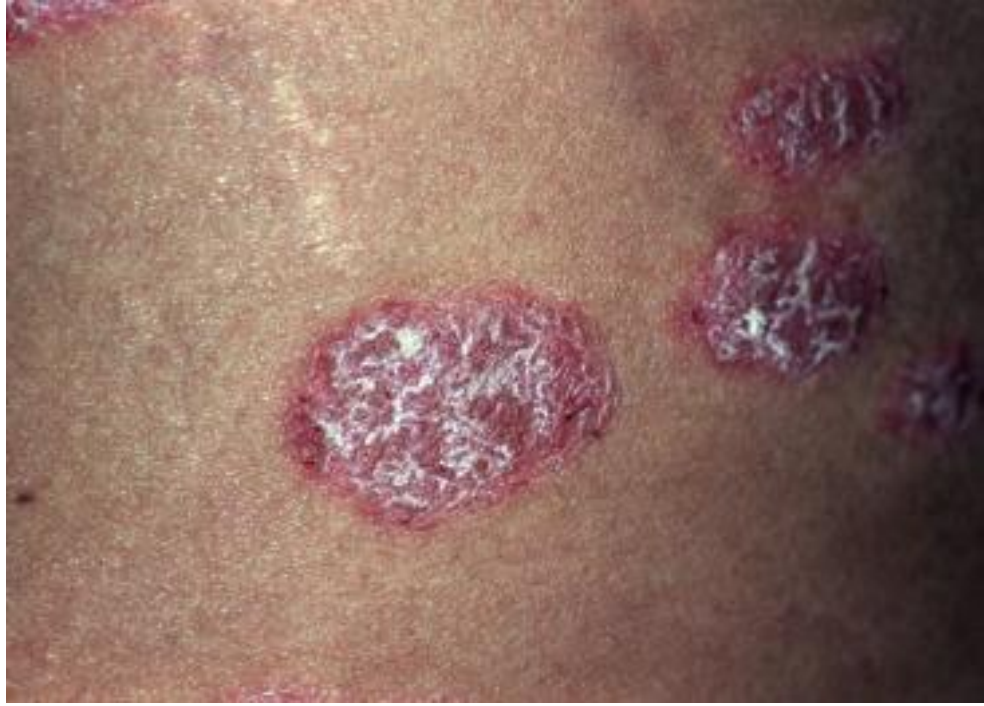


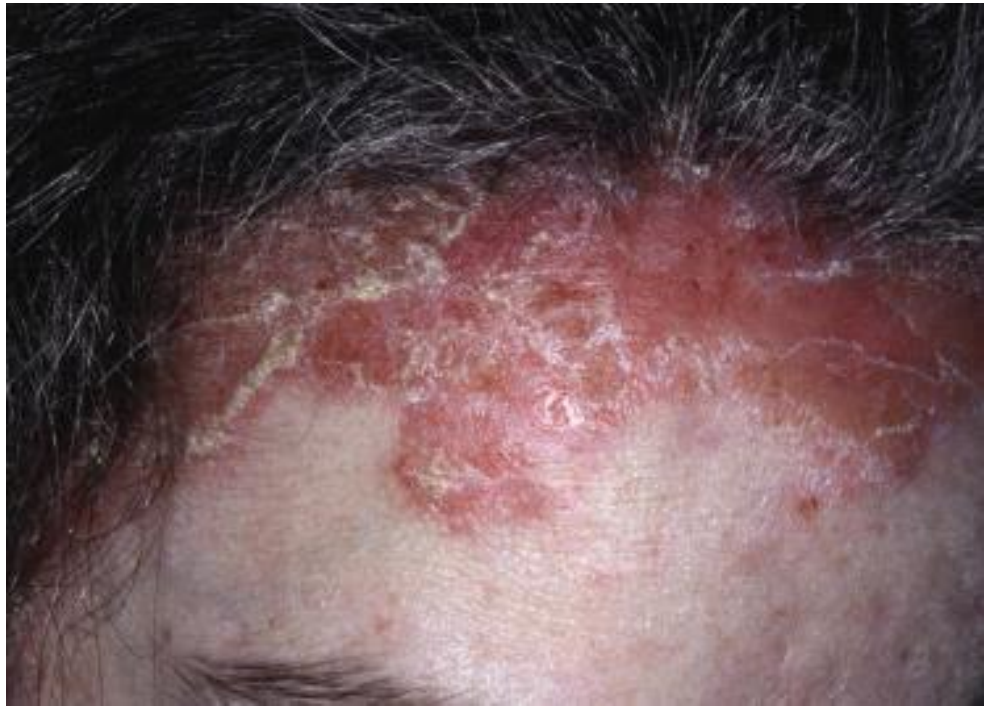


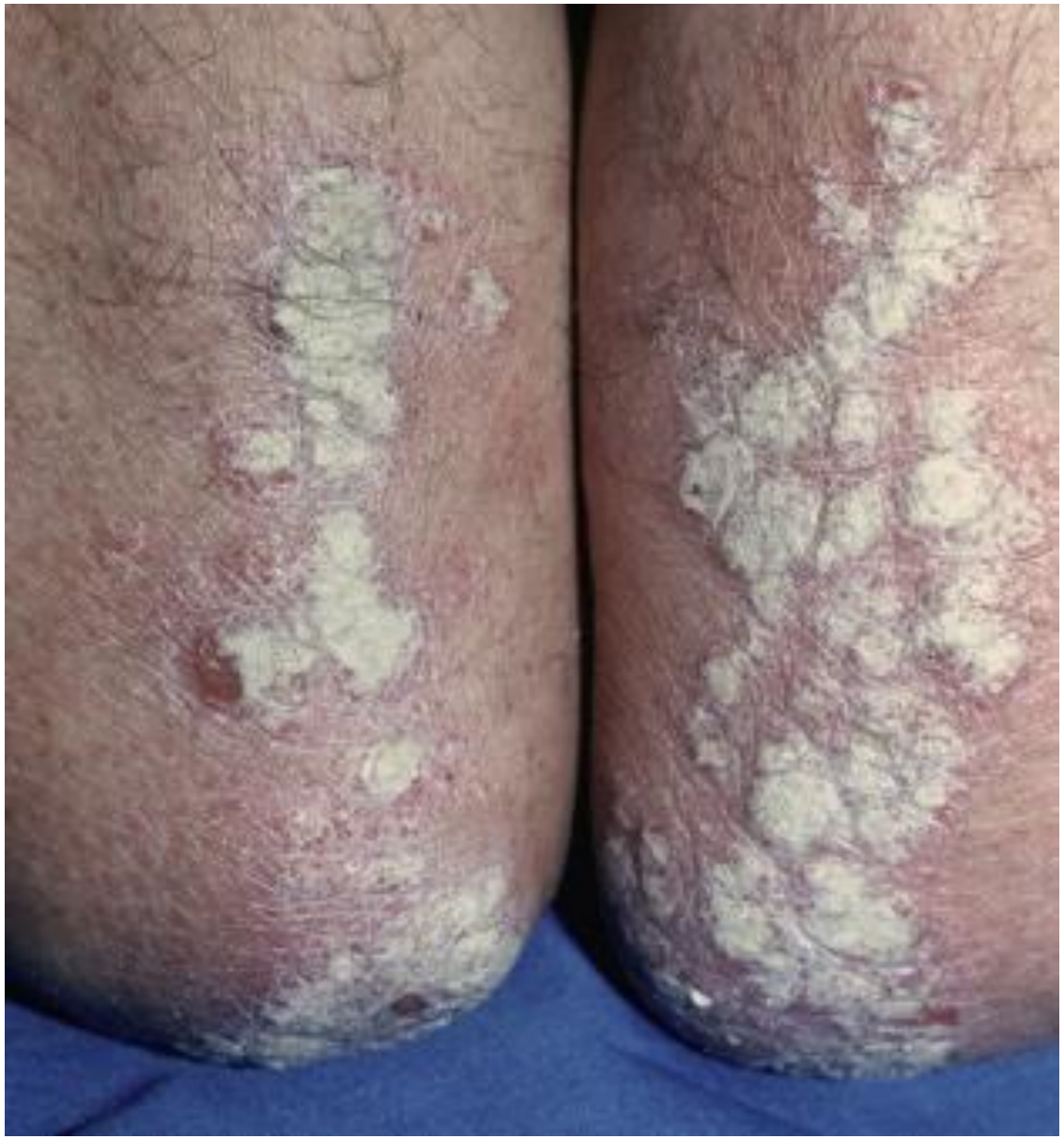


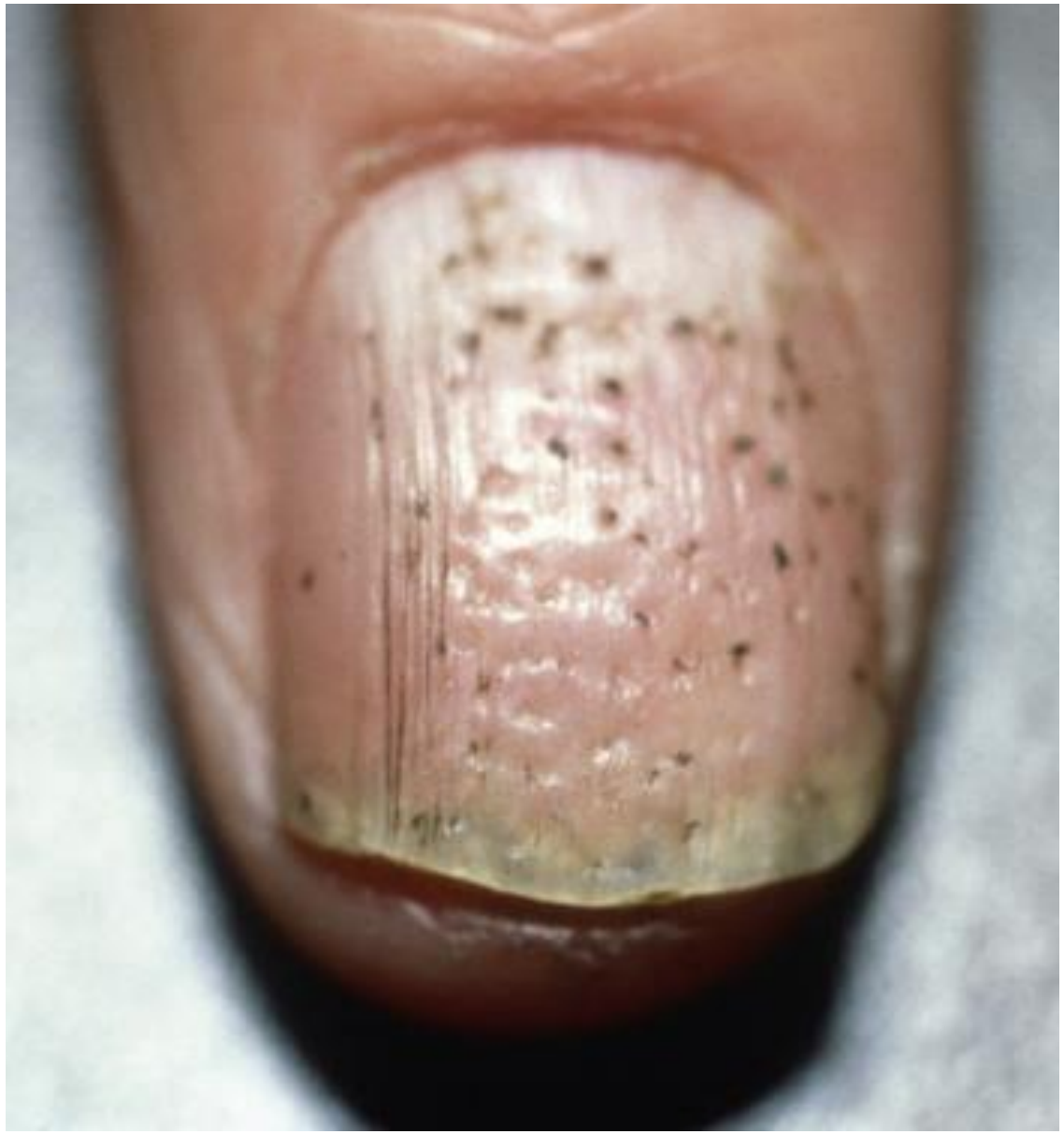

LOUIS
VUITON

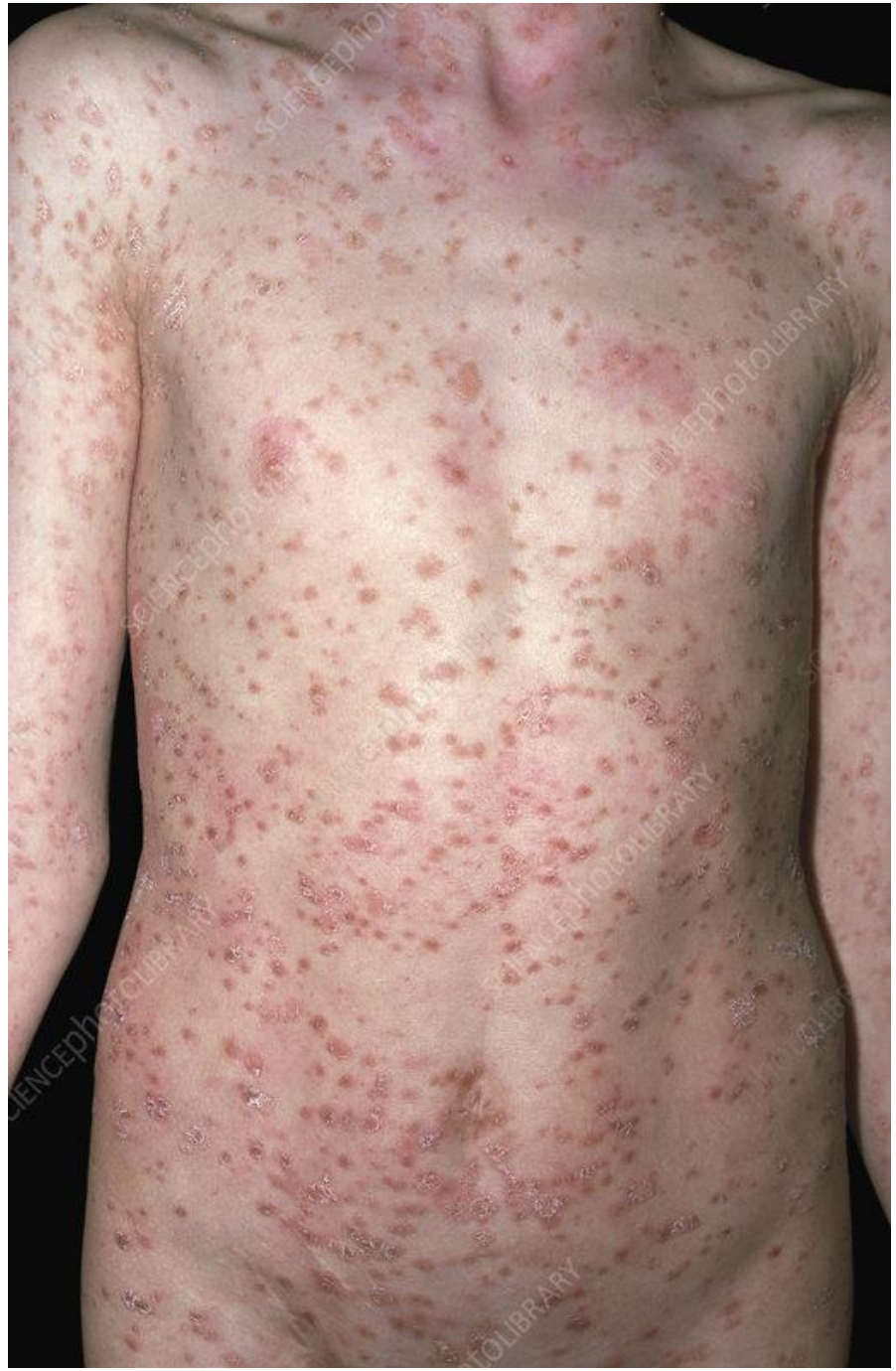


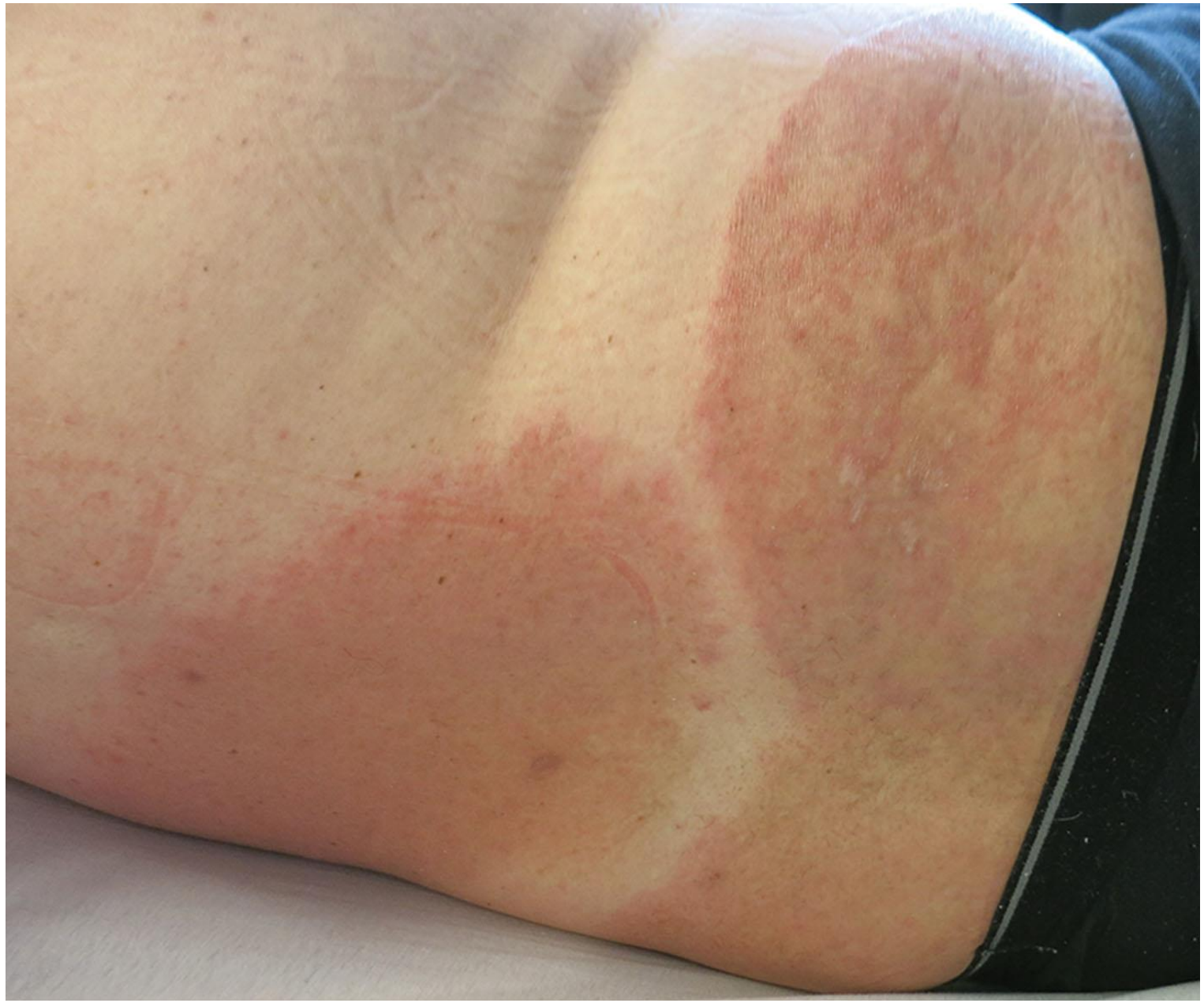


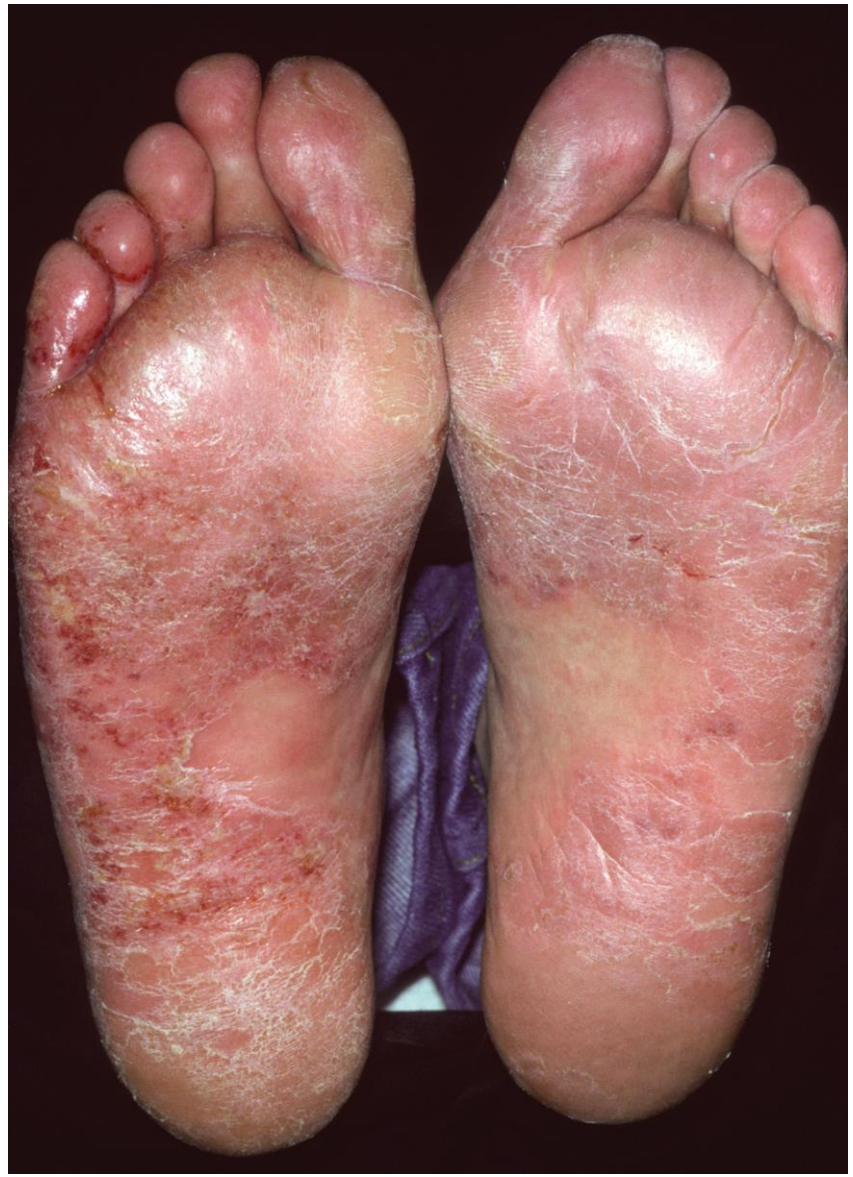


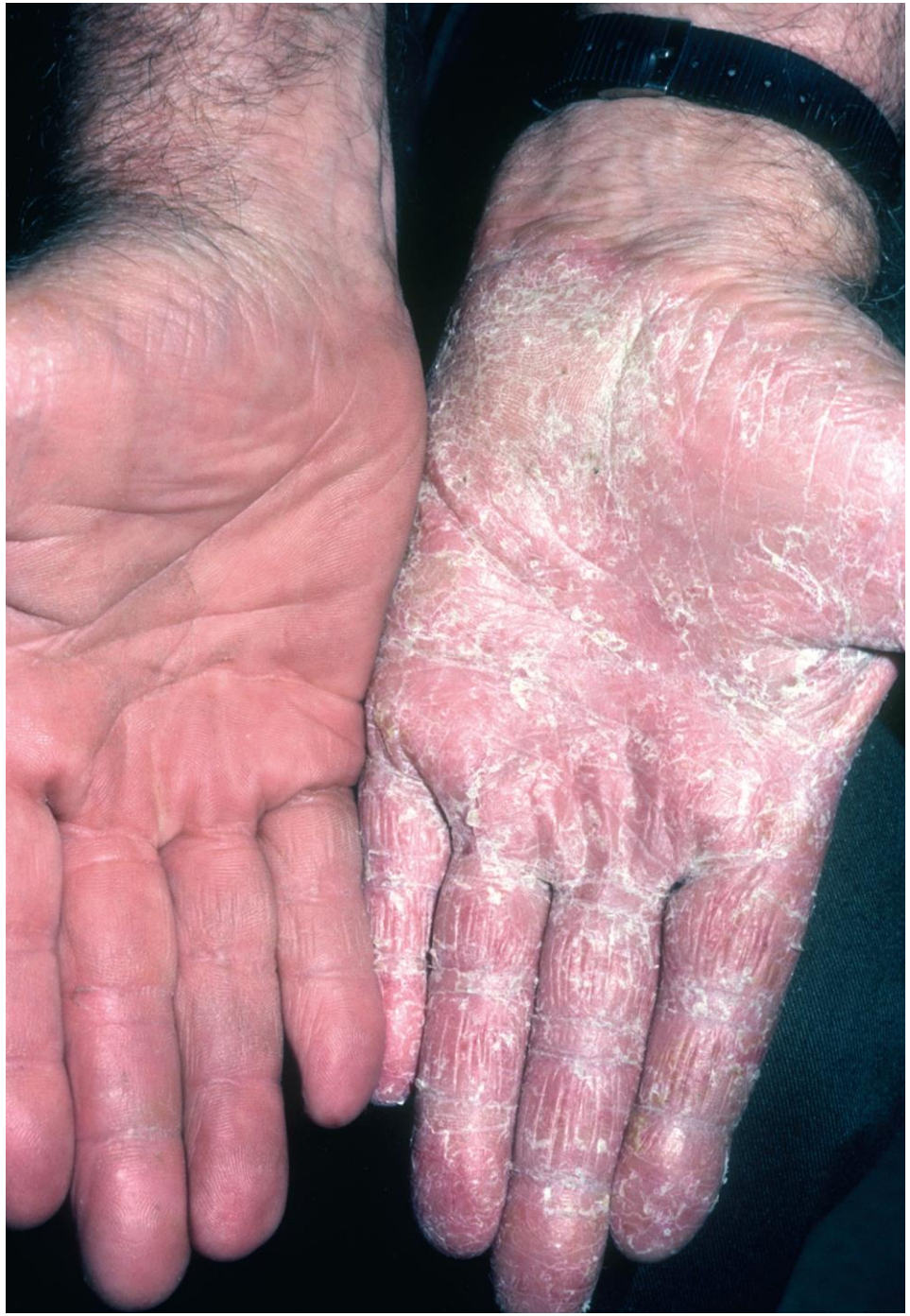






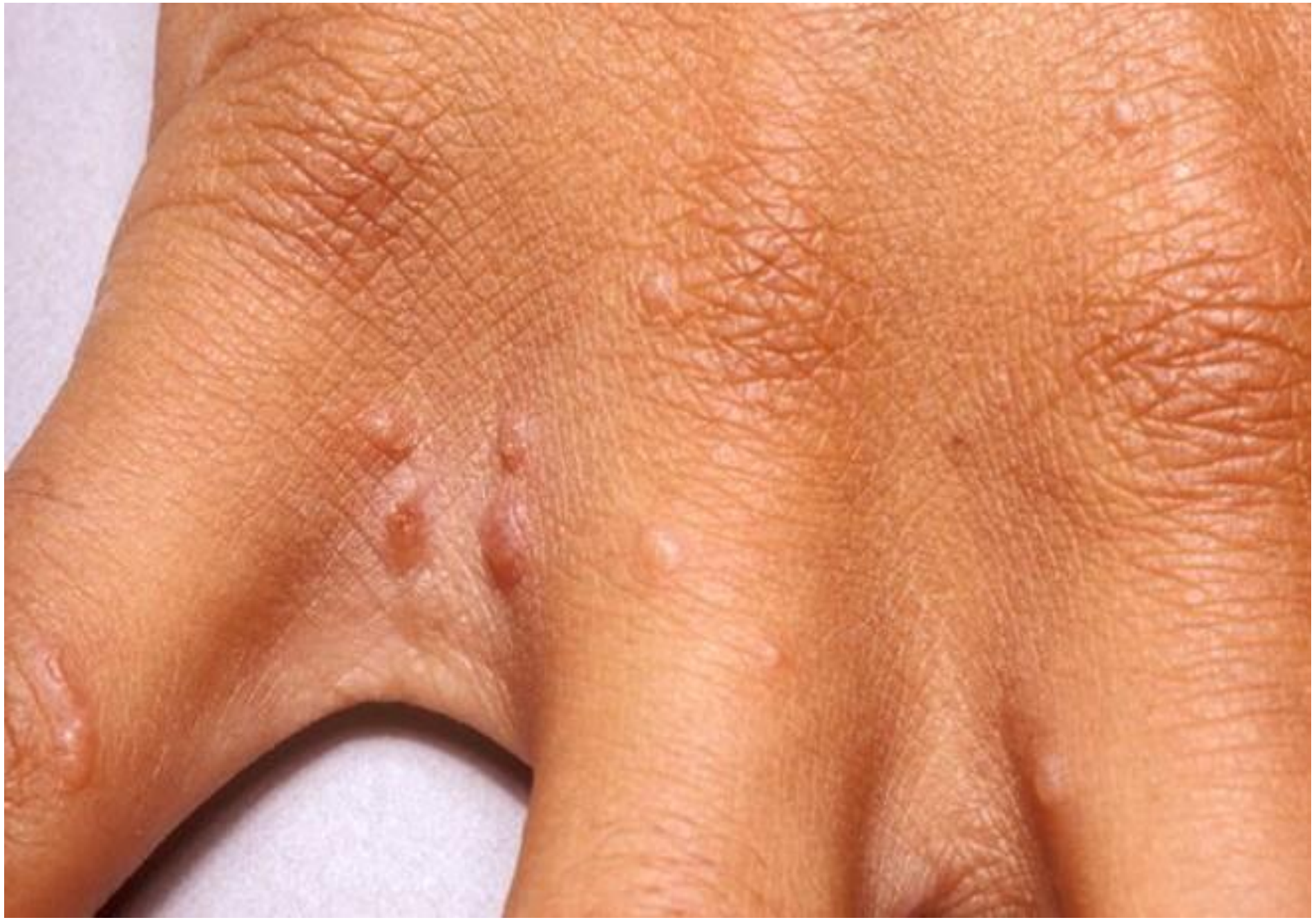


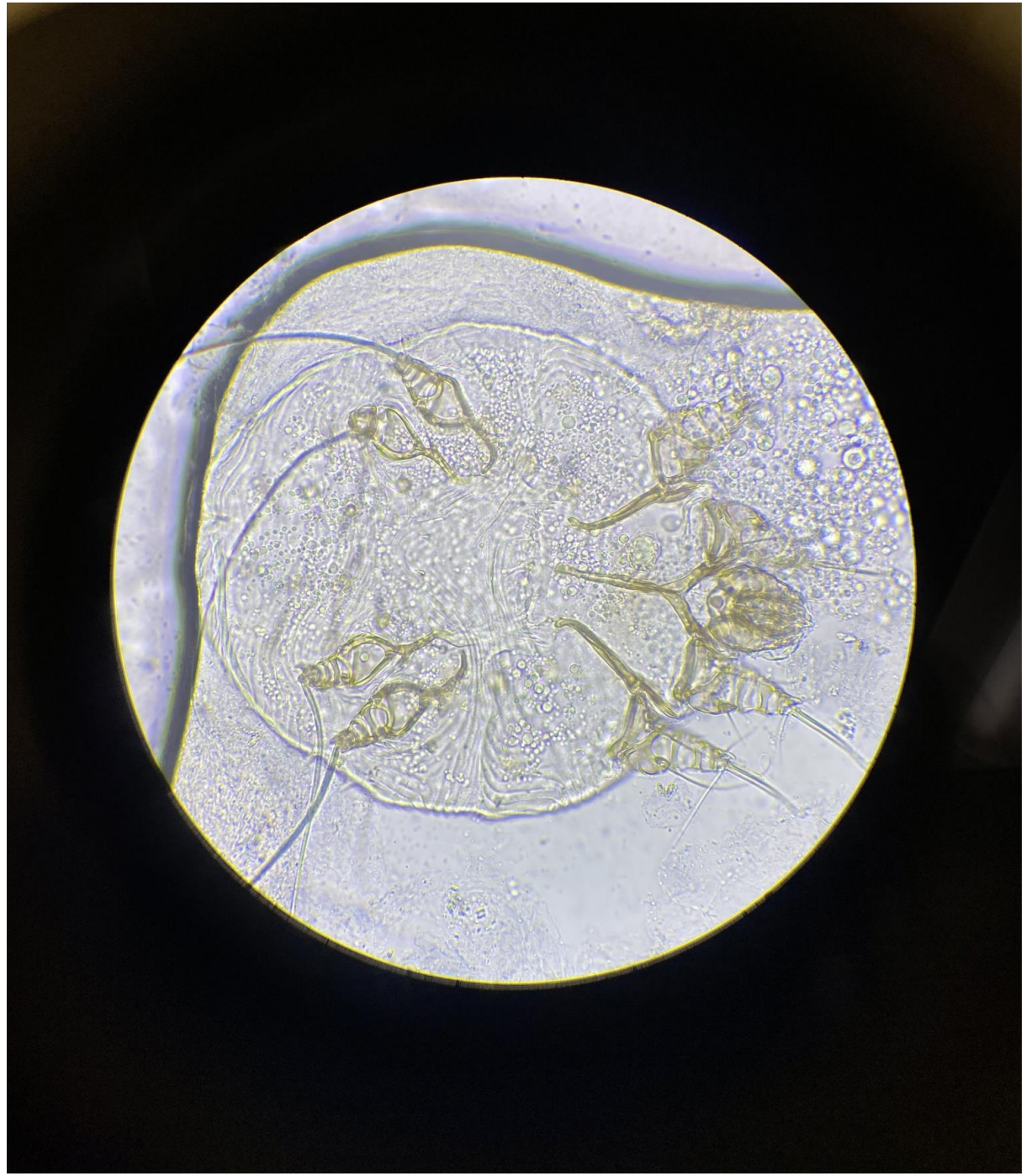


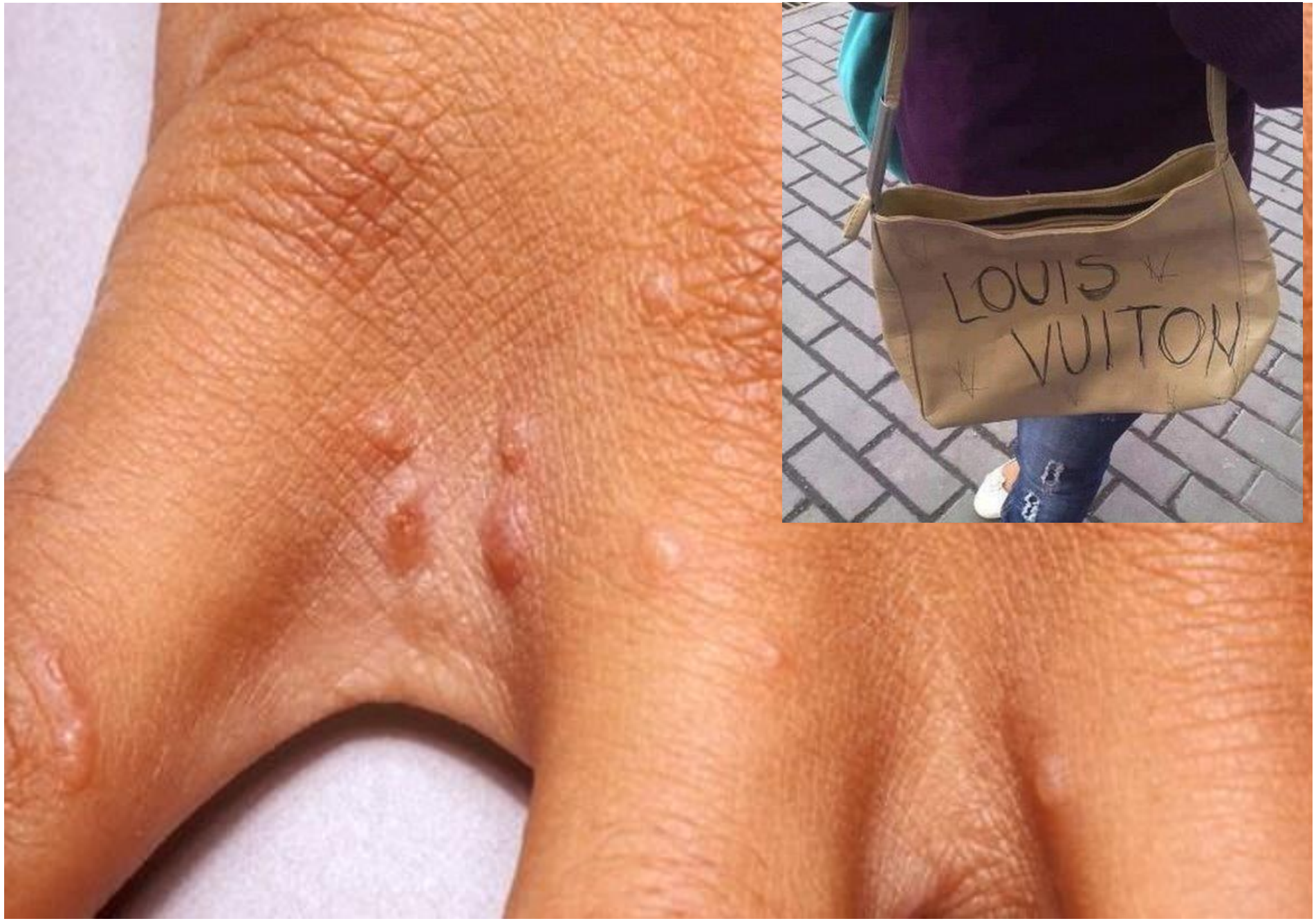


Case

- 21 year old college senior presents with diagnosis of new onset refractory atopic dermatitis for 9 months with severe pruritus
- Limited relief with numerous topical steroids, now on Ruxolitinib cream
- Short courses of oral corticosteroids helped but with rapid return of symptoms upon cessation
- Patient was started on Dupilumab 3 months prior to visit. He presents for second opinion due to lack of improvement






LOUIS
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- Clinical assessment
- KOH scraping
- Biopsy


Allergists and Dermatologists
United!

Dupilumab: Additional Considerations

- Dupilumab has expanding indications for TH2 mediated disease with a favorable safety profile
    - Site reactions
    - Conjunctivitis
    - Oral HSV
    - Eosinophilia
    - Head and neck dermatitis
- Two newer/emerging adverse events to be aware of
    - CTCL
    - Arthritis

Progression of Cutaneous T Cell Lymphoma (CTCL) with Dupilumab Therapy

- The most common form of CTCL is Mycosis Fungoides (MF)
  - Seen predominantly in adults
  - Presents as a recalcitrant papulosquamous eruption
  - Distribution varies but consistent sites of involvement are the axilla and hips/ buttocks

- In the pre-mycotic stage, evolving MF can resemble eczema/AD
  - What happens if we give a patient with evolving MF or active MF Dupilumab?

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JAMA Dermatol. 2023;159(11):1240-1247

Progression of Cutaneous T Cell Lymphoma (CTCL) with Dupilumab Therapy

- Treatment of presumed AD with dupilumab unmasked misdiagnosed MF
  - In one series, three of 530 patients (0.6%) with MF were misdiagnosed as AD
  - These patients experienced clinical worsening after initial response to dupilumab treatment

- Treatment of known MF with dupilumab was associated with more rapid disease progression disease

- Be cautions with recalcitrant new onset dermatitis in an adult with no prior hx of AD!

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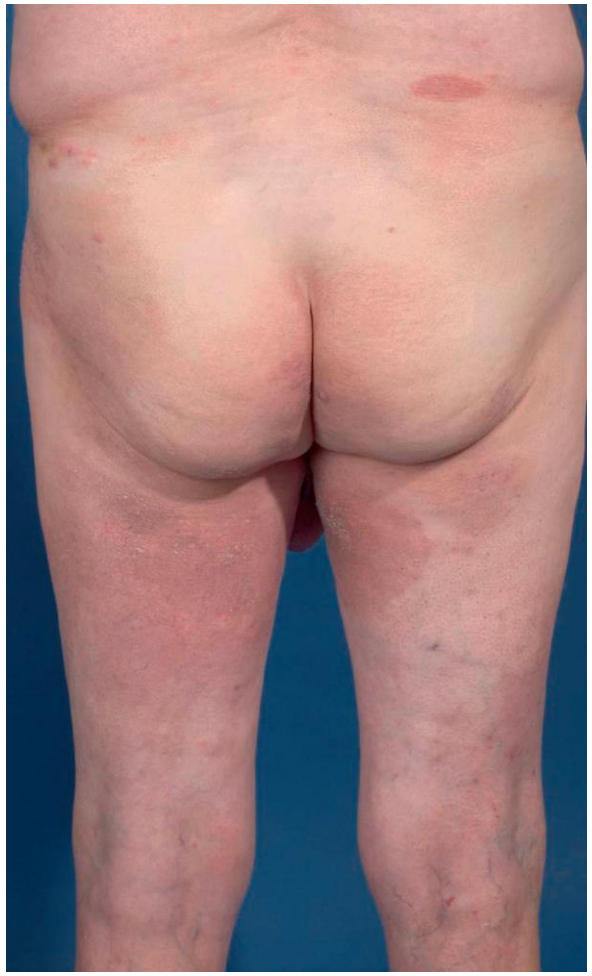
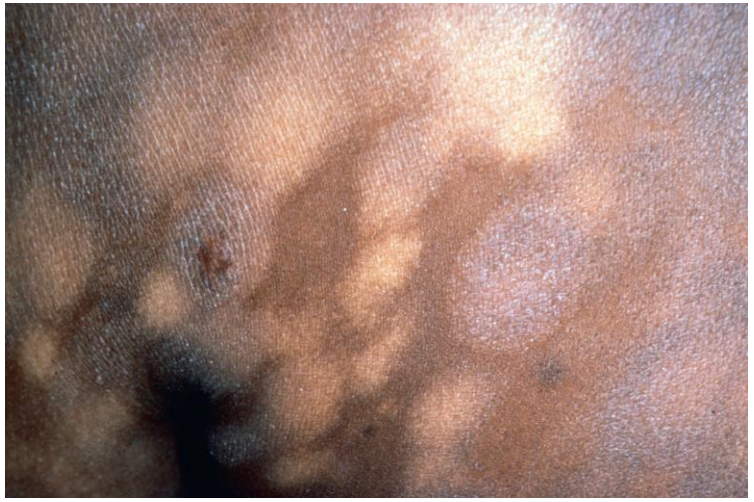
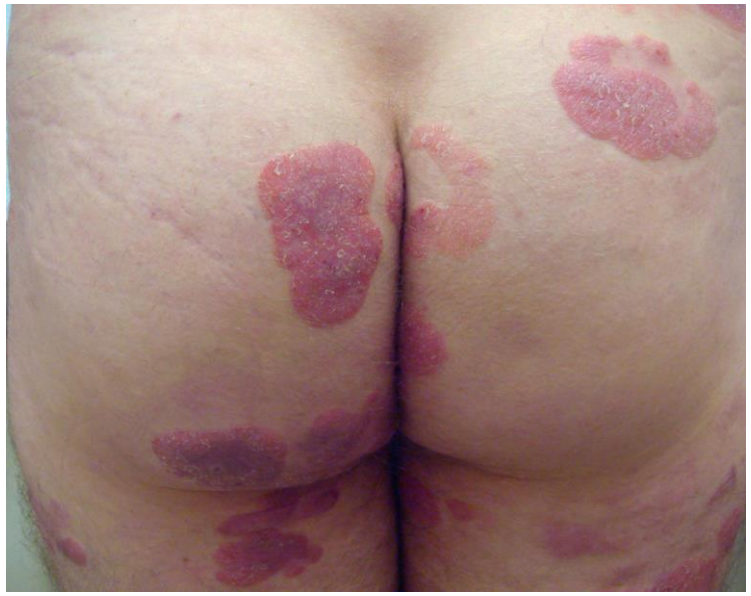
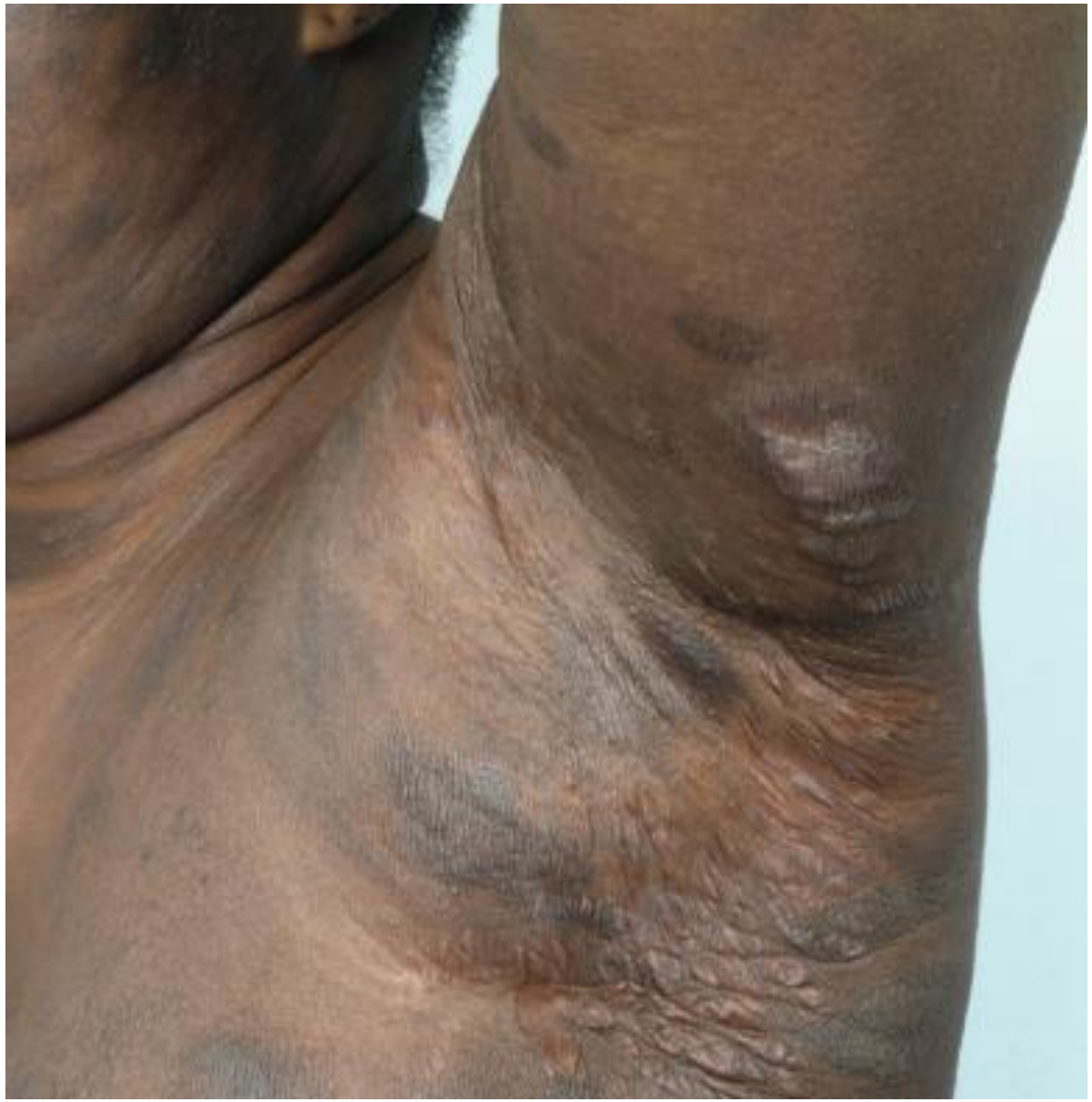
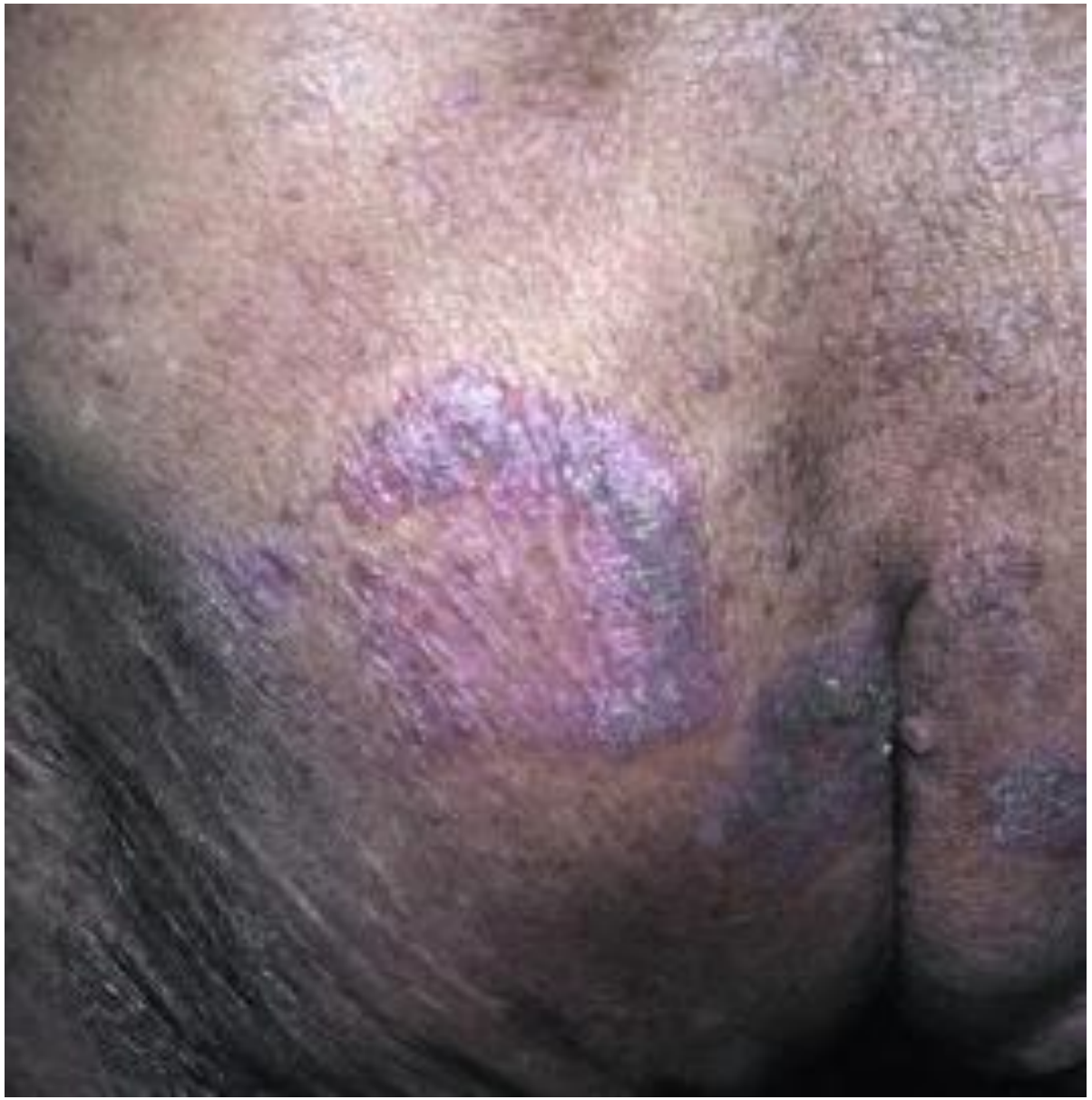
JAMA Dermatol. 2023;159(11):1240-1247

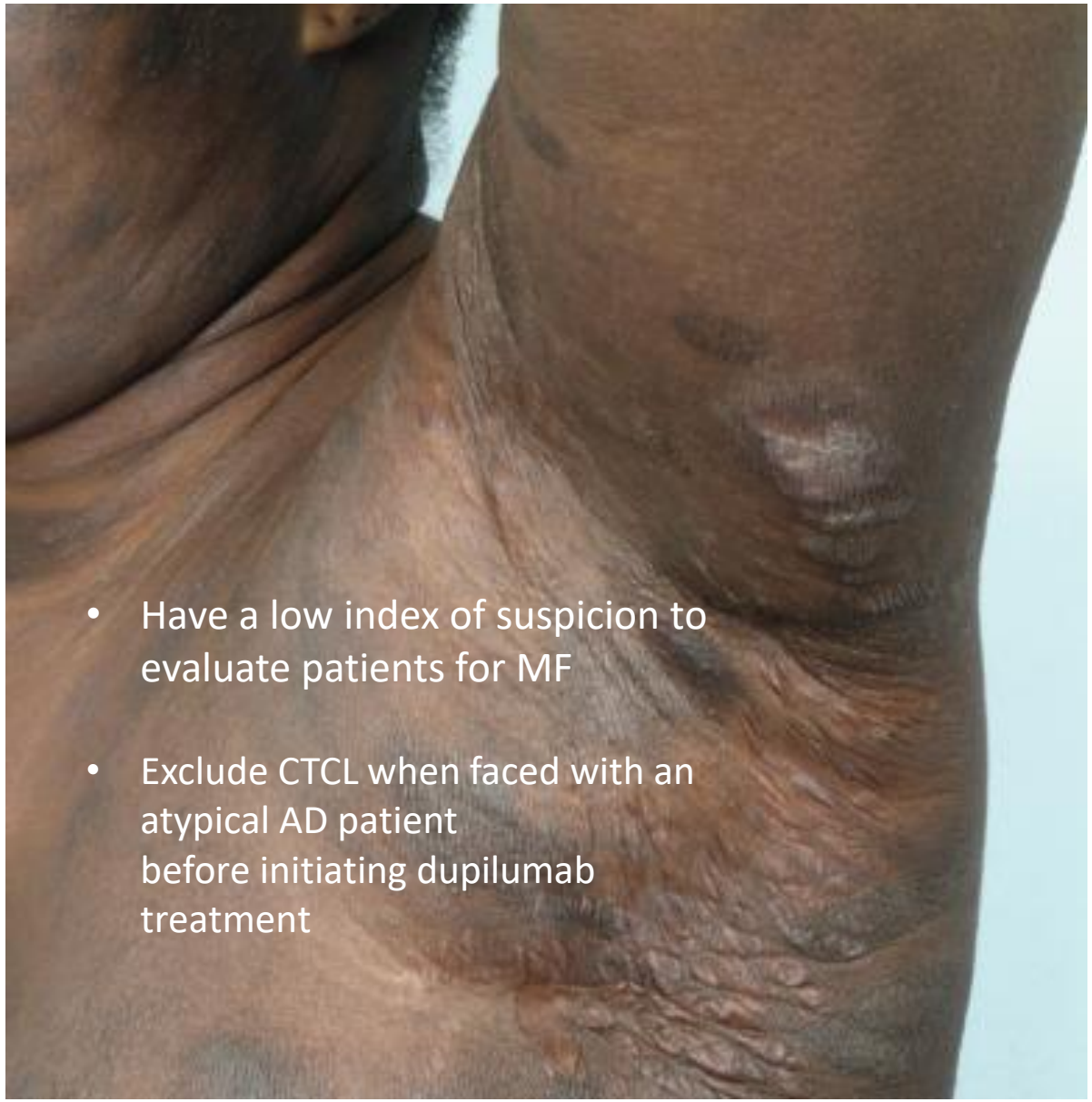




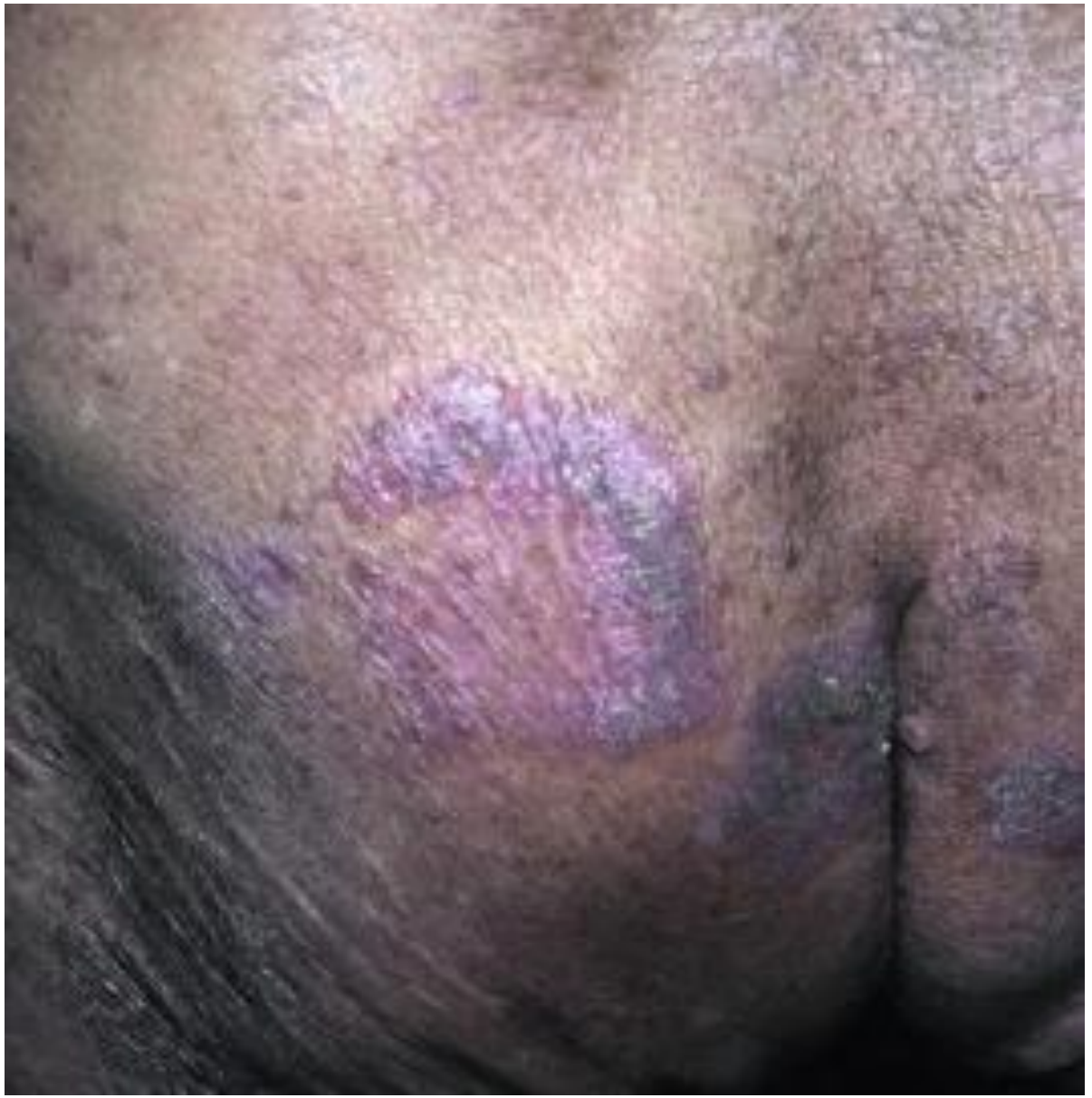








- Have a low index of suspicion to evaluate patients for MF
- Exclude CTCL when faced with an atypical AD patient before initiating dupilumab treatment



Dupilumab Induced Arthritis

- Dupilumab was initially approved in 2017 for atopic dermatitis. Since then, it has seen expanded indications with increased use
  - Eosinophilic esophagitis
  - Asthma
  - Prurigo nodularis
  - CRS with nasal polyposis
  - AD in patients ≥ 12 with Moderate to severe uncontrolled hand and foot dermatitis

- Dupilumab induced arthritis was first described in 2019

Dupilumab Induced Arthritis

- Tends to be symmetrical, acral and generalized
  - Spares axial skeleton
  - Seen mostly in patients receiving Dupilumab for atopic dermatitis
  - Not associated with underlying RA/SLE
  - Rheumatoid factor, ESR, CRP and anti-citrullinated protein antibodies normal
  - Improves with cessation
- Most cases onset after 4 months of therapy
- Retrospective observational study of patients with moderate-to-severe AD on dupilumab found 6/169 (3.6%) developed arthritis/arthralgia

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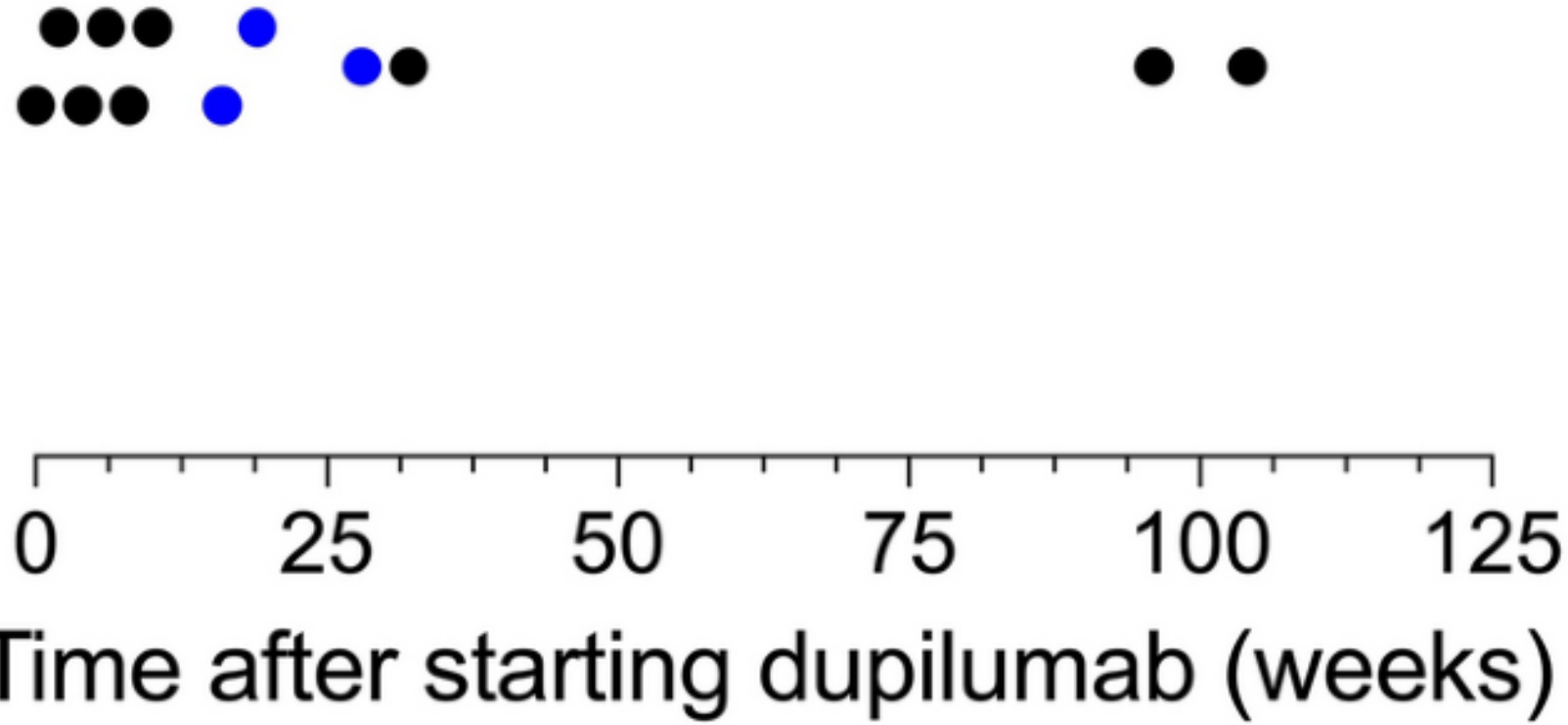
American Journal of Clinical Dermatology. 2023: (24) 859–864

Dupilumab-associated arthritis onset



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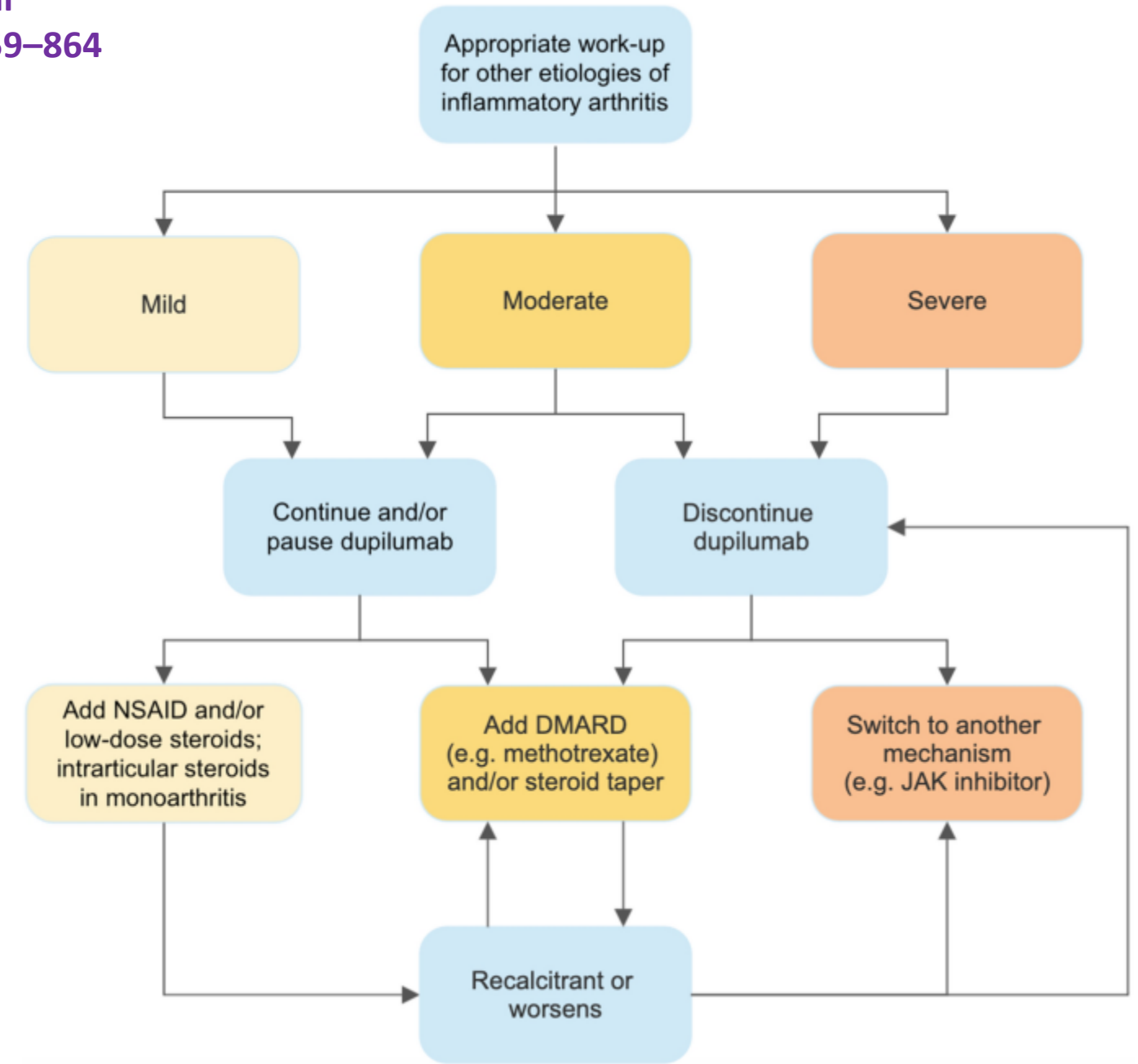
American Journal of Clinical Dermatology. 2023: (24) 859–864



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Cutaneous Toxicities of Immune Checkpoint Inhibitors (ICI)

- ICI's have an expanding role in the treatment of numerous malignancies
    - anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies are used to treat numerous cutaneous malignancies

- Cutaneous side effects are among the most frequently reported adverse reactions to these dermato-oncological therapies
    - ICI's 'cause dermatology' to happen

Cutaneous Toxicities of Immune Checkpoint Inhibitors (ICI)

- Incidence
  - Anti-CTLA-4 monotherapy incidence of cutaneous irAEs is 44-59%
  - Anti-PD-1 34-42% and anti-PD-L1 monotherapy up to 20%
  - Combination therapy with anti-PD-1 and anti-CTLA-4 agents has the highest incidence: 59–72%

- Recognizing the morphology of these reactions facilitates classification and treatment
  - The main reactions are eczematous, psoriasisform, morbilliform, and lichenoid
  - Rarer eruptions include pemphigoid and SJS/TEN

Immune Checkpoint Inhibitors (ICI): Used to treat melanoma, cSCC, Merkel Cell Cancer, and numerous other metastatic tumors

- Anti-PD1
  - cemiplimab, nivolumab and pembrolizumab
- Anti-PD1L
  - atezolizumab, avelumab and durvalumab
- Anti-CTLA4
  - ipilimumab

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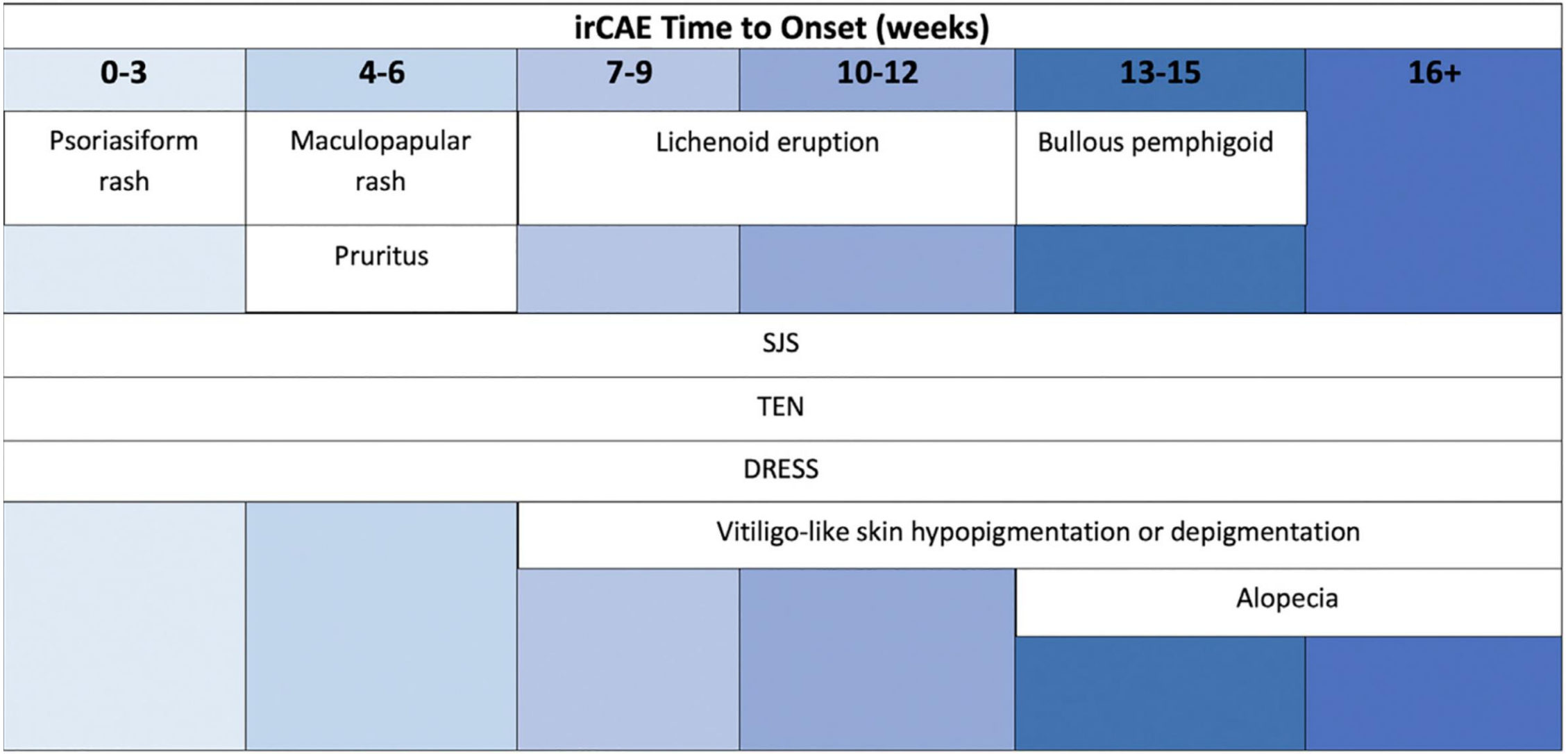
Cutaneous Toxicities of Immune Checkpoint Inhibitors (ICI)

- Etiology of cutaneous irAE's
  - Activation of T cells against common antigens in target tumor cells and normal tissues
    - Vitiligo/Pemphigoid/SLE
  - Increased release of proinflammatory cytokines and antibodies activating T and B cells
    - Psoriasis/lichenoid/eczematous

Grading cutaneous irAE

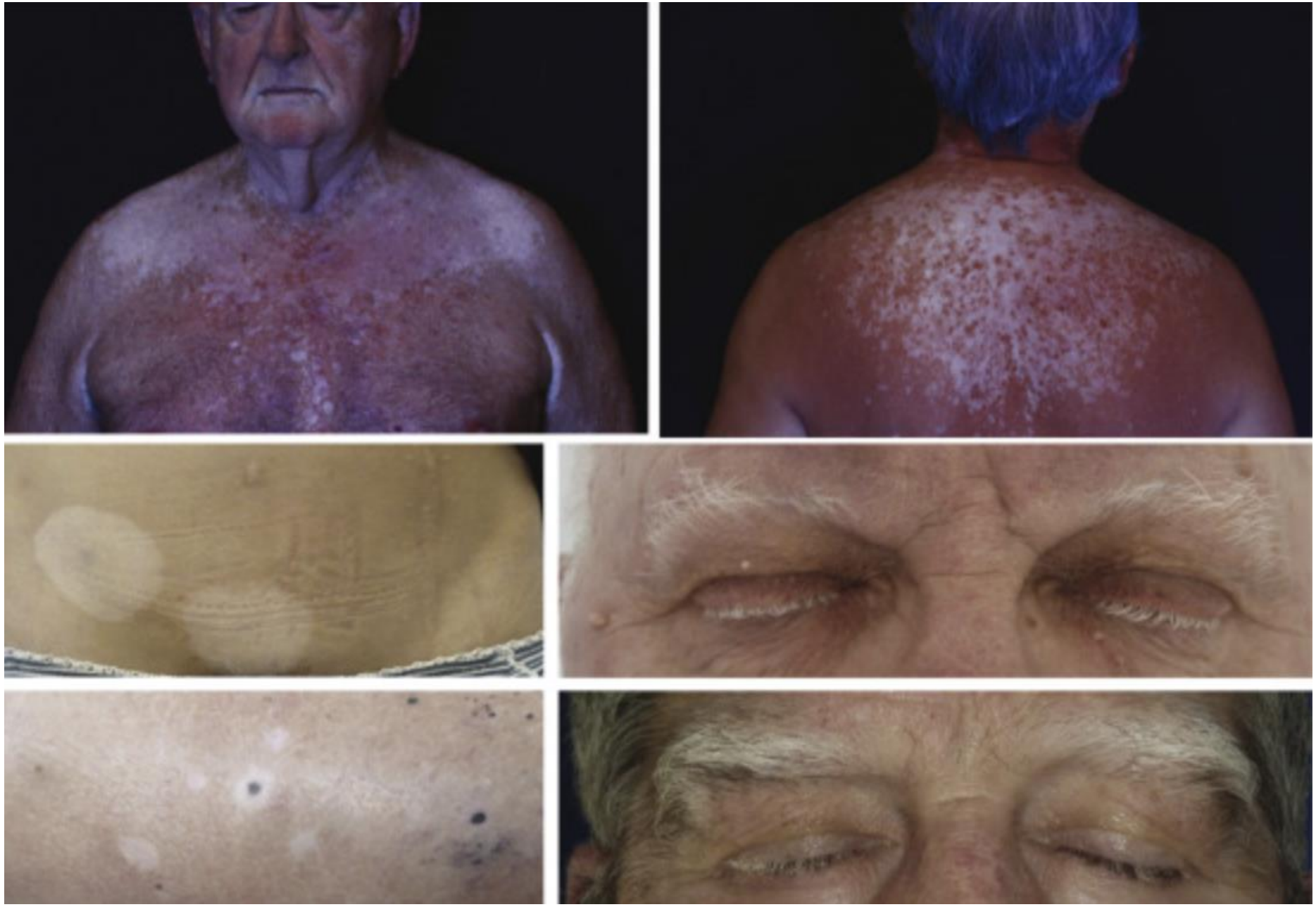
Grade	Findings
1	Asymptomatic with macules/papules covering majorly <10% of BSA
2	Macules/papules covering 10% to 30% of BSA can be symptomatic as well as asymptomatic.
3	About >30% of BSA is covered. The appearance of macules/papules with or without symptoms.
4	It is the most severe cutaneous response and can be life-threatening, such as SJS, TEN, and bullous dermatitis involving about >30% of BSA



J Am Acad Dermatol. 2020 Nov; 83(5): 1255–1268

Cutaneous Toxicities of Immune Checkpoint Inhibitors (ICI)

- **Vitiligo**
  - Mostly in patients receiving ICI for melanoma
  - Onset variable (7-36 weeks into course of ICI)
  - Represents a favorable prognostic indicator
  - May not require treatment

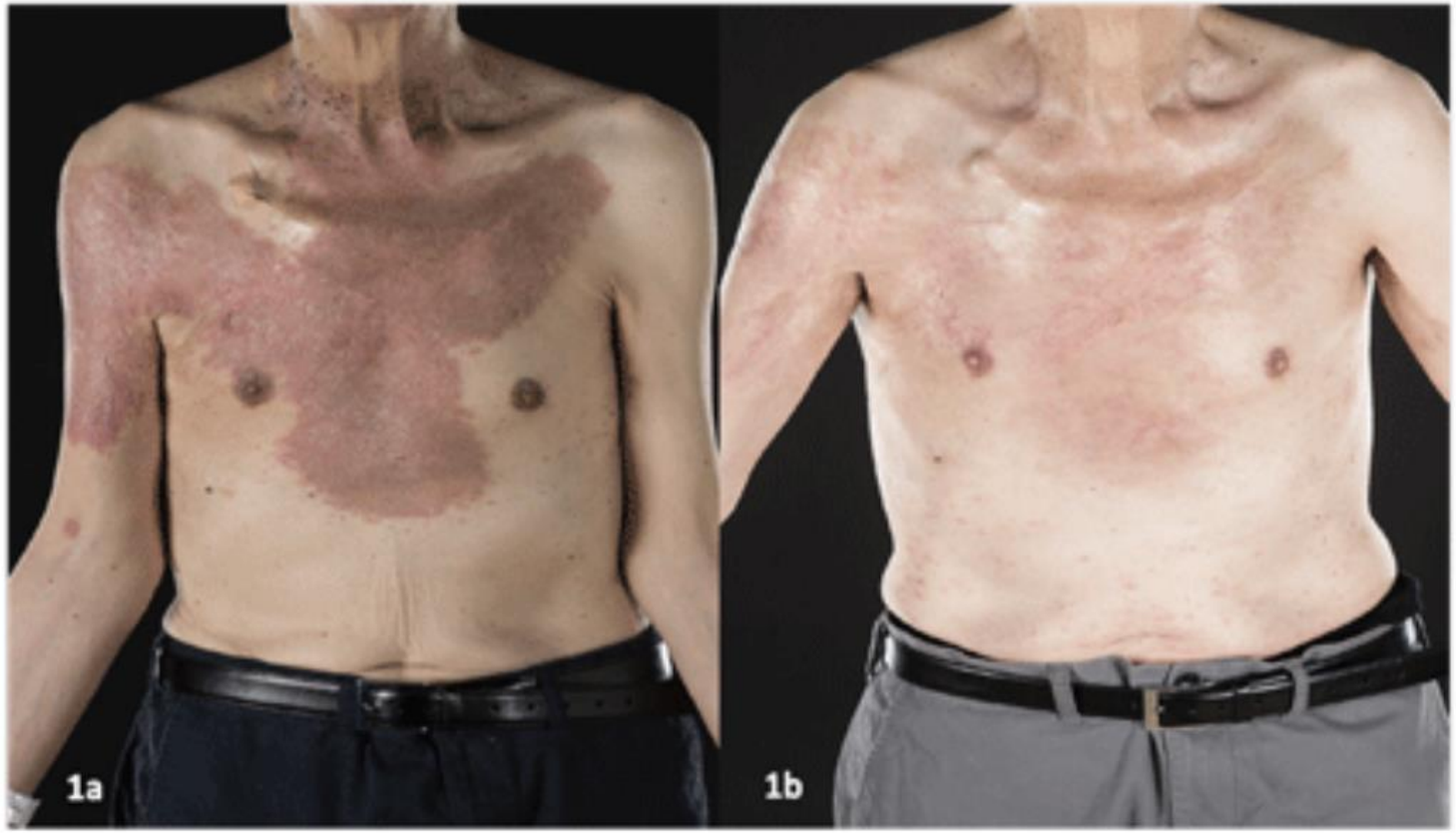


JAAD Int. 2021 Oct 19:5:112-120

Cutaneous Toxicities of Immune Checkpoint Inhibitors (ICI)

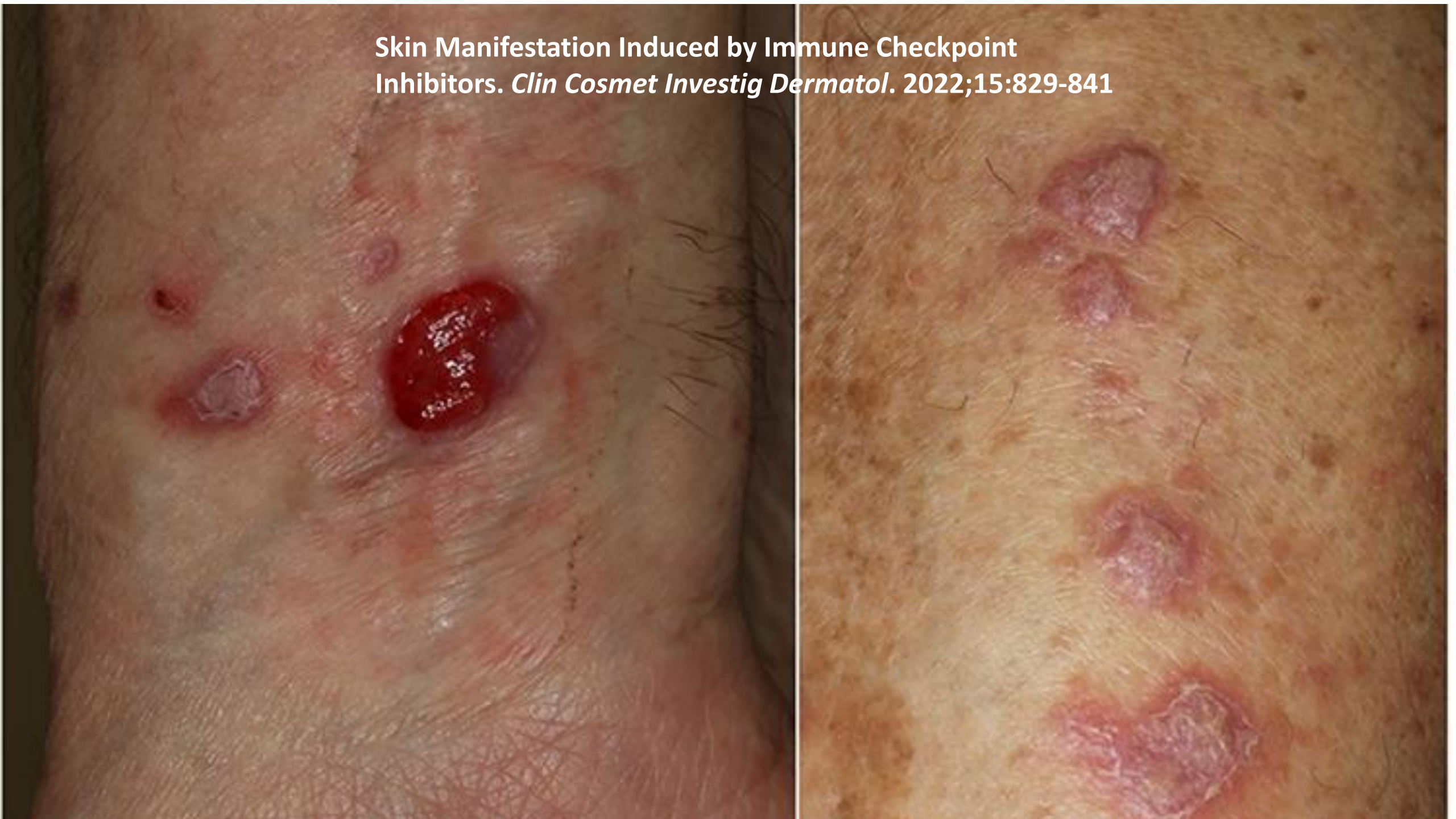
- **Psoriasis**
  - Guttate, plaque and inverse patterns and psoriatic arthritis
  - Can be de novo or reactivation of disease
  - Treatment
    - Topical steroids, Tapinarof cream of Roflumilast cream
    - Acitretin
    - Phototherapy
    - Biologics
      - Avoid anti-IL17 agents due to risk of colitis with ICI
      - Favor anti-IL23 if biologic required
    - Cessation rarely necessary
  - May portend an increased risk of endocrine immune-related adverse events

FIGURE 1. (A) Psoriatic eruption post Nivolumab treatment. (B) Resolution of psoriatic rash post treatment with acitretin.



Cutaneous Toxicities of Immune Checkpoint Inhibitors (ICI)

- **Lichenoid Eruption**
  - Amongst most common reactions
  - Onset 6-12 weeks
  - Can be bullous, may involve mucosae
  - Therapy
    - Topical steroids
    - UVB Phototherapy
    - For Grade 3: Cessation, oral corticosteroid, methotrexate



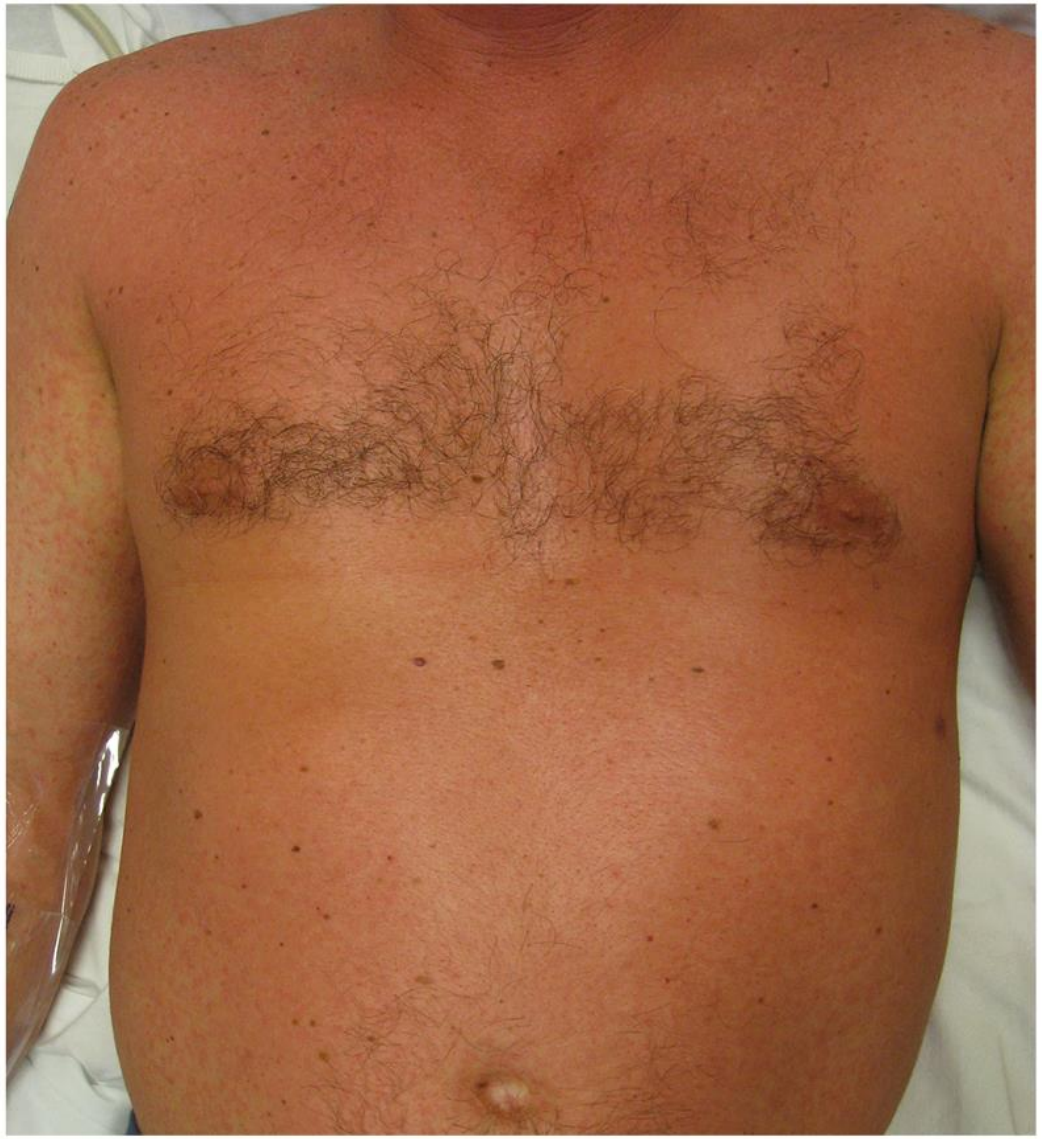
Skin Manifestation Induced by Immune Checkpoint Inhibitors. *Clin Cosmet Investig Dermatol*. 2022;15:829-841

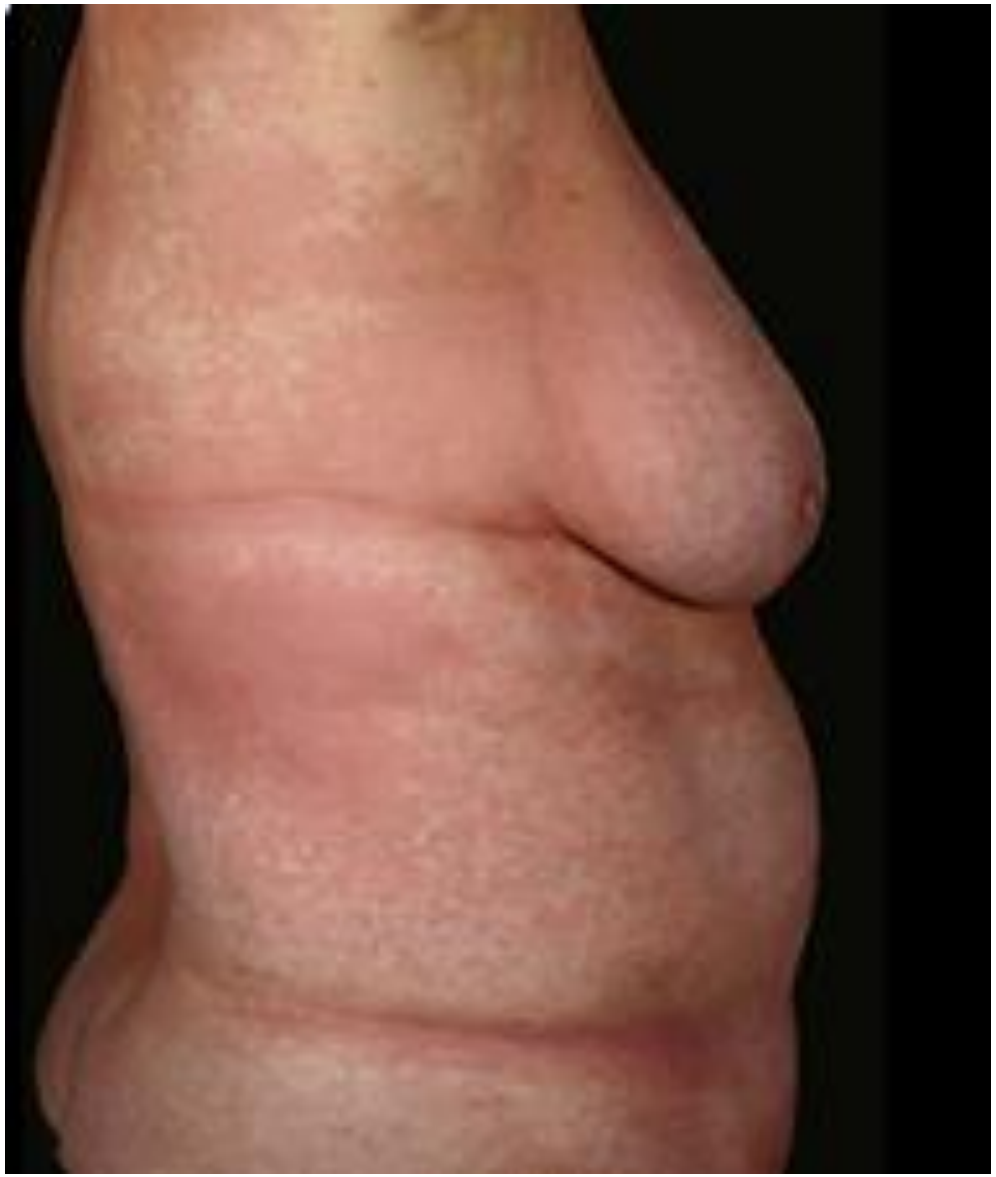
Cutaneous Toxicities of Immune Checkpoint Inhibitors (ICI)

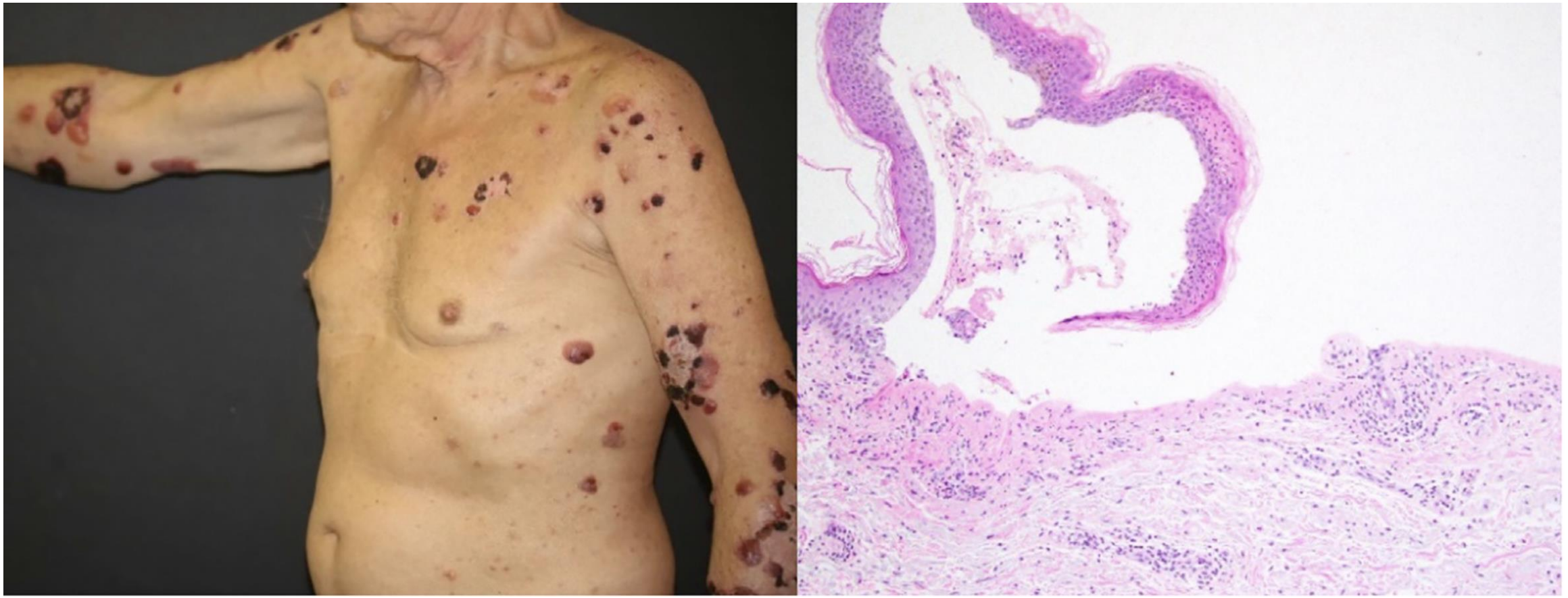
- Eczematous
  - Exacerbation or denovo eruptions
  - Therapy
    - Grade 1 and 2: topical corticosteroids, ruxolitinib cream, UVB
    - Grade 3: UVB, dupilumab, oral corticosteroids, cessation of ICI

Cutaneous Toxicities of Immune Checkpoint Inhibitors (ICI)

- Morbilliform Eruptions (maculopapular)
  - Most common with ipilimumab
  - Onset 3-6 weeks into treatment
  - Distributed on torso and extensural surfaces of extremities
  - Pruritic
  - Therapy: Topical corticosteroids



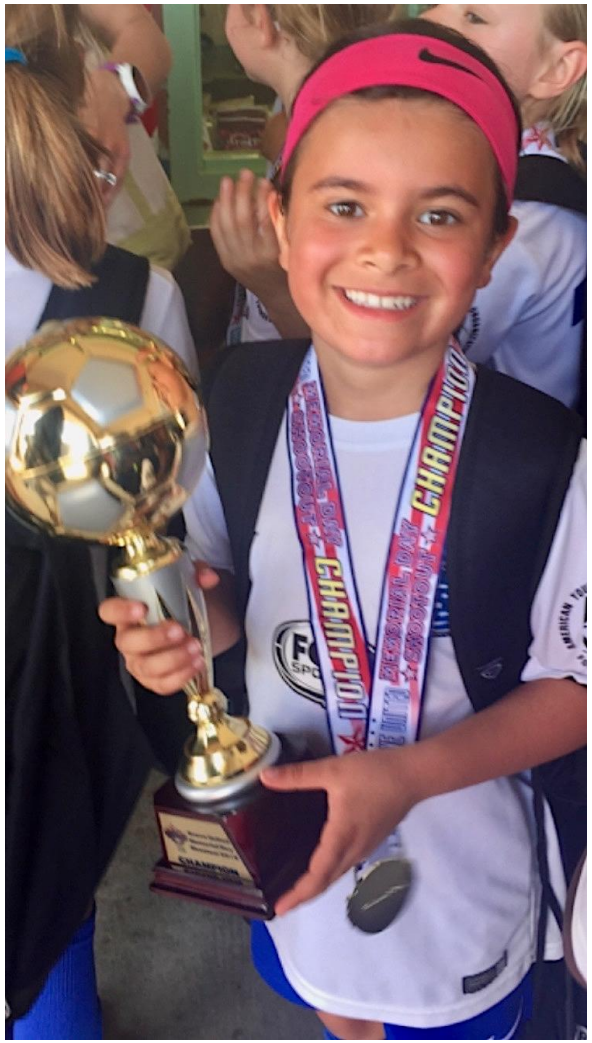




J Am Acad Dermatol. 2020 Nov; 83(5): 1255–1268

Conclusions

- Sulfites are the contact allergen of the year for 2024
- New and expanding options for the topical therapy of atopic dermatitis offer alternatives to corticosteroids
- Dupilumab is efficacious and safe but can unmask CTCL and cause arthritis
- Immune checkpoint inhibitors have expanding indications. Recognition and management of cutaneous irAE improves patient tolerance and may reduce treatment interruptions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