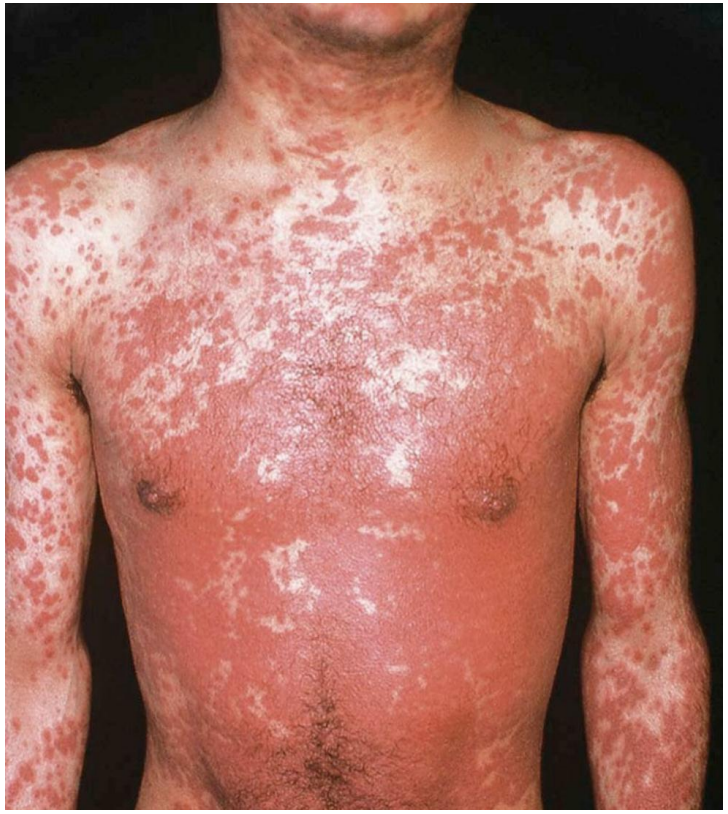


Drug Eruptions

Abdulaziz Madani, M.D

Assistant professor, consultant

Department of Dermatology, College of medicine

King Saud university

Introduction

- The skin is one of the most common targets for adverse drug reactions.
- 1-5% of patients receiving antibiotics and anticonvulsants may develop a drug eruption.
- ~2% of all drug-induced skin reactions are considered ‘’serious’’
- Skin reactions to drugs are responsible for ~3% of all disabling injuries that occur during hospitalizations.
- Either due to:

- Immunologic response
- Non-immunologic (Overdose, side effect, drug-drug interaction, metabolism…etc)

Diagnostic approach for drug eruptions

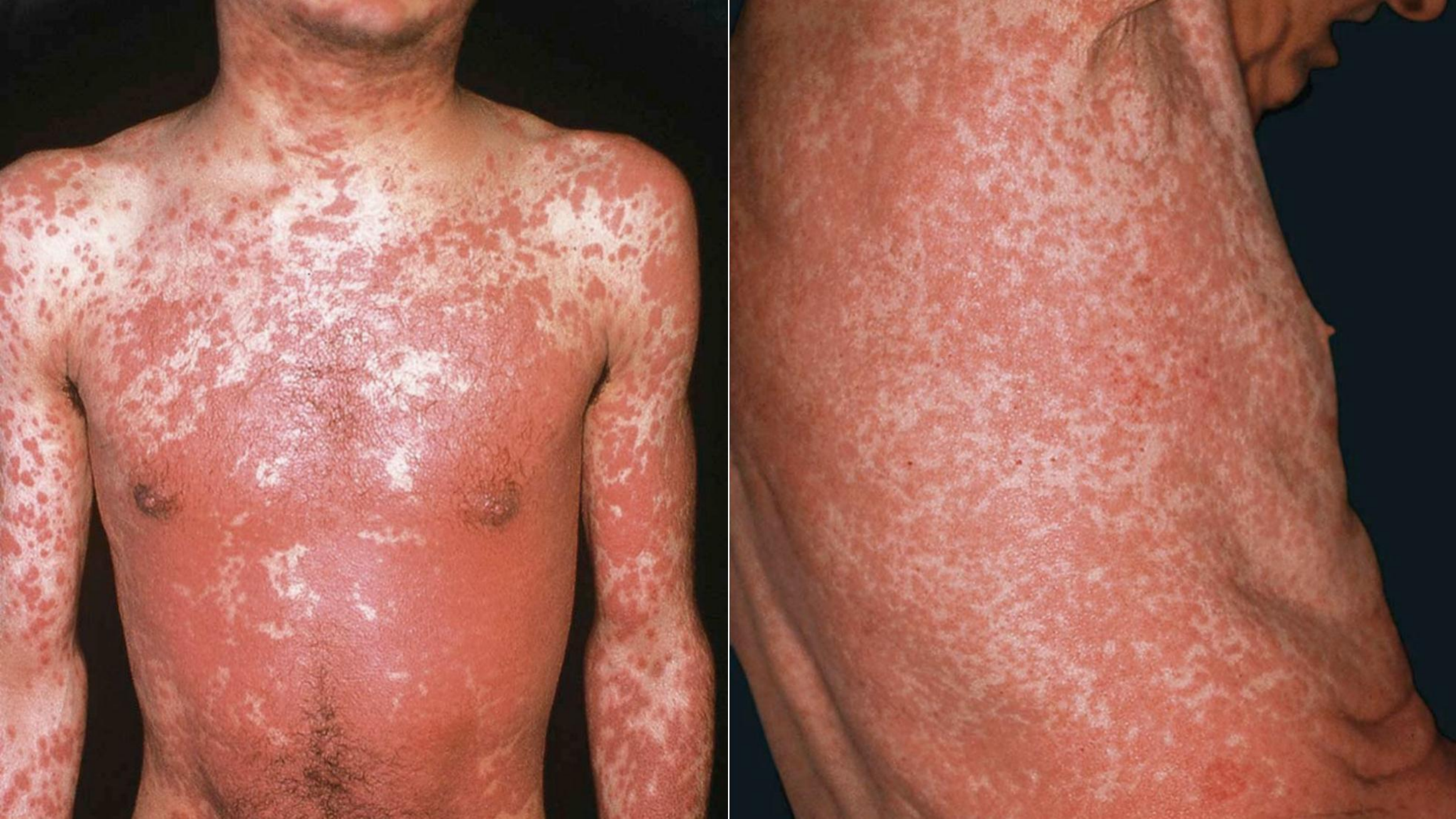
- **Clinical characteristics**
- Type of primary lesion
- Distribution and number of lesions
- Mucous membrane involvement, facial edema
- Associated signs and symptoms.
- **Chronological factors**
- Document all drugs to which the patient has been exposed
- Date of eruption, time interval..
- **Literature search**

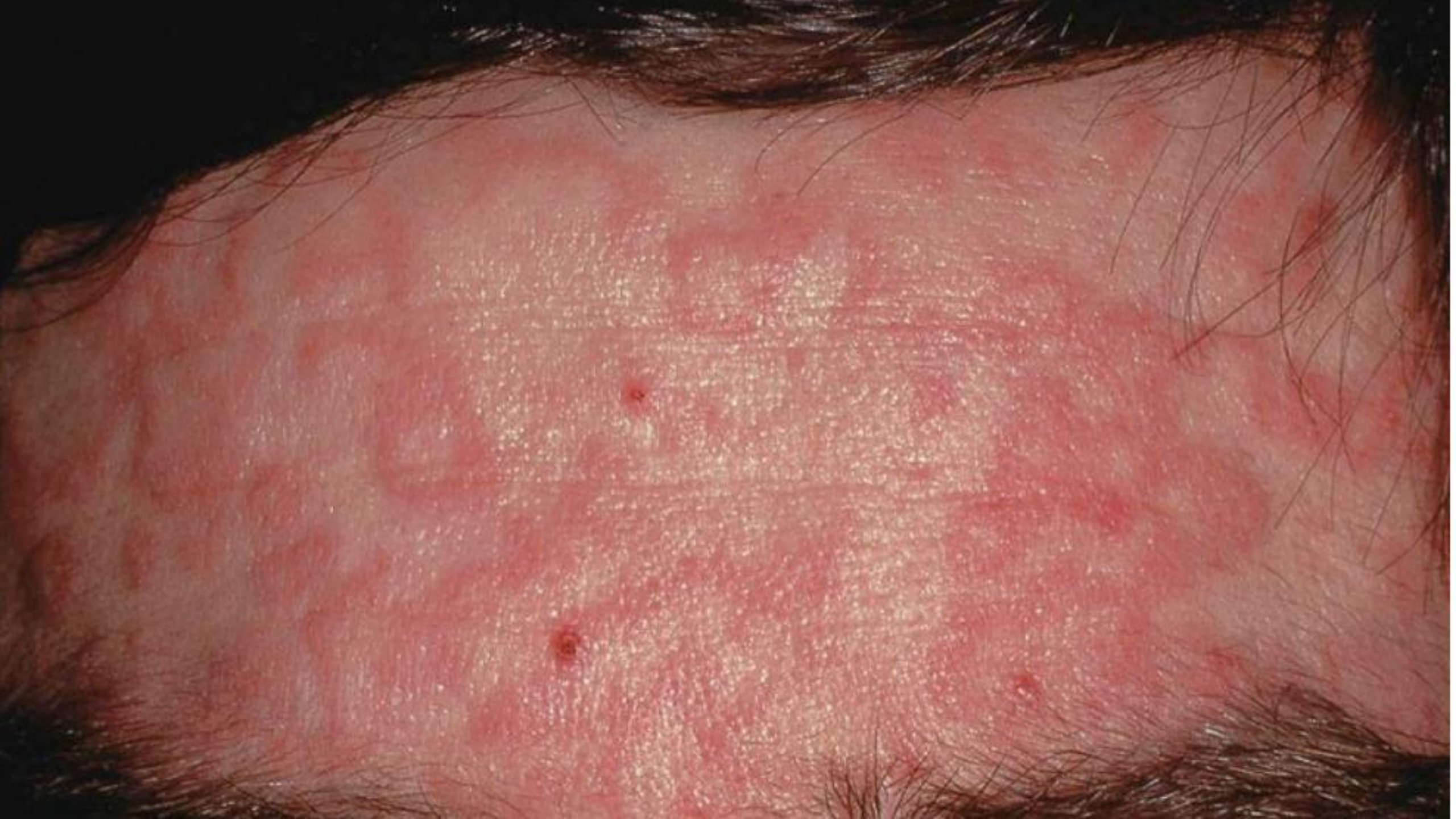
Major drug-induced eruptions

Exanthematous eruptions	Urticaria	Anaphylaxis	Fixed drug eruption
Acute generalized exanthematous pustulosis (AGEP)	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Stevens-Johnson syndrome (SJS)	Toxic epidermal necrolysis (TEN)

Exanthematous Drug Eruptions

- The most common drug reaction affecting the skin.
- Classically begins 7 to 14 days after the start of a new medication.
- Begins as erythematous macules (symmetric) that sometimes becomes palpable.
- Begins on the trunk and upper extremities and progressively becomes confluent.
- Mucous membranes are usually spared.
- Pruritis and low-grade fever and often present.
- The eruption disappears spontaneously after 1-2 weeks without complications.
- The following classes of drugs have a significantly higher incidence: Aminopenicillins, Sulfonamides, Cephalosporins and anticonvulsants.





Exanthematous Drug Eruptions

- **Always look for the following:**
- Edema of the face + blood eosinophilia (DRESS)
- Mucous membrane lesions or painful dusky skin (SJS, TEN)

- **Histology:**
- Nonspecific changes, eosinophils may be present.

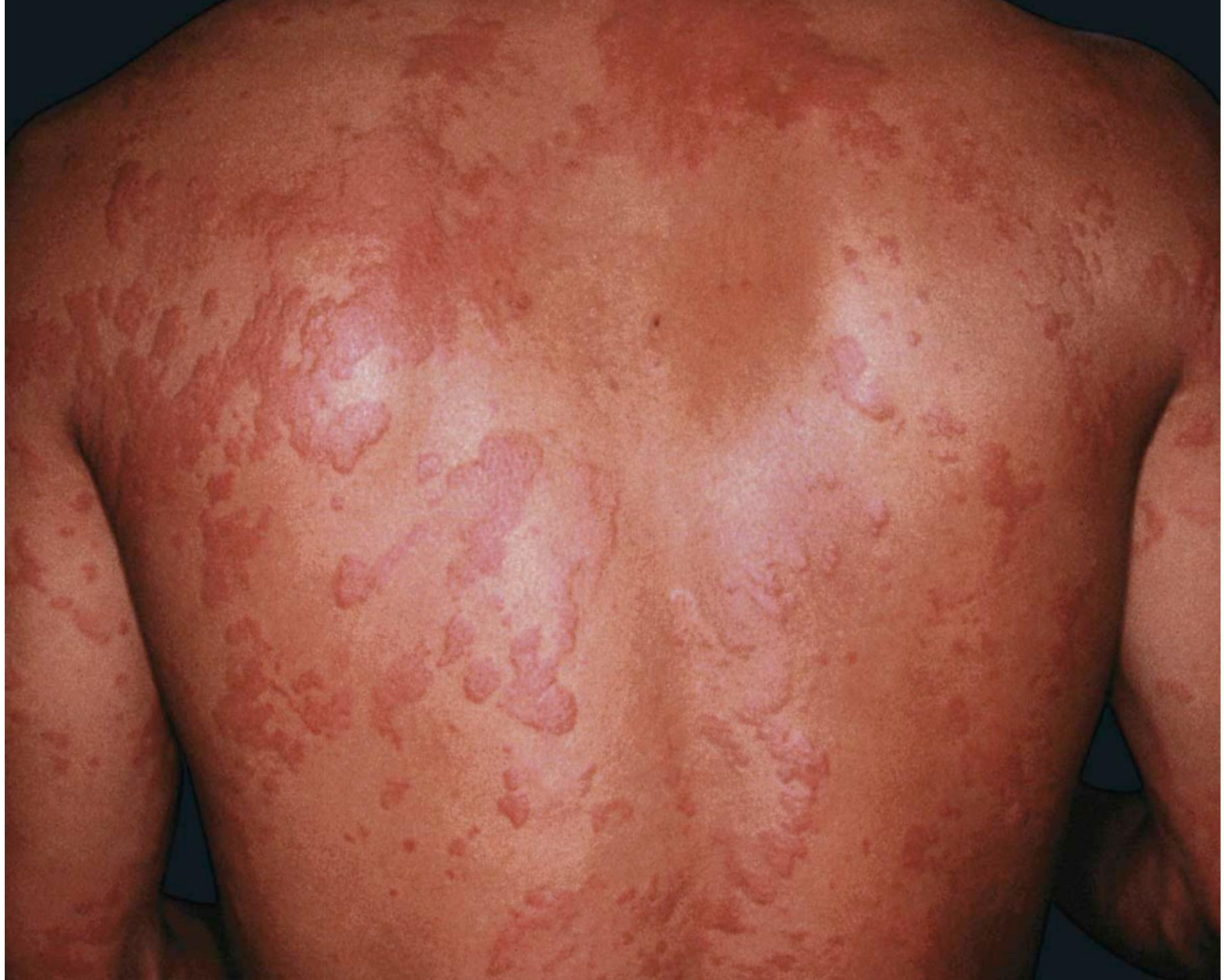
- **The major DDx**
- Viral exanthem (often indistinguishable)
- Drug etiology favored in adults, viral favored in pediatric patients.
- The presence of peripheral blood eosinophilia favors a drug reaction.

- **Treatment:**
- Supportive
- Discontinue the offending drug. (risk vs benefit)
- Topical antipruritics and corticosteroids may help to alleviate pruritis.

Urticaria, Angioedema and Anaphylaxis

- **Urticaria:**

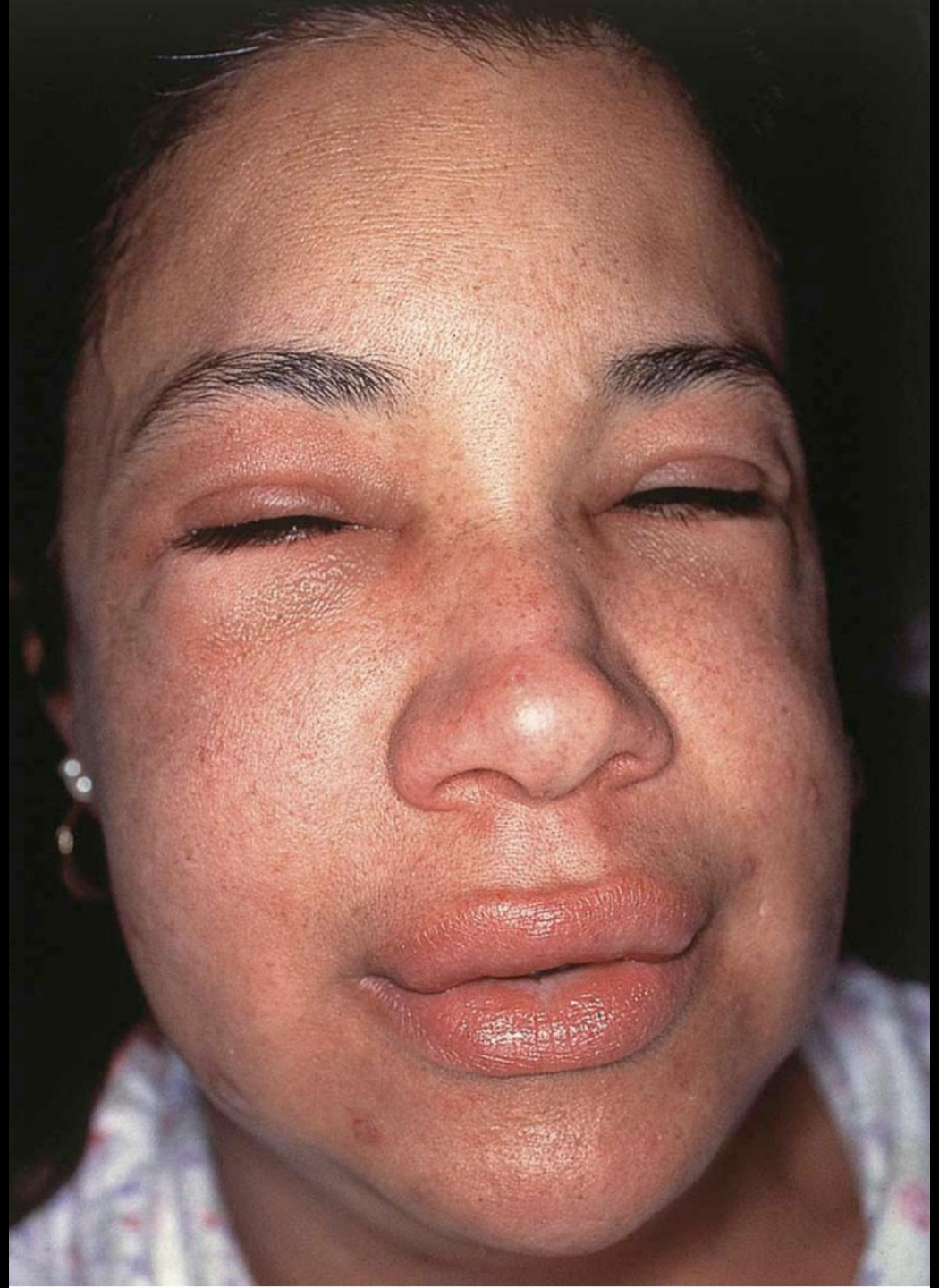
- Transient erythematous and edematous papules and plaques that are usually associated with pruritis.
- They can appear anywhere in the body including palms,soles and scalp.
- Duration is usually a few hours to 24 hours.
- Skin is normal after they resolve.
- Acute: Less than 6 weeks. Chronic: Persist longer.
- Drugs associated with <10% of all cases of urticaria (acute > chronic)
- Mostly antibiotics (Penicillins, cephalosporins).
- Tx: Discontinue drug, Antihistamines.



Urticaria, Angioedema and Anaphylaxis

- **Angioedema:**

- Transient edema of the dermal, subcutaneous and submucosal tissue.
- Associated with urticaria in 50% of cases.
- May be complicated by life-threatening anaphylaxis.
- ACE inhibitors (1 day to several years after starting)
- Usually on the face (eyelids, lips), less often on genitals and extremities.
- Unilateral or asymmetric.
- Can involve the larynx, epiglottis, oropharynx and intestinal wall.
- ACE inhibitors, Penicillins and NSAIDs.



Urticaria, Angioedema and Anaphylaxis

- **Anaphylaxis:**

- An acute life-threatening reaction that can results from exposure to a number of drugs.
- Penicillin (1 per 5000)
- Combines skin with systemic manifestations (hypotension, tachycardia).
- Serious cases tend to appear within minutes and more common with parenteral administration as compared to oral ingestion.

- **Treatment**:

- Discontinue drug and strict avoidance in the future.
- Systemic steroids
- SubQ epinephrine in cases of life-threatening angioedema or anaphylaxis.

Photosensitivity

Photosensitivity

- Cutaneous photosensitivity may be:
- Idiopathic
- Due to endogenous photosensitizers (Porphyrins)
- Due to Exogenous photosensitizers (Medications)

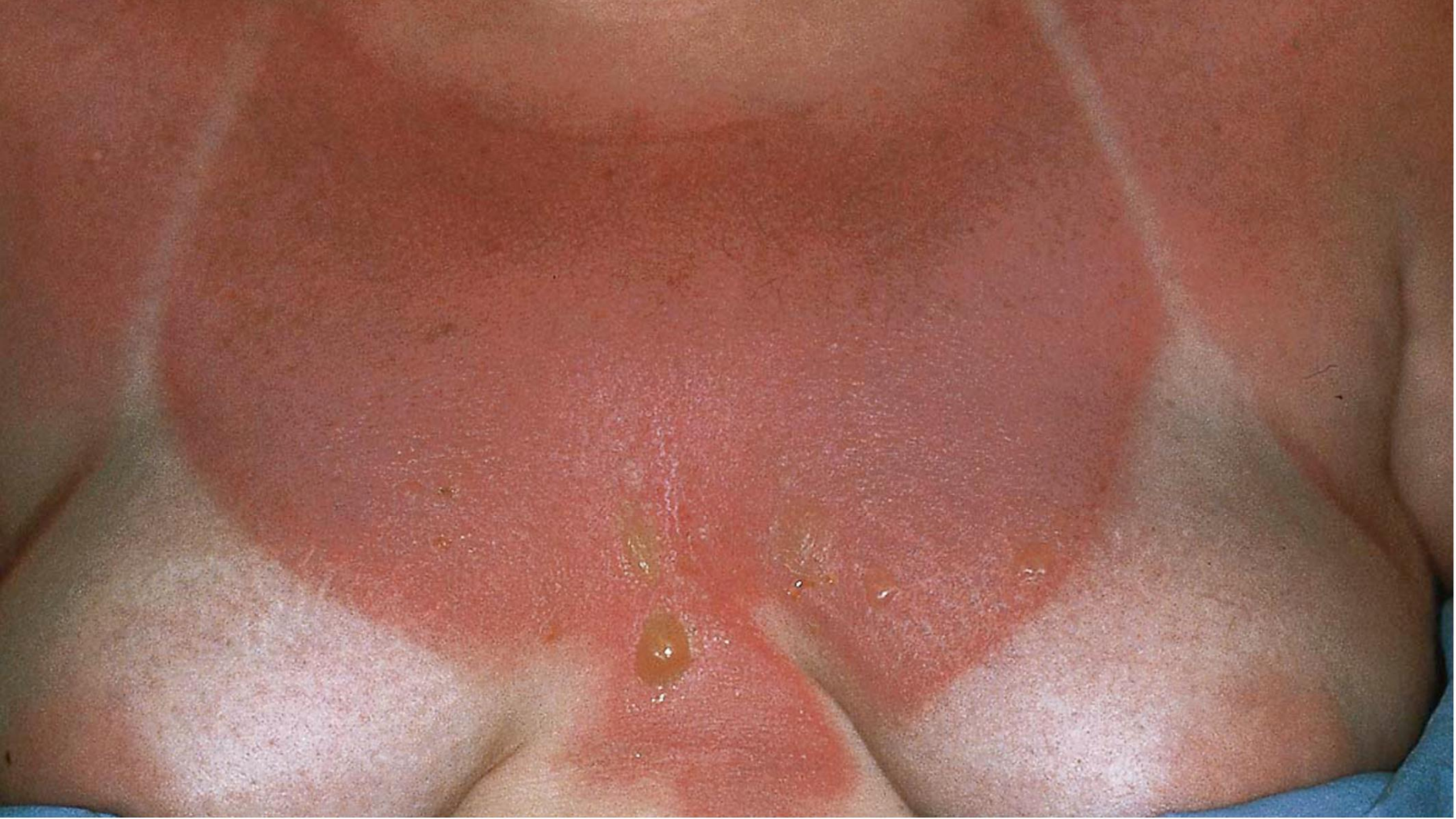
- The photosensitivity drug reactions are classically divided into 2 major types:

1- Phototoxic (more common)

2- Photoallergic

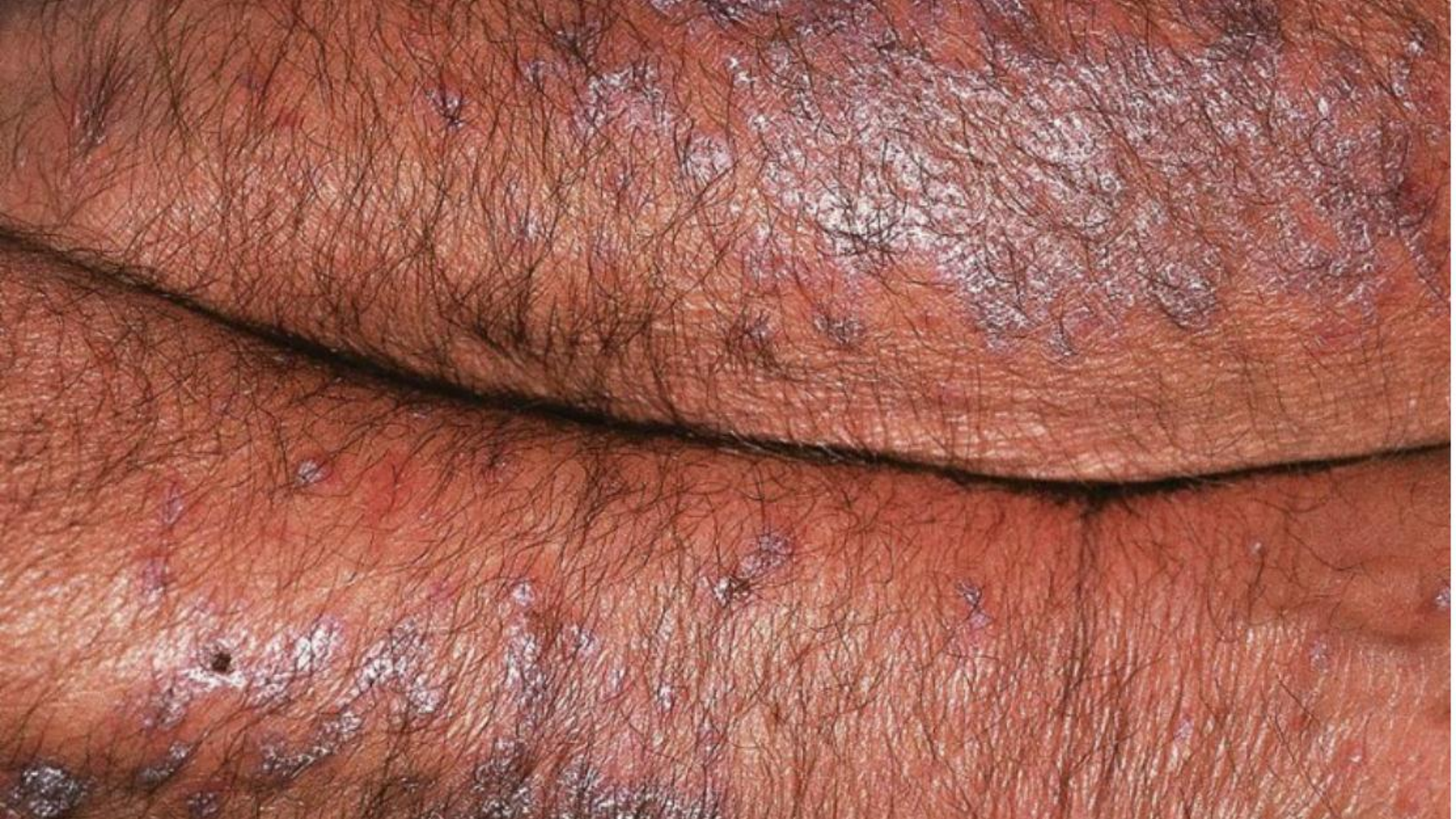
Phototoxicity

- Fairly common and predictable.
- Can occur in any person who receives a sufficient amount of a phototoxic drug together with sufficient exposure to UVR.
- Clinically: an exaggerated sunburn in a shorter than expected time.
- Limited to sun-exposed areas and followed by hyperpigmentation.
- Most common drugs: Tetracyclines (doxycycline), NSAIDs, Fluoroquinolones.
- Administring a short half-life drug in the evening decreases the risk.



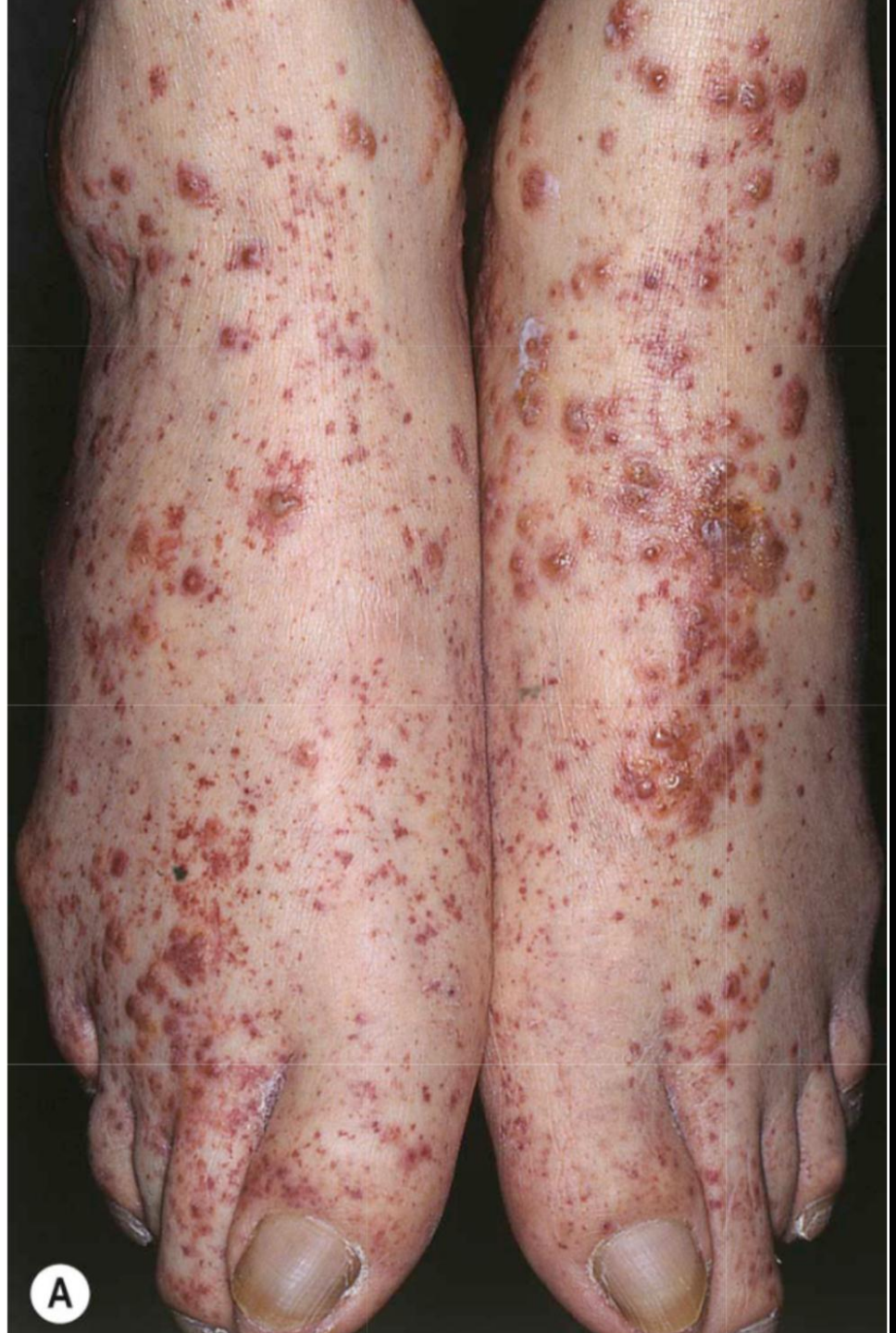
Photoallergy

- Occur as a result of cell-mediated hypersensitivity (to an allergen activated or produced by the effect of light on a drug).
- UVR is required to convert the drug into an immunologically active compound (Photo-allergen) that induces the immune response.
- More chronic than phototoxic.
- Clinically: Pruritic and resemble dermatitis or lichen planus but primarily in sun-exposed sites.
- Most common drugs: Thiazide diuretics, Sulfonamides antibiotics, Sulfonylureas and phenothiazines (all contain sulfur)
- Tx: Drug withdrawal, Topical steroids, physical barriers, reduce sun exposure + broad-spectrum sunscreens.



Vasculitis

- ~10% of the cases are due to drugs.
- Clinically: Purpuric papules on the lower extremities.
- Systemic involvement is very unusual.
- Occurs 7-21 days after drug administration and less than 3 days following re-challenge.
- Most common drugs: Penicillins, NSAIDs, Sulfonamides and cephalosporins.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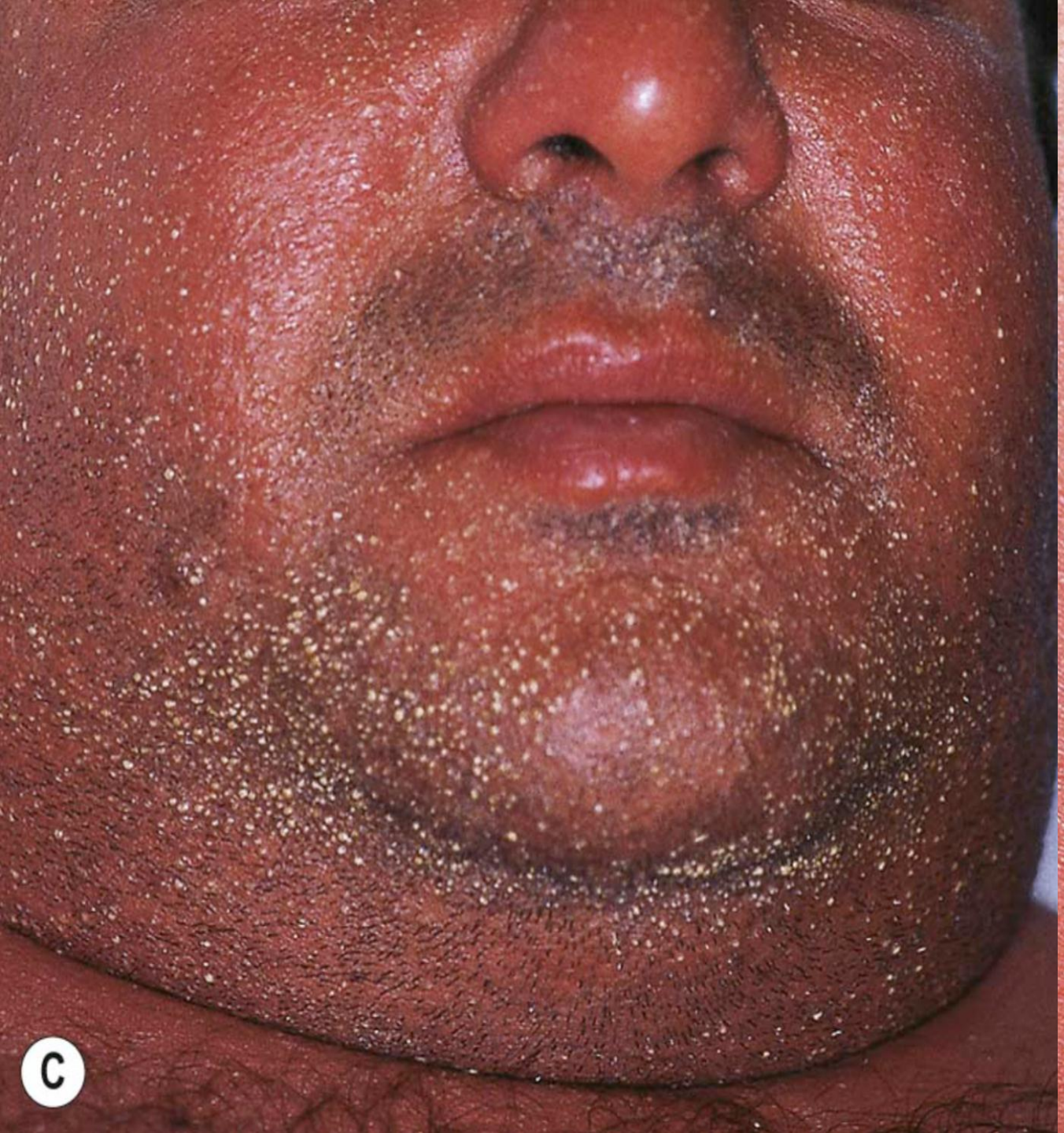
Neutrophilic drug eruptions

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)

SWEET'S SYNDROME (ACUTE FEBRILE NEUTROPHILIC DERMATOSIS)

Acute generalized exanthematous pustulosis (AGEP)

- Acute febrile drug eruption.
- Numerous small, non-follicular, sterile pustules, arising within large areas of edematous erythema.
- More than 90% of cases are drug-induced.
- The onset is usually within 2 days of starting the medication.
- Lesions begin on the face or intertriginous zones (groin, axillae) and then disseminate within a few hours.
- The lesions last for 1 to 2 weeks and are followed by a superficial desquamation.
- DDx: Acute pustular psoriasis
- Drugs: Antibiotics (Beta-lactam and macrolides), CCB and Antimalarials.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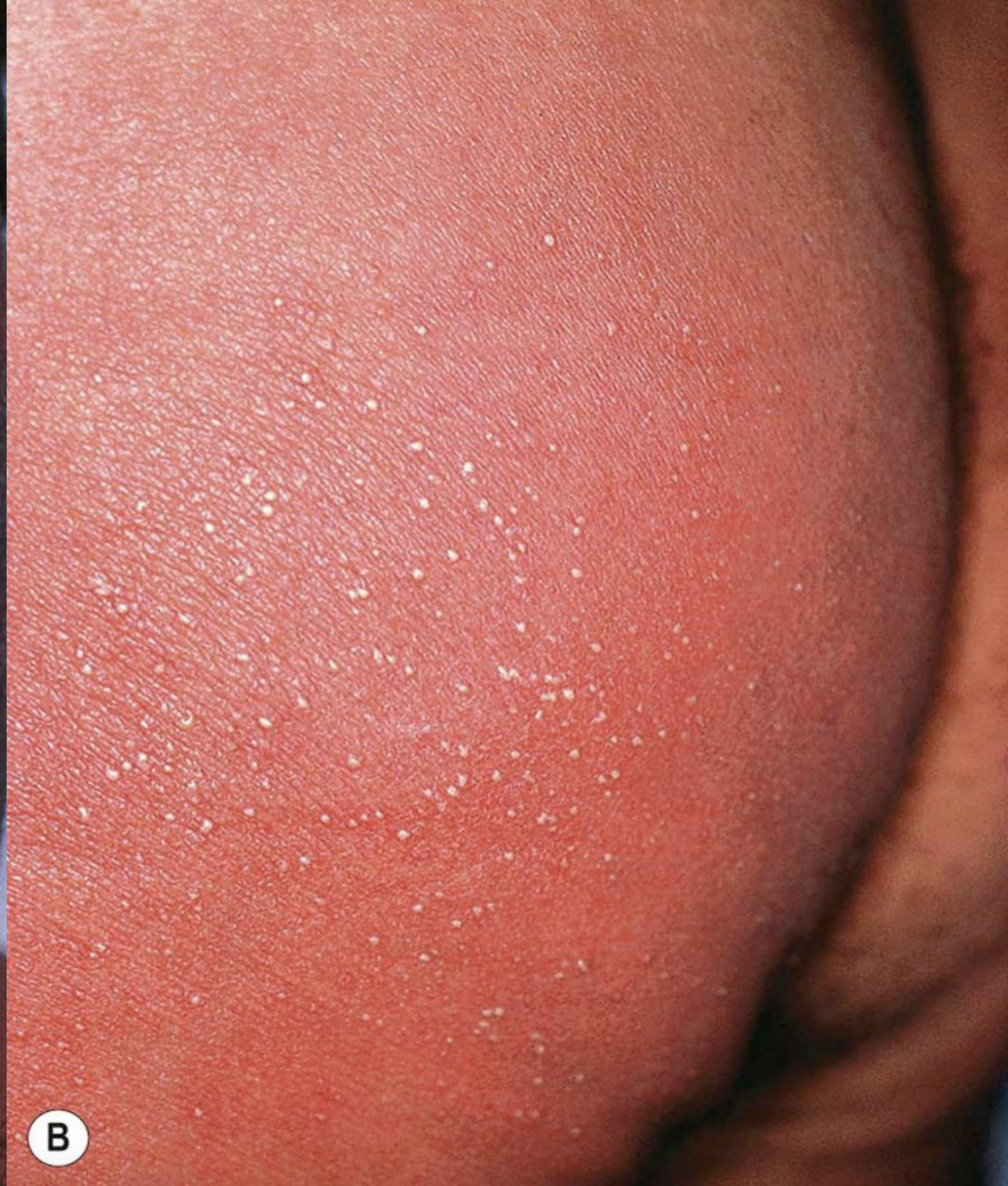
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Sweet's syndrome (Acute febrile neutrophilic dermatosis)

- This syndrome is characterized by fever, peripheral blood neutrophilia, and painful erythematous plaques that favor the face and upper extremities.

- Drugs represent <5% of all cases and starts about a week after the onset of drug administration.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

- AKA Drug-induced hypersensitivity syndrome (DIHS)
- Due to alteration in the metabolism of drugs + immune mechanisms.
- Possible role for viruses HHV-6 and HHV-7?
- Drugs: Anticonvulsants (phenobarbital, Carbamazepine and phenytoin) and sulfonamides.

- **Clinically:**

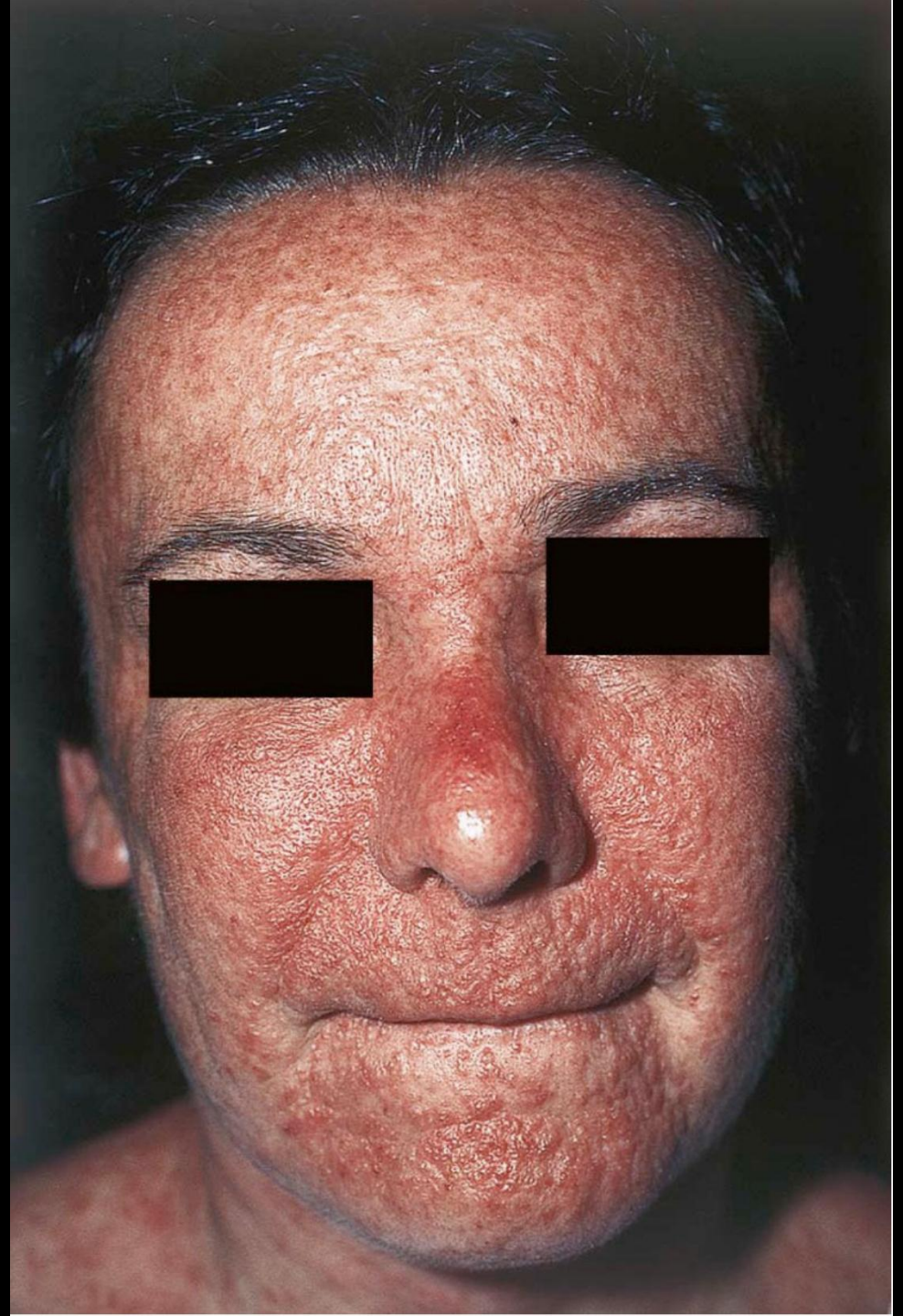
- Starts 2-6 weeks after drug initiation.
- Fever (85%) and a cutaneous eruption (75%) are the most common symptoms.
- Begins as a morbilliform eruption, which later becomes edematous, with follicular accentuation.
- The face, upper trunk and extremities are the initial sites of involvement.
- Edema of the face is a hallmark of DRESS.

DRESS

- Lymph nodes are often enlarged.
- The most common and most severe site of visceral involvement is the liver (majority of deaths associated with this syndrome.
- Other organs involved: Heart, lungs, kidneys and thyroid.
- Prominent eosinophilia is a very characteristic feature.

- **Treatment:**

- Early withdrawal the offending drug. (may not be sufficient for obtaining a full recovery)
- Topical steroids for mild cases.
- Systemic steroids for life-threatening heart and lung involvement.

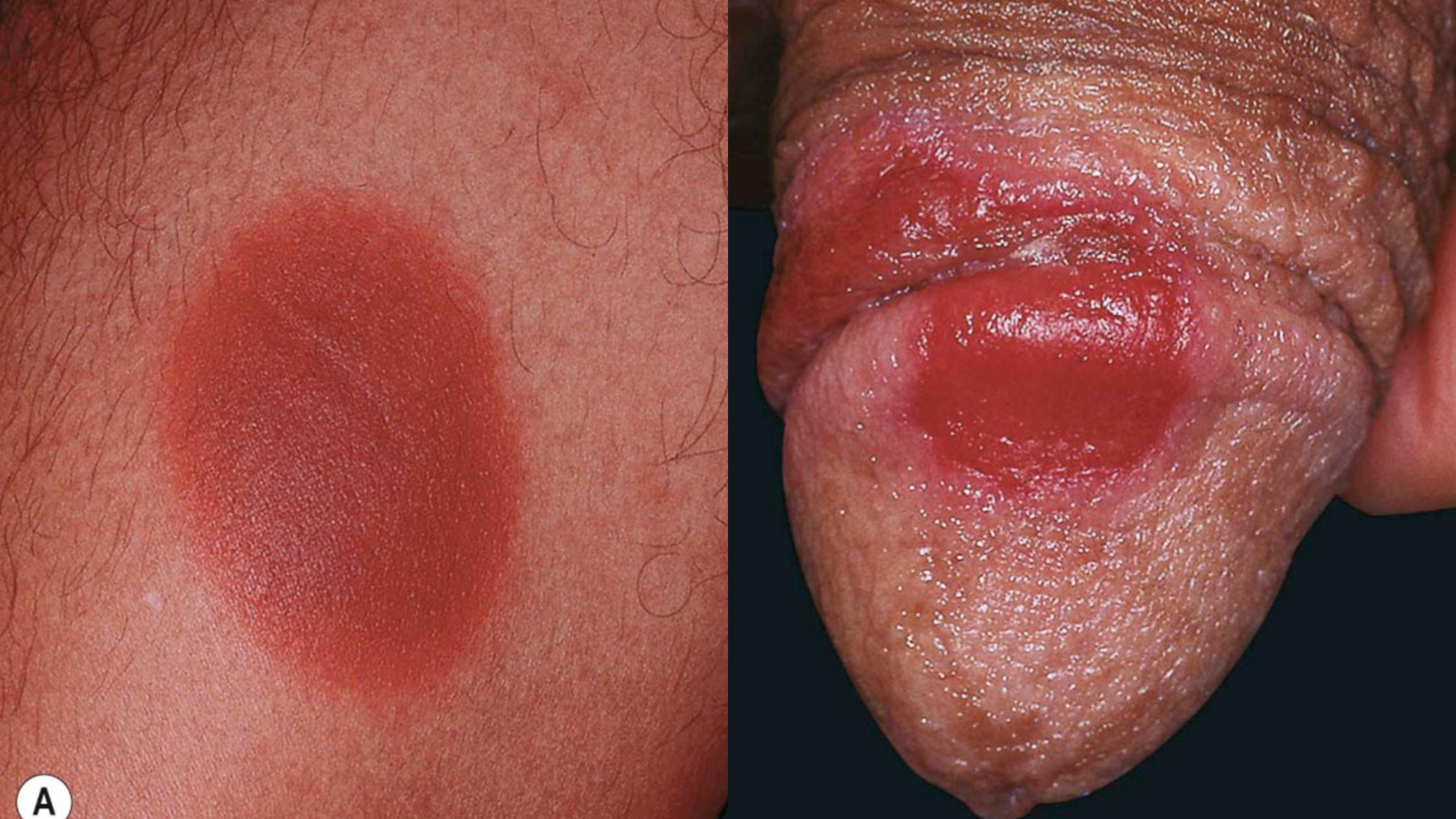


Bullous Eruptions

- Fixed drug eruption
- Linear IgA bullous dermatosis
- Drug-induced bullous pemphigoid
- Drug-induced pemphigus
- Steven-Johnson syndrome and TEN

Fixed drug eruption

- Lesions develop 1-2 weeks after a first exposure and within 24 hours within subsequent exposures.
- One or a few round, sharply demarcated, erythematous and edematous plaques are seen.
- Sometimes a dusky, violaceous hue and a central blister may be seen
- Favors the lips, face, hands, feet and genitalia.
- The lesions progressively fade over several days (leaving PIH behind).
- Lesions recur at exactly the same sites upon re-administration of the drug.
- There is a generalized form of FDE (similar clinically to EM/SJS).
- A non-pigmenting variant of FDE occurs mainly with pseudoephedrine.
- Drugs: Sulfonamides, NSAIDs, Barbiturates, Tetracyclines and Carbamazepine.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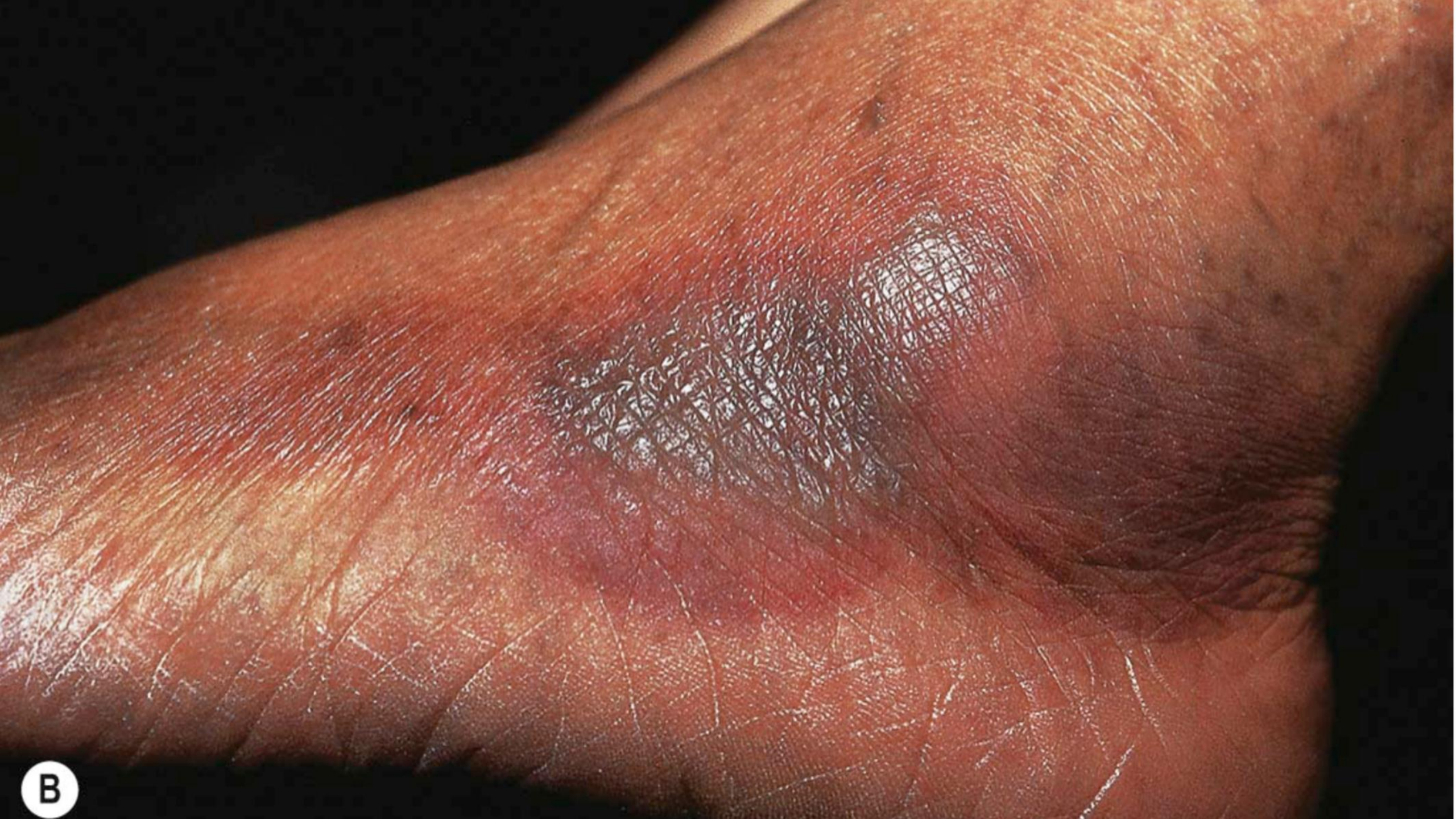
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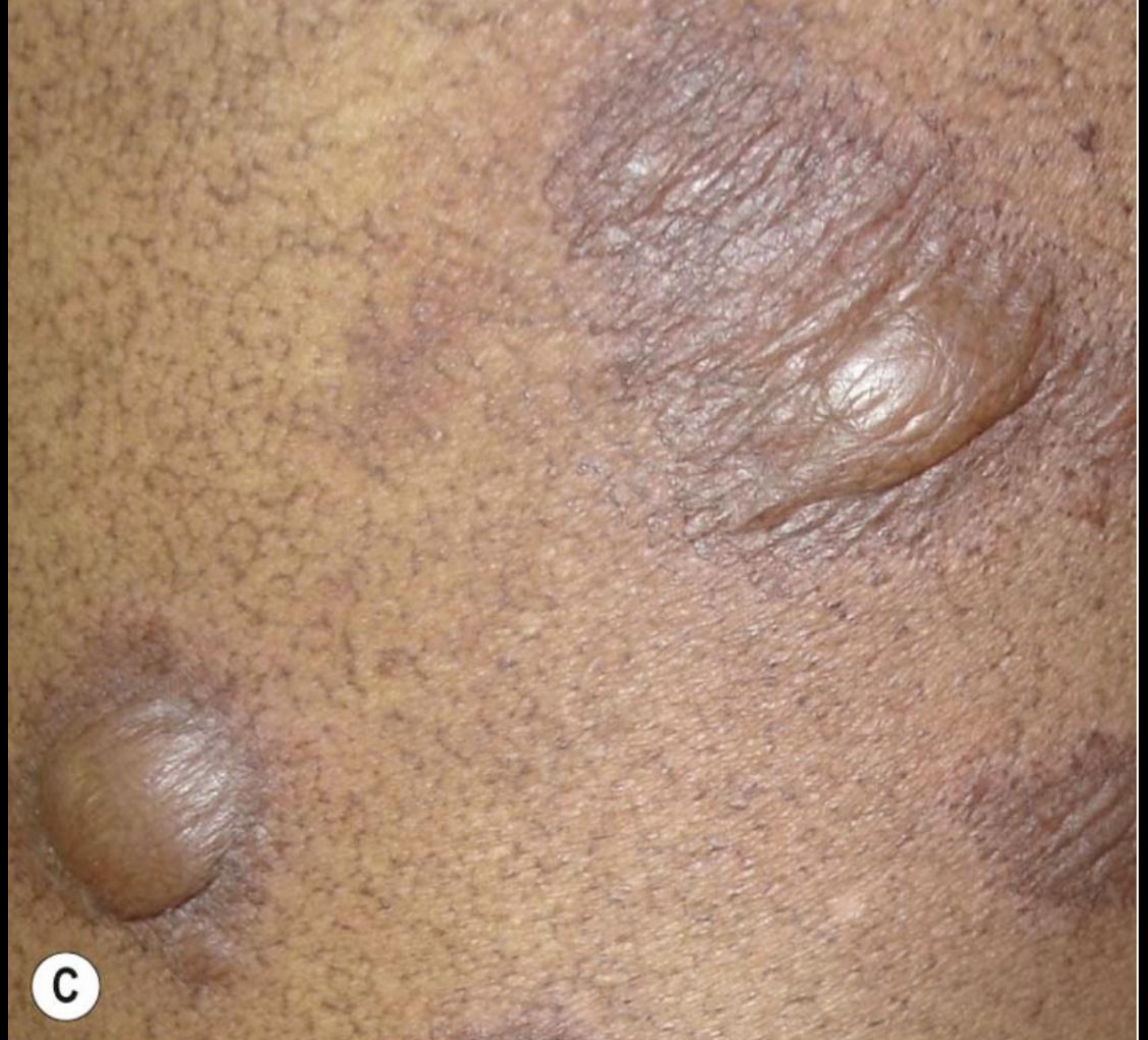
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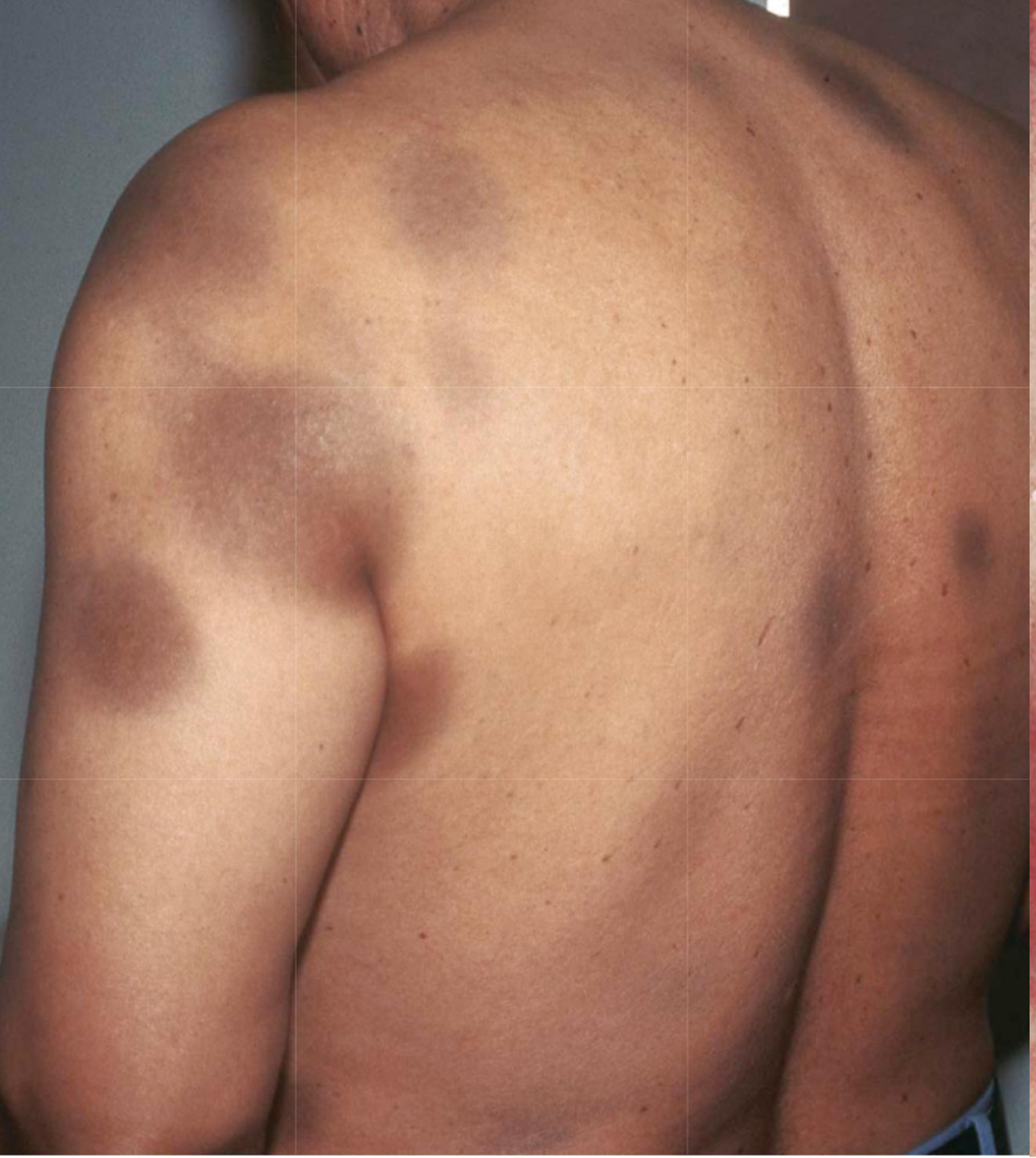
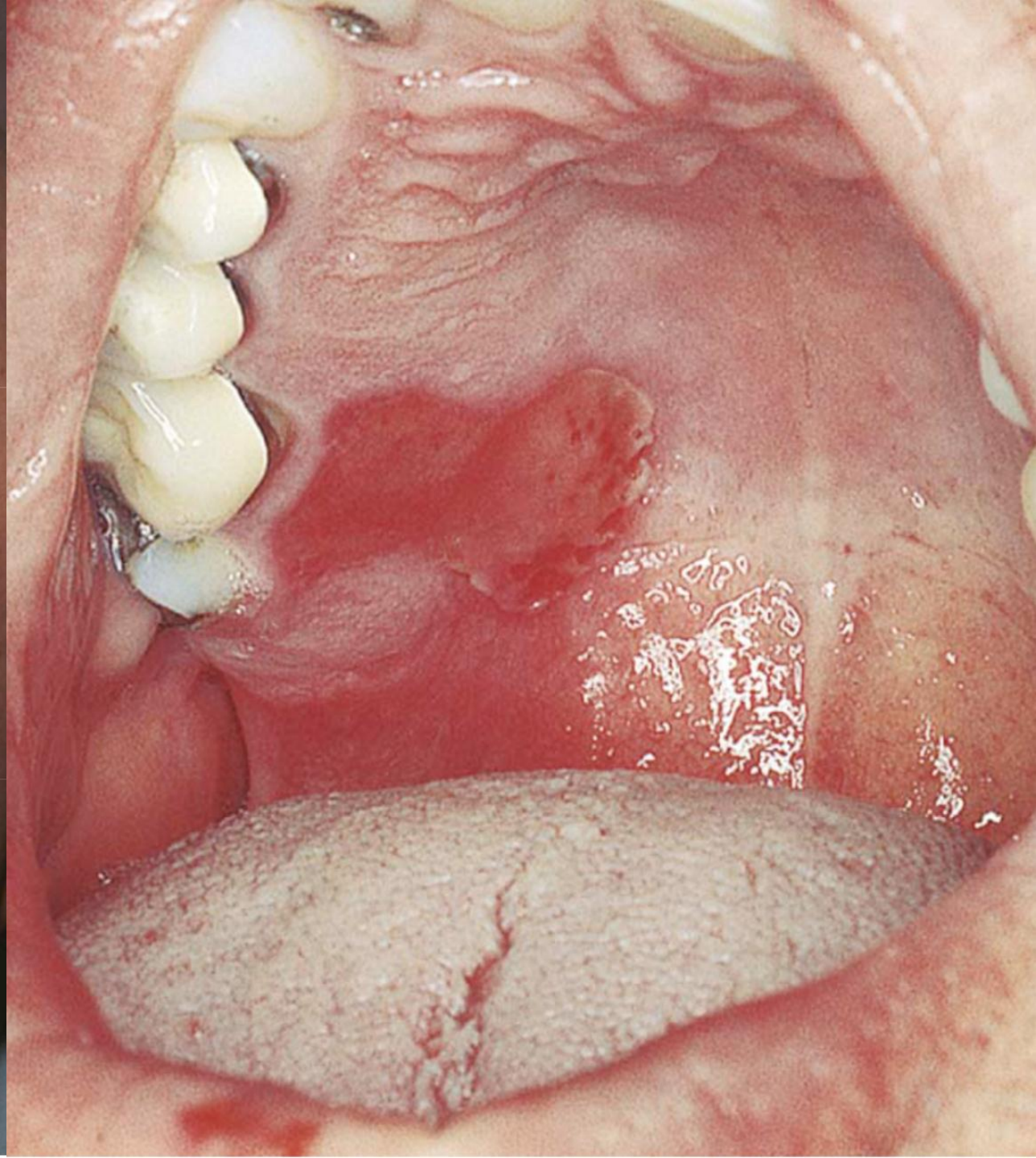
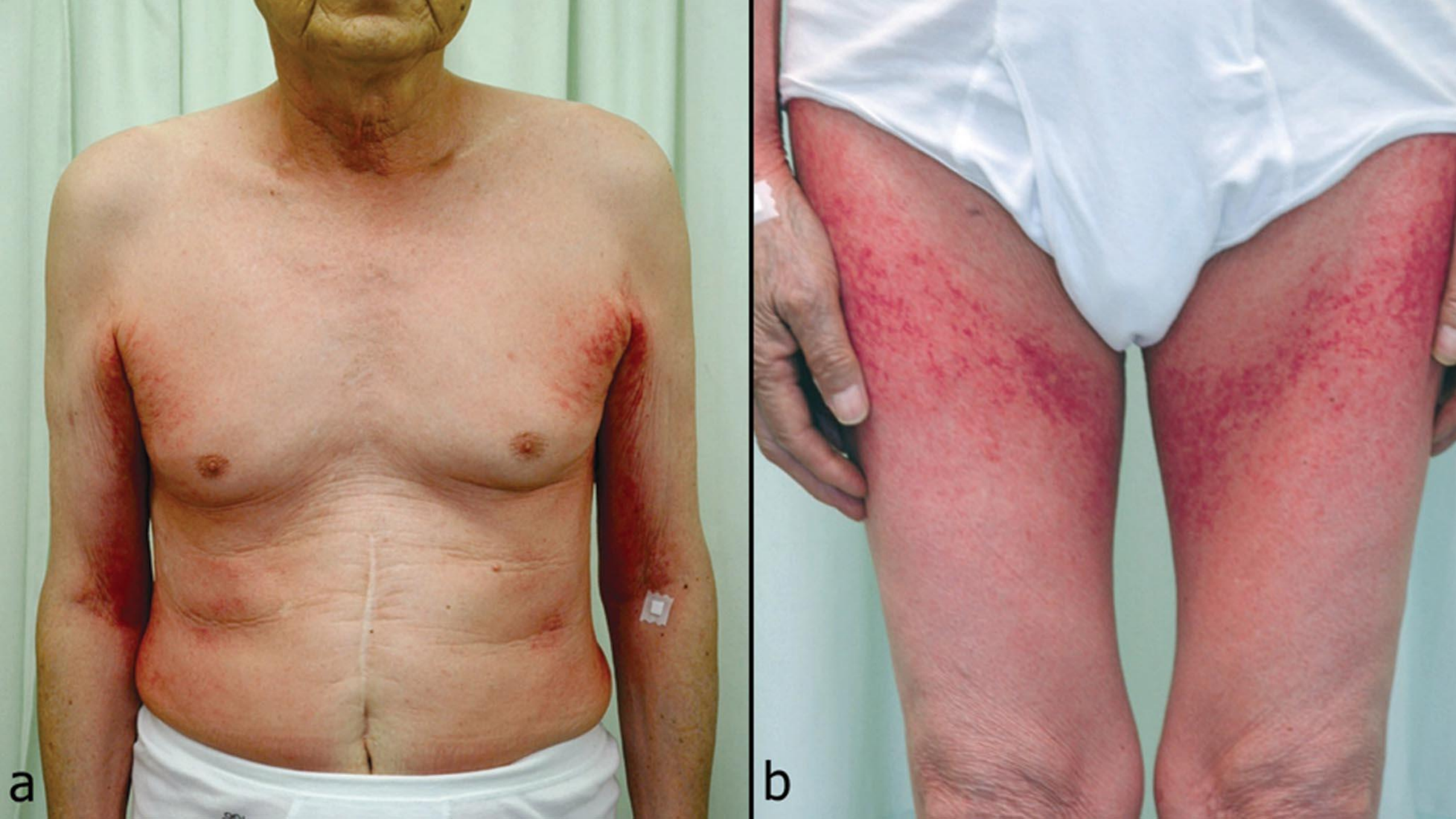




Symmetrical drug-induced intertriginous and flexural exanthema (SDRIFE)

- Sharply demarcated, symmetrical areas of erythema over the anogenital region after exposure to systemic drugs.
- Aminopenicillin & Cephalosporin are the most common drugs.
- There is usually involvement of at least one flexural site.

SYMMETRICAL DRUG-RELATED INTERTRIGINOUS AND FLEXURAL EXANTHEMA (SDRIFE) – CLINICAL CRITERIA
• Exposure to a *systemically* administered drug*, occurring with either the initial or a repeated dose (excluding contact allergens) • Sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area • Involvement of at least one other intertriginous site/flexural fold • Symmetry of affected areas • Absence of systemic symptoms and signs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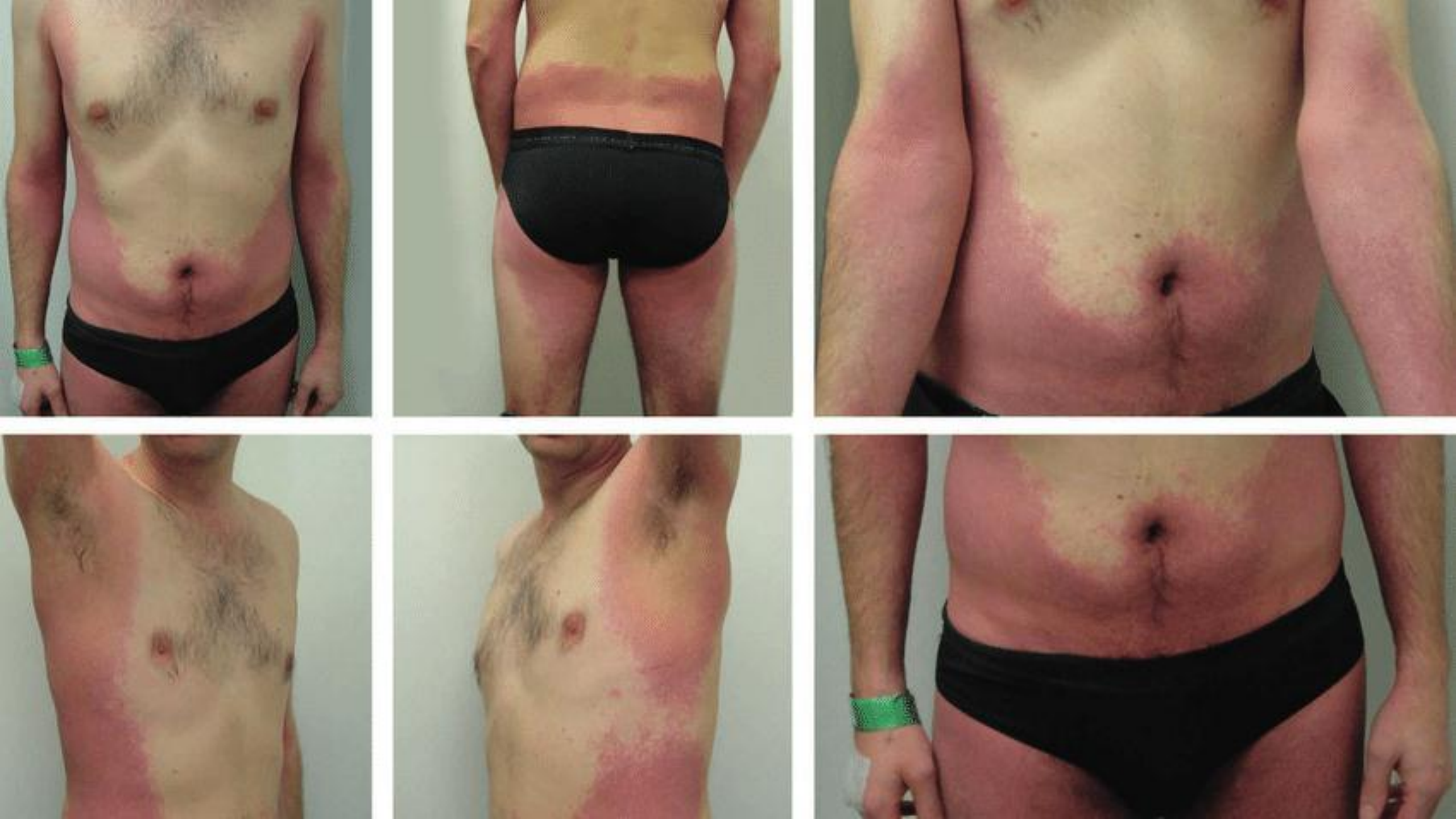
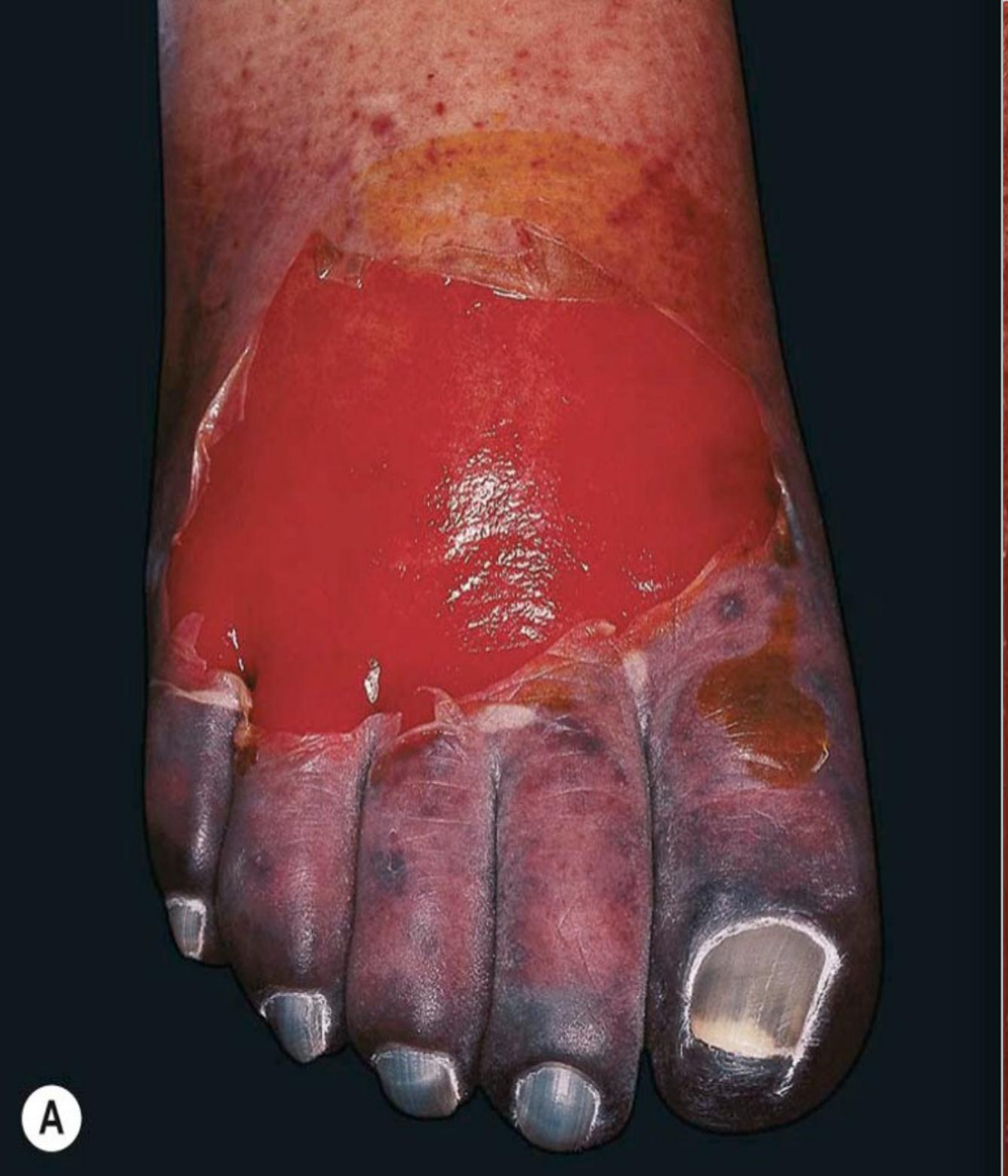


Others

- Anticoagulant-induced skin necrosis
- Serum sickness-like eruption
- Drug-induced lupus
- Drug-induced psoriasis
- Acneiform eruptions
- Pigmentary changes
- Pseudolymphoma
- Chemotherapy reactions

Anticoagulant-induced skin necrosis

- Rare, sometimes life-threatening.
- Induced by Warfarin or Heparin.
- Begins 2 to 5 days after therapy.
- Erythematous, painful plaques evolve into hemorrhagic blisters and necrotic ulcers.
- Mainly over the breasts, thighs and buttocks.
- Patients with hereditary deficiency of protein C are at highest risk.
- Tx: Discontinue warfarin & start Vitamin K + I.V infusion of protein C.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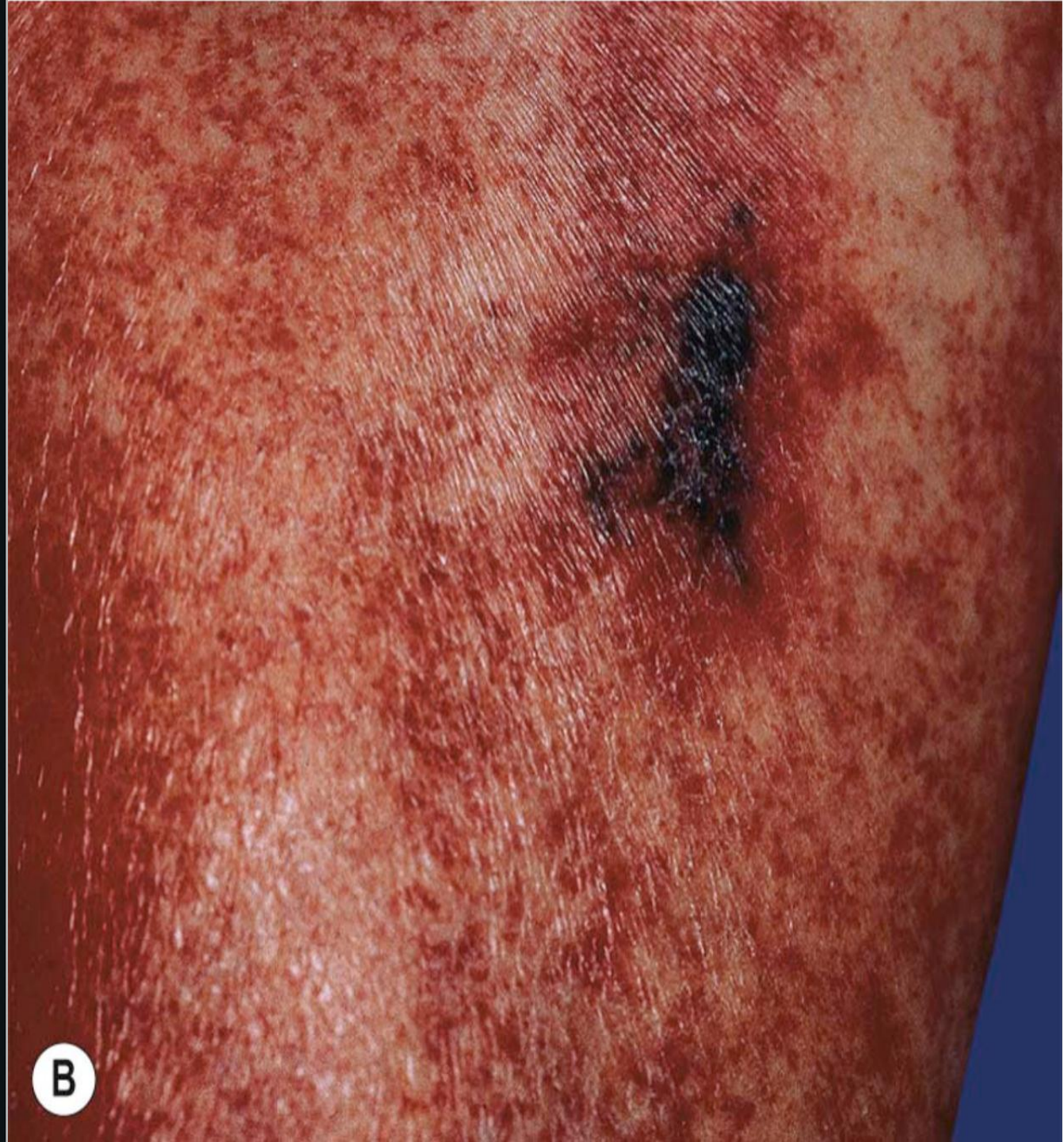
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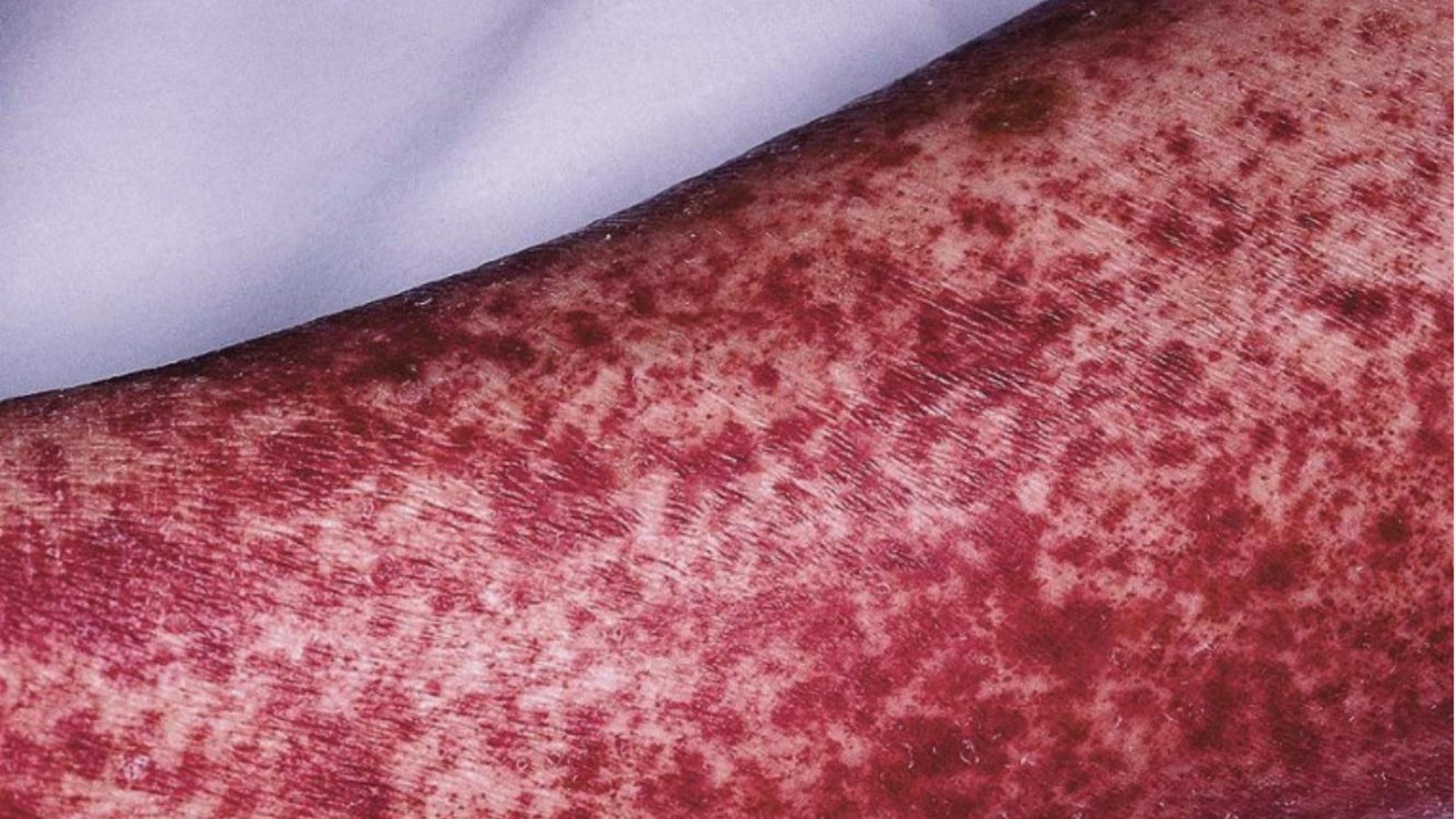
Serum sickness-like eruption

- Mainly in children
- Fever, Arthralgias, arthritis, rash and lymphadenopathy.
- 1 to 3 weeks after drug exposure.
- Unlike true serum sickness, hypocomplementemia, vasculitis and renal disease are absent.
- Occurs in approximately 1 in 2000 children given cefaclor.



Drug-induced Lupus

- **Drug-induced systemic lupus:**

- Fever, weight loss, pericarditis and pulmonary inflammation.

- Skin involvement is rare but includes: malar-erythema, photo eruption and discoid lesions.

- Vasculitis, renal and neurologic involvement is rare.

- Starts over a year after the medication is initiated.

- +ve anti-histone Abs in 95% of cases. (-ve DsDNA)

- Clinical symptoms resolve within 4 to 6 weeks.

- Procainamide, hydralazine, chlorpromazine, isoniazid, methyldopa, quinidine, D-penicillamine and Minocycline.

- **Drug induced subcutaneous lupus:**

- Psoriasiform and annular lesions on the upper trunk and extensor arms.

- Hydrochlorothiazide, CCBs, Terbinafine, NSAIDs, Griseofulvin.

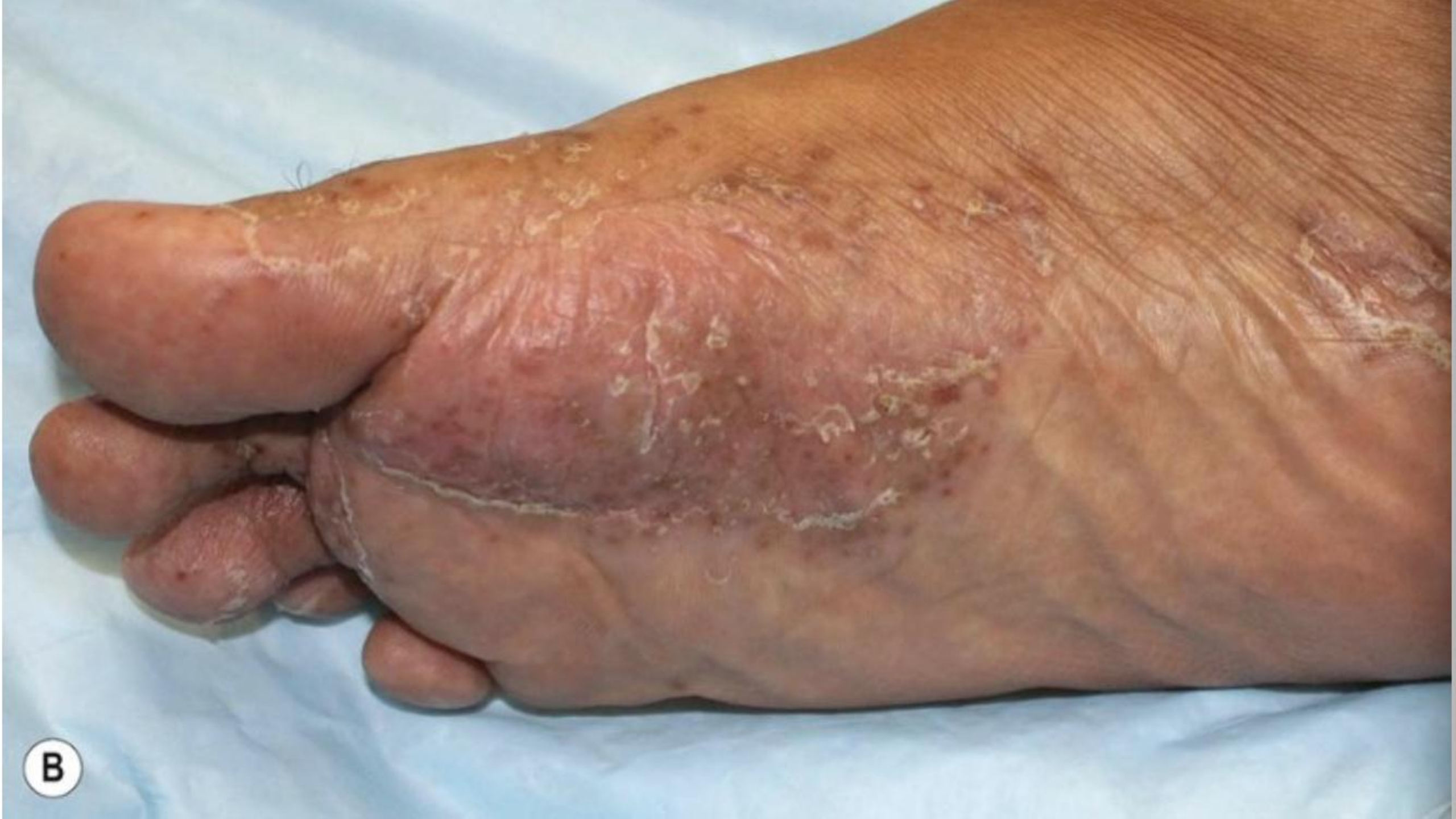
- Resolution of the rash may or may not occur after discontinuation of the responsible drug.

Drug-induced Psoriasis

Drugs can affect a patient in 3 different ways:

1) Exacerbation of pre-existing psoriasis
2) Induction of lesions of psoriasis in clinically normal skin in a patient w psoriasis.
3) De novo psoriasis.

- Terbinafine, NSAIDs, Antimalarials, ACE inhibitors, Lithium and B-blockers.
- TNF-induced Psoriasis.
- Lesions of drug-induced psoriasis usually regress within weeks to a few months of discontinuing the inciting drug.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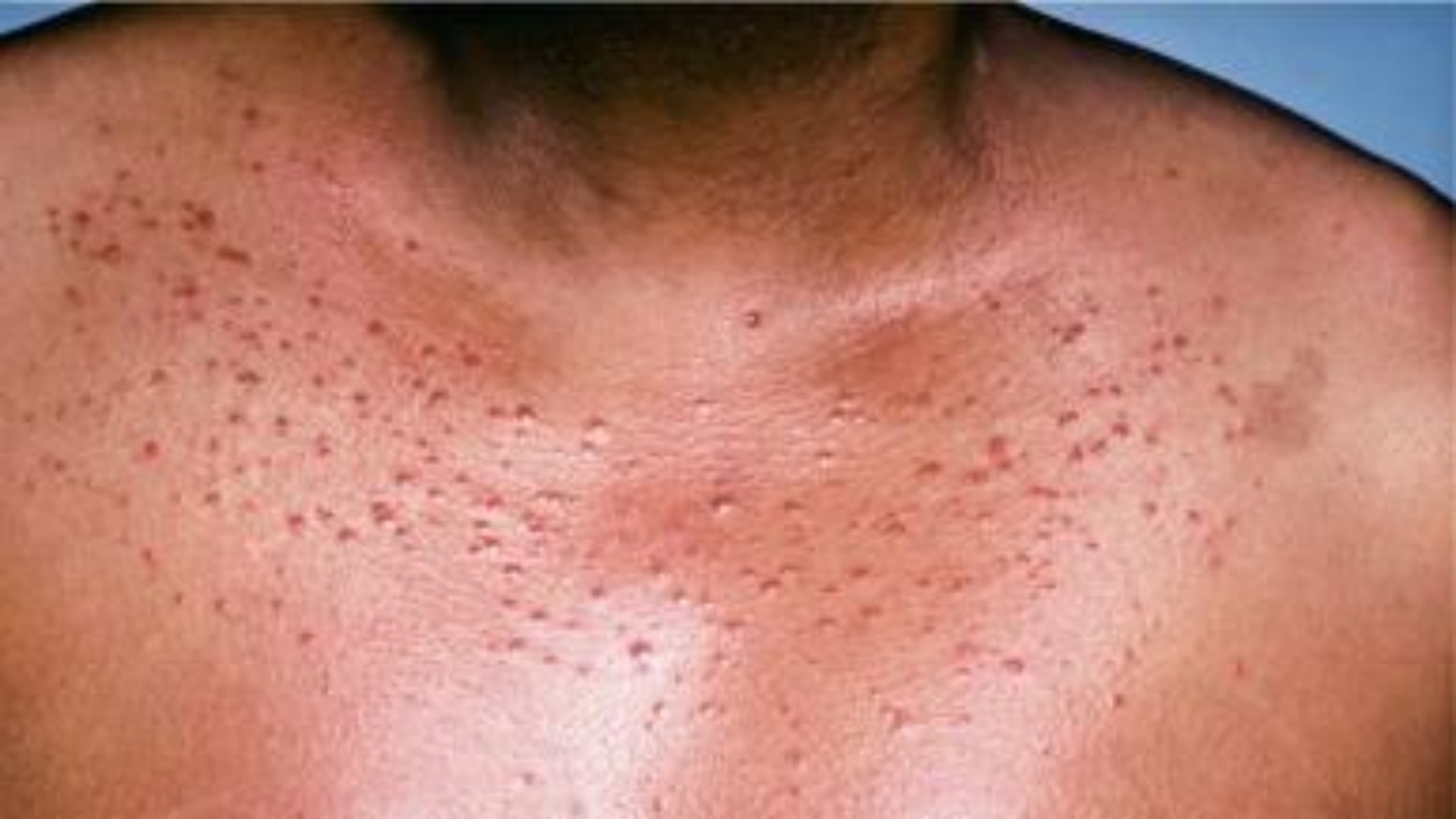
Acneiform eruptions

- Represent ~1% of drug-induced skin eruptions.
- Clinically, just like acne but comedones are absent.
- Corticosteroids, Androgens, hydantoins, lithium, progestin-containing OCPs.



Pigmentary changes

- Hyperpigmentation:

Usually more pronounced in sun-exposed areas.

- Minocycline
- Antimalarials
- Amiodarone
- Silver, gold and arsenic
- Bleomycin

- Hypopigmentation:

- Chronic use of topical steroids