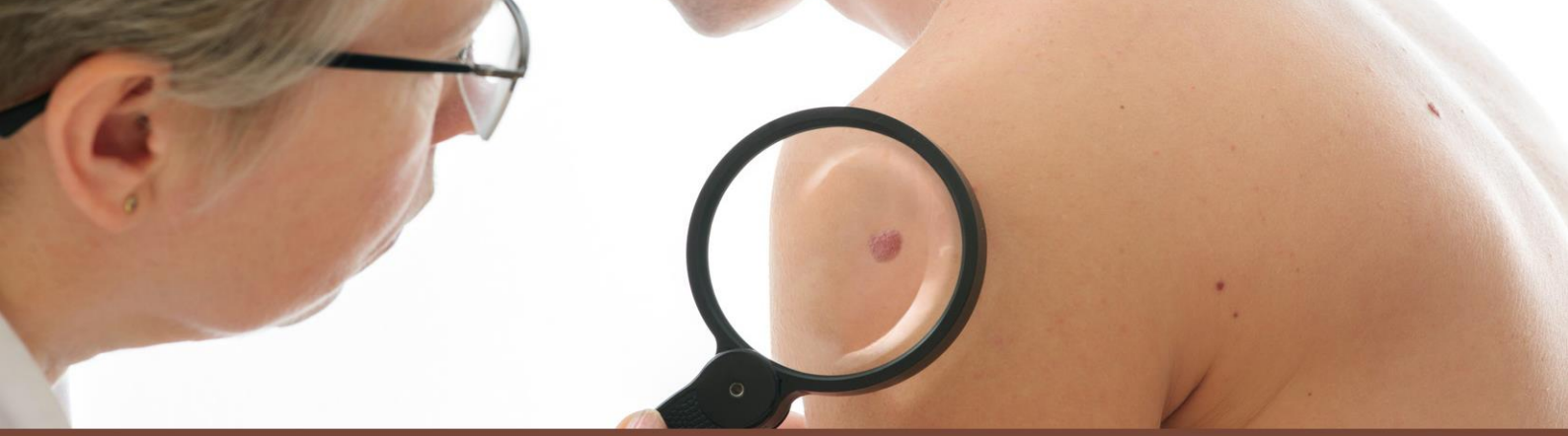

433 Teams

DERMATOLOGY

Adverse cutaneous drug reactions (L15)

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Objectives:

NOT GIVEN!!

Color index:slides,doctor notes,432 notes

ADVERSE CUTANEOUS DRUG REACTIONS:

Are common (2-3% of patients)

Most reactions are mild, accompanied by pruritus and resolve promptly after drug withdrawal. Severe, life threatening ACDRs are rare and unpredictable

They can mimic all the morphologic expressions in dermatology.

Must be the first consideration in the differential diagnosis of a suddenly appearing eruption (other causes take time).

When taking history ask about herbal remedies, eye or ear drops some patients do not consider these to be medication. Also, ask about chemicals found in drinks like Quinine found in tonic Water, Aniline found in yellow food dye, and food preservatives that contain Salicylates

Majority are caused by immunologic mechanisms (Gel and coombs types I, II, III and IV) and in most reactions both cellular and humeral immunity are involved

Provoked by systemic or topical administration including eye/ear drops, suppositories/ pessaries

Mechanism:

The mechanism of drug reactions can be classified into two main groups:

1) Immunologically Mediated ACDRs (Allergic drug reactions) accounts for 80%

2) Non-immunologic ACDRs (Non-allergic drug reactions)

Immunologic:

- In order to developed this type of reaction the patient has to have genetic susceptibility

TYPE	PATHOGENESIS	CLINICAL PATTERNS
Type I	IgE mediated, Immediate type	Urticaria/ Angioedema Anaphylaxis
Type II	Drug + Cytotoxic antibodies cause lysis of cells	Patechiae d° thrombocytopenic purpura Drug-induced pemphigus
Type III	Immune complexes formed of Immunoglobulins and drugs	Vasculitis / serum sickness
Type IV	Cell-mediated, delayed type	Morbillifom exanthems, fixed drug eruptions, lichenoid eruptions, Stevens-Johnson Syndrome/ TEN

Type 4 is the most common pathogenic route of cutaneous drug reactions

Nonimmunologic ACDR:

TYPE	MECHANISM
Idiosyncrasy	Hereditary enzyme deficiencies/ Idiopathic
Cumulation	Dose dependent eg: pigmentation gold, amiodarone or minocycline
Photosensitivity	Formation of toxic photoproducts the effect of ultraviolet irradiation on a drug (eg. Formation of singlet oxygen/ free radicals)
Irritancy/ toxicity of a topically applied drugs including injections sites.	Direct physical and chemical toxicity
Pseudoimmunologic: direct release of inflammatory cytokines	Mast cell degranulation, alternate complement system, cycloxyginase inhibitors, others

It happens by direct effect on the terminal immunological pathway (mast cells, complement system); you get the same end result as immunological mediated reaction.

Clinical types of ACDR :

Exanthematous (most common)

Urticaria/ angioedema (second most common) serious if it involves the respiratory tract.

Fixed drug eruptions

Anaphylaxis/ anaphylactoid rxns

Serum sickness

DRESS Syndrome

ACDR- related pigmentation/ necrosis/ alopecia/ nail changes.

ACDR mimicry of other dermatoses:

Acneiform, Bullous, dermatomyositis-like, Drug hypersensitivity syndrome, Eczematous, EM, SJS, TEN, Erythema Nodsum, Exfoliative dt., Erythroderma, Lichenoid, LE, Photosensitivity, Pityriasis rosea-like, Pseudolymphoma, Pseudoporphyria, Psoriasiform eruption, Purpura, Pustular eruptions, Scleroderma-like reactions, Sweet syndrome, Vasculitis

Guidelines for assessing possible ACDRs:

- Exclude other causes esp. infections
- Examine interval between introduction and induction
- Determine if similar reactions occurred with the same or similar compounds . (e.g. Penicillins and cephalosporins)
- Note any improvement after withdrawal (Usually the rash will clear in 2-3 days to weeks but, Some drug rashes last longer than others e.g. gold which can last for months)
- Note any reaction after readministration

Findings indicating possible life-threatening ACDR:

- Arthralgia
- Blisters/epidermal detachment/ positive Nikolsky sign
- Confluent erythema
- Enlarged lymphnodes
- Facial edema/central facial involvement
- High fever (>40°c)
- Mucous membranes erosions
- Palpable purpura
- Skin necrosis
- Skin pain
- Shortness of breath, wheezing, hypotension
- Swelling of the tongue/ oral mucosa
- Urticaria/ Angioedema

Diagnosis :

is usually made on clinical findings Biopsy : is helpful in defining the type of reaction pattern but not in identifying the offending drug.

CBC : eosinophil count• >1000/microL, lymphocytosis with atypical lymphocytes

Chemistry : abnormal LFT (to detect DRESS syndrome)

Skin Test/RAST : helpful in IgE-mediated reaction (penicillin) Limited and may be dangerous (can induce anaphylaxis)

Management :

- DC the culprit drug/drugs (cf. morbilliform vs. angioedema, SJS and TEN)
- Symptomatic treatment
- Prevention: awareness; premedication

Exanthematous Drug Reactions:

Definition: A cutaneous eruption that mimics a measles-like viral exanthem. (synonyms: Morbilliform drug rash, maculopapular drug reaction). Most common type of cutaneous drug reaction but less common in the very young.

The following medications are known to cause ACDR:

- Anticonvulsants - Sulfonamides - NSAIDs - Antibiotics

Pathogenesis

Exact mechanism unknown. Probably delayed hypersensitivity.

Most commonly incited drugs (10-20%): penicillins, carbamazepine, allopurinol, gold salts. Less common (3-5%) : sulfonamides (bacteriostatic, diuretic, antidiabetic), NSAIDs, hydantoin derivatives, isoniazid, chloramphenicol, erythromycin + others (<1%).

Special situations: Mononucleosis, HIV, Allopurinol, cross-drug hypersensitivity.

Clinical Manifestations

Onset: peak incidence at ninth day after administration, 2-3 days after readministration.

Symptoms: severe pruritis (if painful think TEN) ± fever, chills

Signs: - symmetric trunk + extremities (in children face and extremities)

bright red macules/papules -> confluent: sheet-like / polycylic/ reticular patches -> erythroderma, ->scaling/desquamation with healing

usually spare face, periareolar area and surgical scars. Exanthem on buccal mucosa

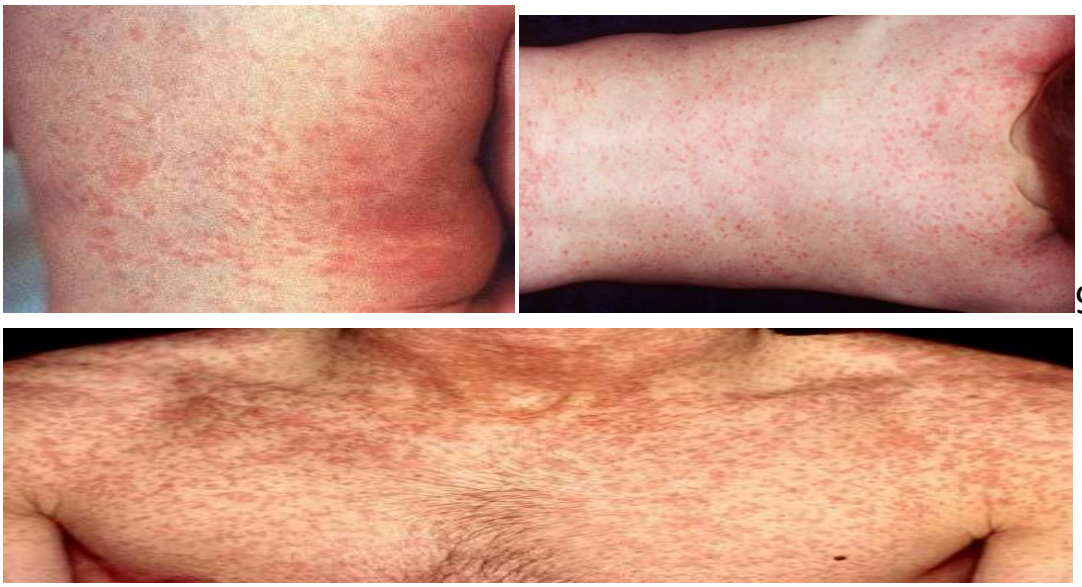
Diagnosis

Clinical Diagnosis

- Histopathology: perivascular lymphocytes and eosinophils
- Blood: eosinophilia

Differential Diagnosis

- Viral exanthems
- Secondary syphilis
- Atypical pityriasis rosea
- Early widespread allergic contact dermatitis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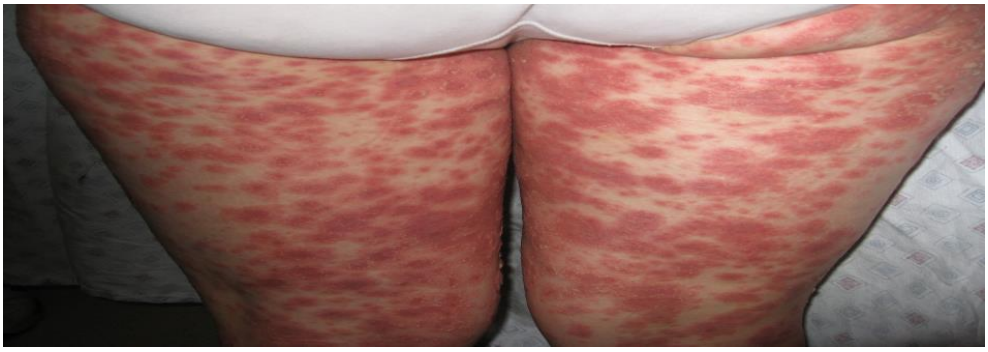
Maculopapules



Exanthematous

Prognosis:

Good but maybe the initial presentation of a more serious eruption, i.e. SJS, TEN, DRESS, or serum sickness.

Treatment:

Definitive (cf. indications for discontinuation of a drug)

Symptomatic

Oral antihistamines, topical and systemic corticosteroids

Prevention

- Awareness of specific drug and cross-reactants

- wearing a bracelet

Drug-Induced Acute Urticaria/Angioedema, Edema and Anaphylaxis:

Definition: transient wheals and edema

Pathogenesis: Immune-mediated (IgE or complement and immune complex)

Non allergic: cyclooxygenase inhibitors, direct degranulation of mast cells, direct complement trigger, kinin metabolism inhibitors.

Medication that can cause Urticari/angioedema: NSAID and Curare (used in anesthesia)

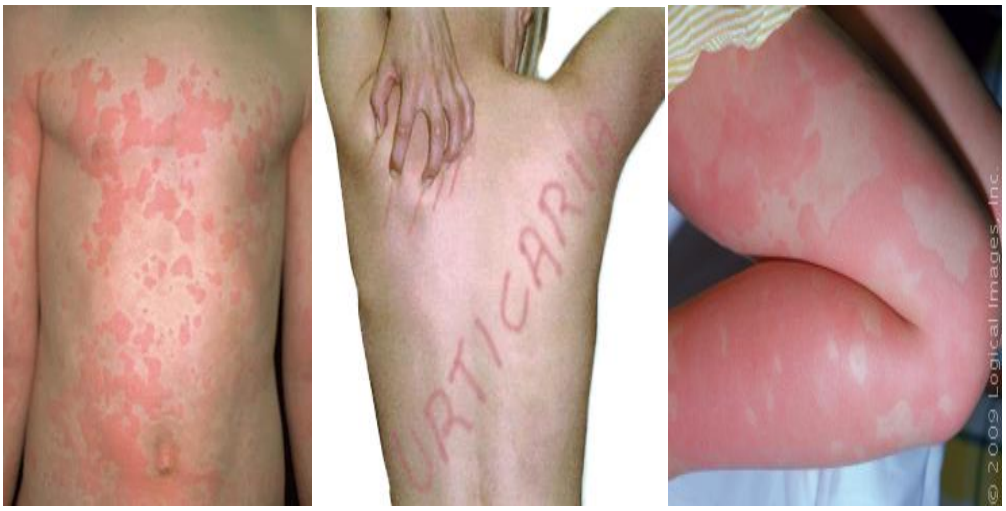
Clinical manifestation : Onset : 1-2 weeks after administration; minutes to hours after re-administration

Symptoms: - pruritus - burning palms/ soles/ auditory canal, dizziness, tongue numbness, palpitation, sudden fatigue, difficulty breathing, headache substernal pressure, crampy abdominal pain.

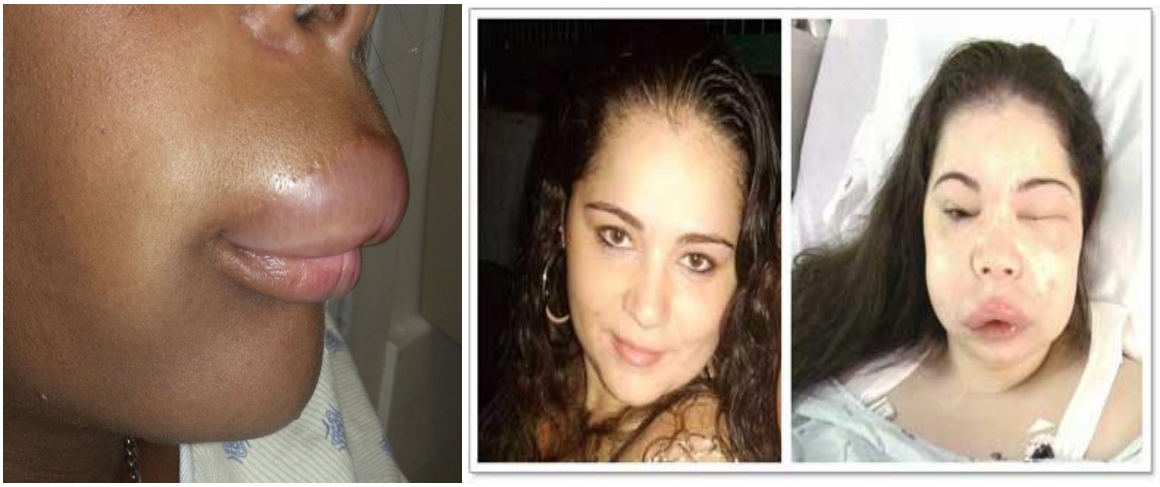
Signs: - Wheals and/or large and deep skin colored swellingsϖ - flushing, yawning, airway edema, sneezing, bronchopasm, laryngeal edema, hypotension, vomiting, diarrhea, arthralgia If

there is burning sensation, pinpoint bleeding, wheals last longer this is Urticaria

Vasculitis Wheals If the patient start having tongue numbness, palpitation, sudden fatigue, difficulty breathing then the patient is going to anaphylaxis and you have to treat him immediately with epinephrine never intubate him while he is having laryngeal edema.



Wheals



Angioedema, serious if it involves the respiratory tract.

Note the unclear boders

Diagnosis

Clinical Diagnosis

- Do biopsy if vasculitis suspected
- Measure complement if vasculitis suspected
- Ultrasonography if edema of bowel suspected

Differential Diagnosis

- Acute allergic contact dermatitis
- Insect bites
- Cellulitis

Prognosis :

- resolves within hours to weeks after drug withdrawal Treatment : - Definitive : discontinuation of a drug
- - Symptomatic : subcutaneous epinephrine (0.3-0.5ml of 1/1000) + airway/ IV access, H1/H2 blockers, sys. Glucocorticoids
- - Prevention: awareness/ wallet card/ bracelet/ pretreatment
- Epinephrine to counter the effect of cytokines, corticosteroids To prevent further release

Fixed Drug Eruption:

Definition

Identical skin lesion(s) that recur at the same location.

Pathogenesis

Unknown

Most common drugs: tetracyclines, antimicrobials phenolphthalein, oral contraceptives, NSAIDs, Salicylates, sulfonamides, metronidazole, barbiturates, food coloring (yellow), quinine

Clinical manifestation

Onset:

Within 30 minutes to 8hours after ingestion of drug in previously sensitized individual

Symptoms:

Usually asymptomatic (painful if eroded)

May be associated with headache (barbiturate analgesic), constipation (phenolphthalein laxative), Cold (OTC yellow dye) Food (yellow dye, quinine, salicylates)

Signs:

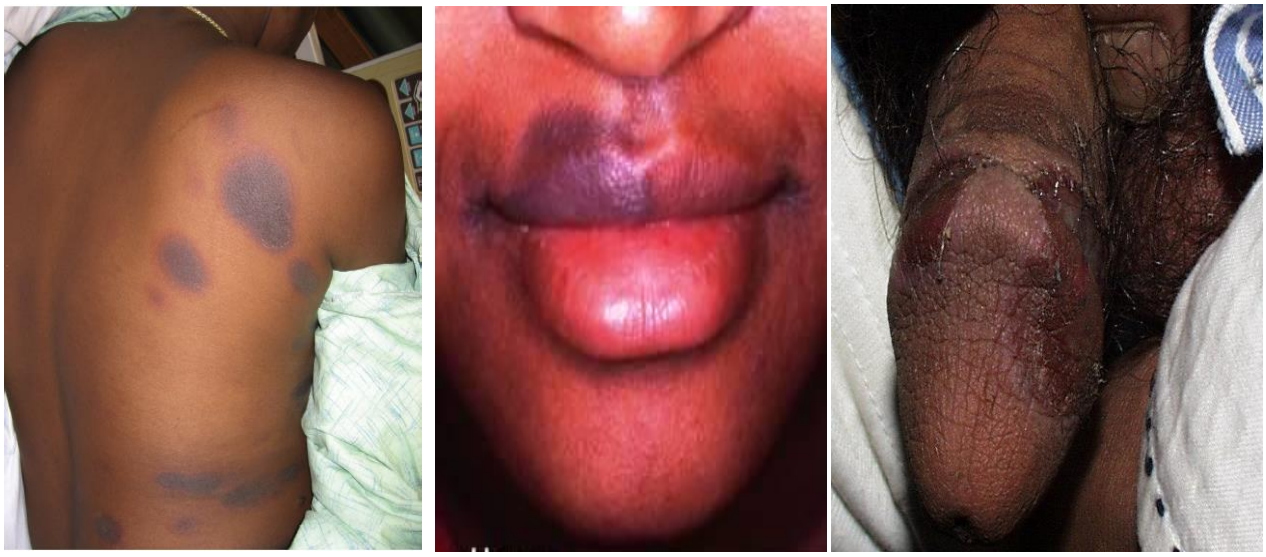
Round/oval usually solitary, sharply demarcated, erythematous macule

-> dusky red/violaceous edematous plaque

-> bulla/erosion

-> dark brown violaceous post inflammatory hyperpigmentation.

Common on genitals and oral mucosa but any site including periorbital, conjunctivae and oropharynx



Sulfonamide drug reacion

Diagnosis

Clinical diagnosis:

Histopathology similar to EM/TEN

Patch test (at the same site)

Differential diagnosis:

EM; Herpes simplex; Aphthae

if extensive: SJS/TEN

Prognosis

Resolves within weeks of withdrawal

Recurs within hours after a single dose

Treatment:

Non-eroded: potent topical glucocorticoid

Eroded: antimicrobial ointment

Widespread/ painful mucosal lesions: oral prednisolone 1mg/kg tapered over few weeks.

Drug Hypersensitivity Syndrome (DRESS):

Definition

An idiosyncratic serious adverse drug reaction that involves skin and other organs.

Pathogenesis

- Hereditary (toxic arene oxide metabolites; slow N-acetylation of sulfonamides)

- Idiopathic

Most common drugs:

- Antiepileptics (phenytoin, carbamazepine, phenobarbital)

- Sulfonamides (antimicrobials, dapsone, sulfasalazine

Clinical manifestation

Onset: 2-8 weeks after first drug administration

Symptoms: Fever, malaise, ± pruritus

Signs: Morbilliform eruption on face, upper trunk and extremities with periorbital edema and mucosal involvement

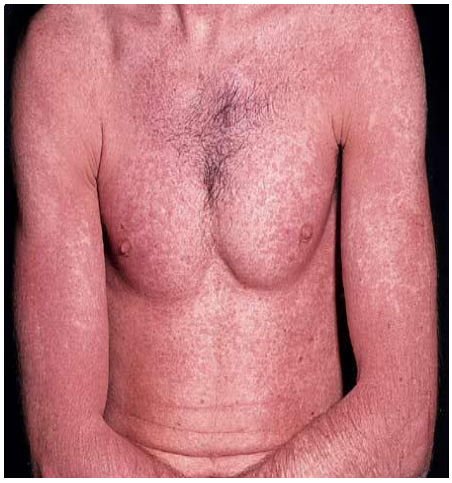
-> generalized exfoliative (erythroderma)

± pustular ± bullous ± purpura on legs

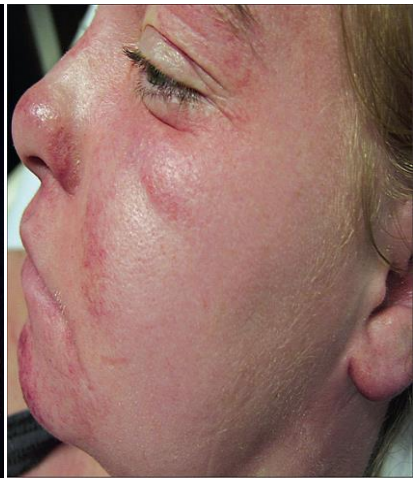
-> scaling/desquamation with healing

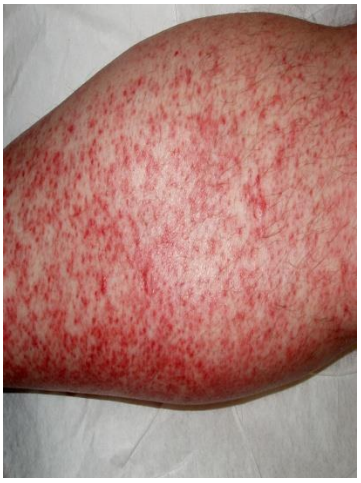
Other:

lymphadenopathy, hepatitis, carditis, nephritis, pneumonititis, hematologic, joints, muscles, thyroid, brain.



Morbilliform eruption





Periorbital edema

Diagnosis

Proposed diagnostic criteria (three criteria required for diagnosis):

1. Cutaneous drug eruption
2. Hematologic abnormalities (eosinophilia ≥1500/microL or atypical lymphocytes
3. Systemic involvement (adenopathies ≥ 2cm in diameter or hepatitis (SGPT ≥ 2N) or interstitial nephritis, interstitial pneumonitis or carditis)

Histopathology: variable lymphocytic infiltrate ±eosinophils/dermal **edema (may simulate CTCL).**

Differential diagnosis

Early: morbilliform eruptions

Later: serum sickness, vasculitis, collagen vascular disease

Rash plus lymphadenopathy: Rubella, EBV, CMV mononuleosis syndrome.

Prognosis

Rash and hepatitis may persist for weeks after withdrawal

Mortality 10% from systemic hypersensitivity eg. eosinophilic myocarditis.

Rare progression to lymphoma

Treatment

Withdrawal

Systemic glucocorticoids (prednisolone 0.5mg/kg/day) results in rapid improvement

Awareness, wallet card/ bracelet

Drug Induced Pigmentation:

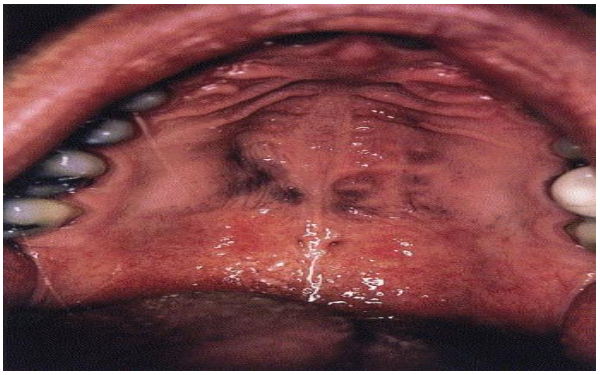
- Relatively common

- Results from the deposition of a variety of endogenous and/or exogenous pigments in the skin.

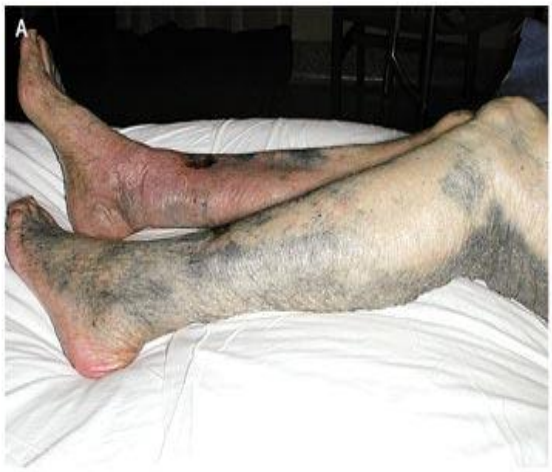
-Drugs involved:

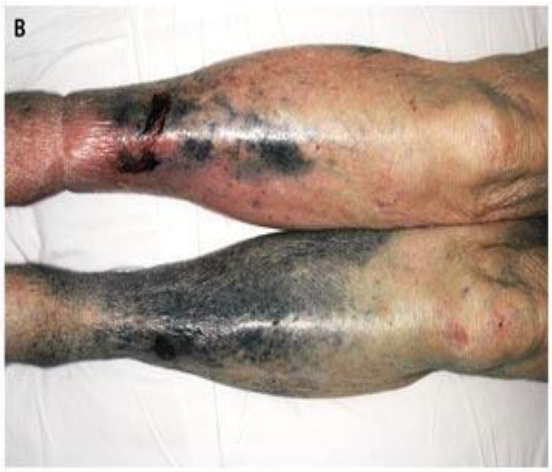
- Amiodarone
- Antimalarial
- Antimicrobial: minocycline, zidovudine, clofazimine
- Hydantoins/chlorpromazine
- Hormones: ACTH, estrogen/progesterone
- Heavy metals: silver, gold, mercury
- Cytostatic: bleomycin, cyclophosphamide,

-5-fluorouracil, dactinomycin, busulfan, doxorubicin, daunorubicin.

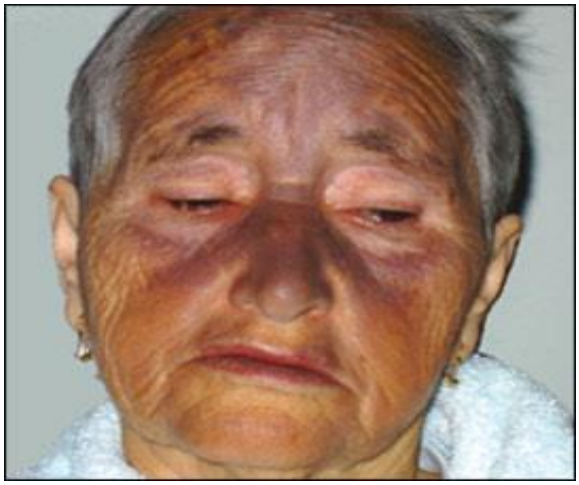


Mincycline induced pigmentation of the teeth

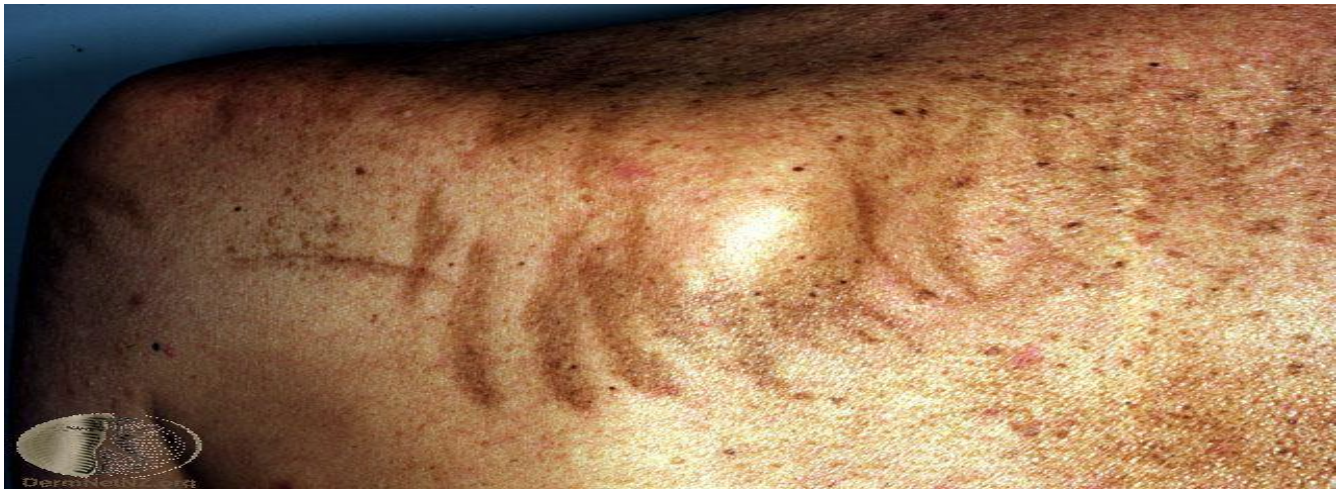




Minocycline induced pigmentation




Amiodarone induced pigmentation



Bleomycin induced pigmentation (Whiplash Configuration)

Minocycline

Usually after total dose of >50 grams

Not melanin but an iron-containing brown pigment in dermal macrophages

Stippled/ diffuse, blue-/slate-grey

Extensor legs, face (esp. periorbital), sites of trauma or inflammation, hard palate, nails, teeth, bones/cartilage/thyroid.

Disappears within months after discontinuation.

Antimalarials

Occur in 25% who take the drug for >4 months.

Due to melanin/hemosiderin

Brownish, grey brown and/or blue black. (quinacrine: yellow-green)

Over shins, face, nape of neck, hard palate, under finger- and toenails, cornea, retina, (quinacrine: yellow sclerae)

Disappears within few months.

ACDR- related necrosis:

-After oral drug or at sites of injection

Warfarin cutaneous necrosis: Idiosyncratic

Onset: 3-5 days of anticoagulation therapy. Due to a transient hypercoagulable state and thrombus formation.

Risk factors: high initial dose, obesity, female, hereditary deficiency of protein C, protein S or antithrombin III.

Sharply demarcated, deep purple to black necrosis.

Lesions vary with severity of reaction: petechaie to acchymoses to tender hemorrhagic infarcts to extensive necrosis

->deep tissue sloughing/ ulceration.

Usually single. On areas of abundant fat. Acral areas spared.

Coagulation studies: within normal limits

Differential Diagnosis

- Purpura fulminans (DIC),

- Hematoma in overly anticoagulated patient, - Necrotizing soft tissue infection,

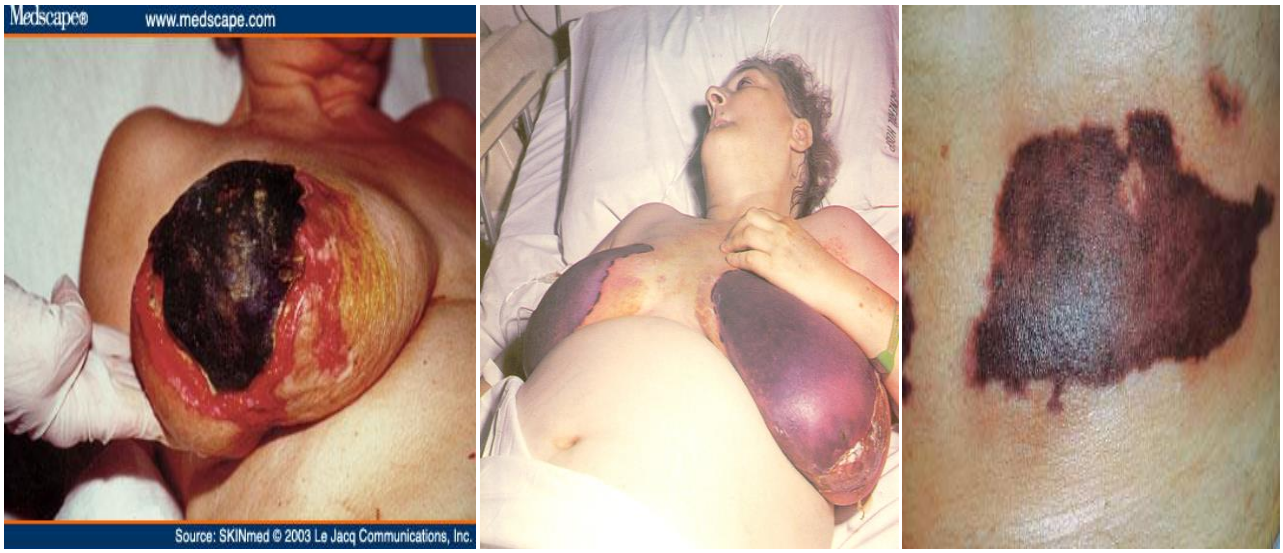
- Vasculitis,

- Recluse spider bite.

Course/ Prognosis

May subside/heal by granulation or require surgical intervention.

Life threatening if extensive in an elderly debilitated patient.



Warfarin induced Cutaneous necrosis

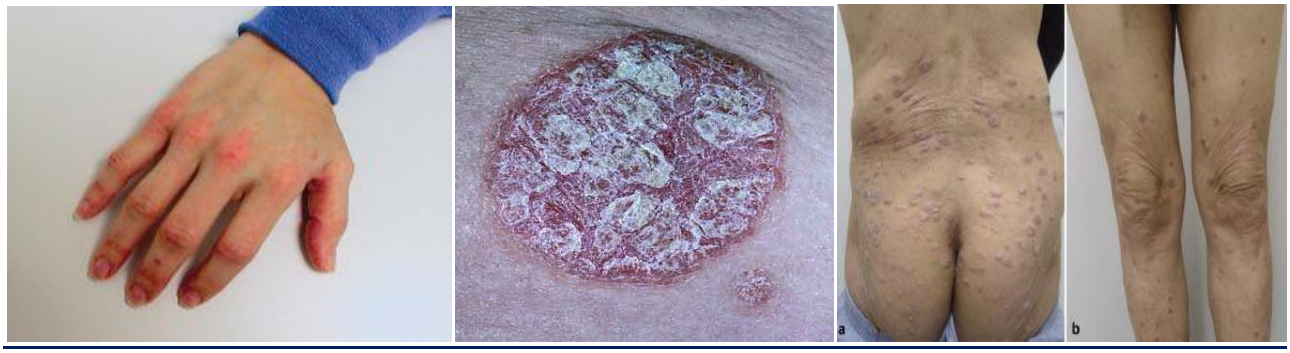
Other causes of ACDR-related necrosis:

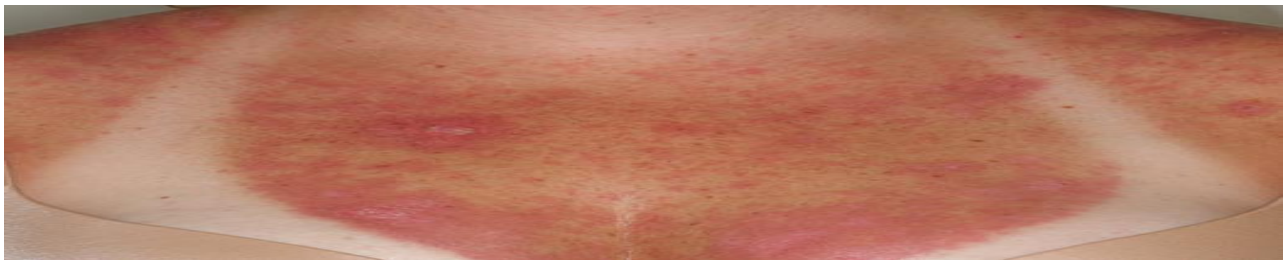
-Heparin/ Interferon-α/ embolia cutis medicamentosa at site of injection

- Ergotism: acral gangrene (suppositories perianal)

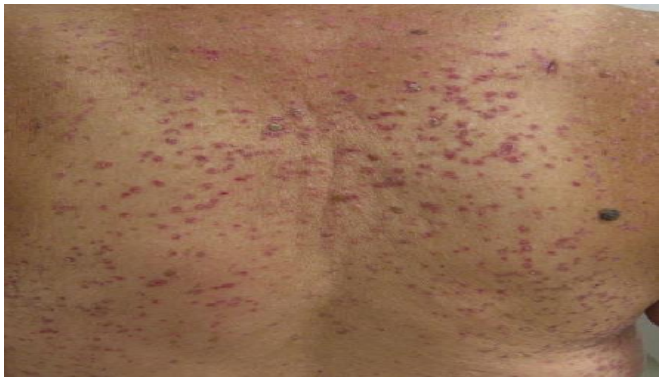
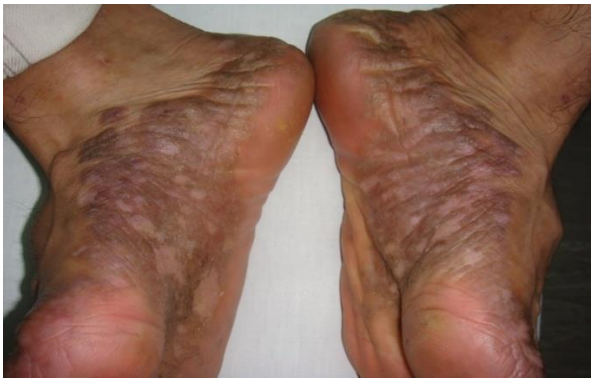
- At pressure sites in deeply sedated patients.

ACDR mimicry of other dermatoses:

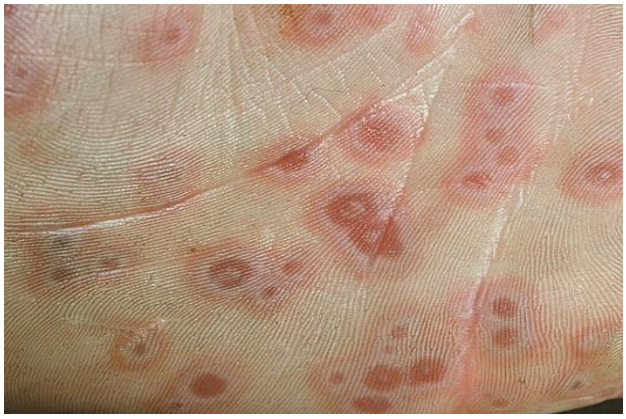
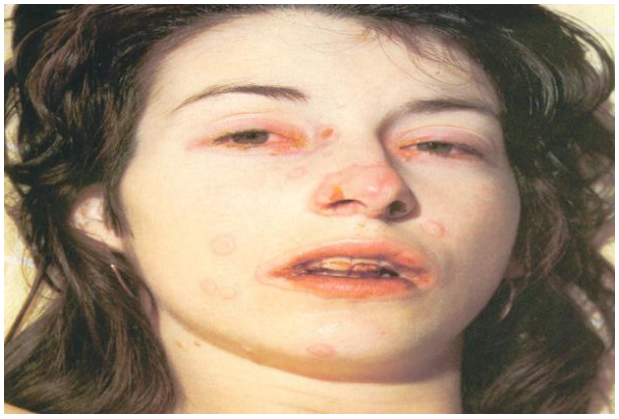




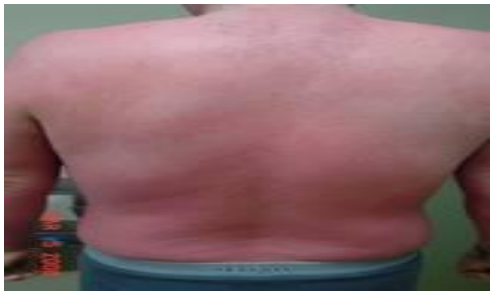
Psoriasiform

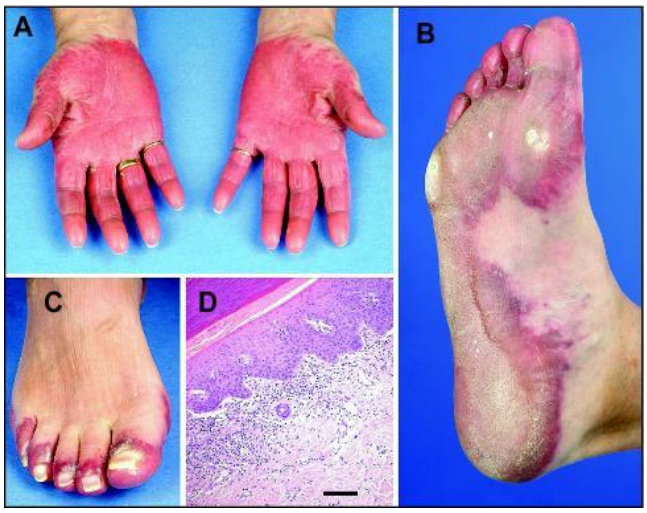
Lichenoid

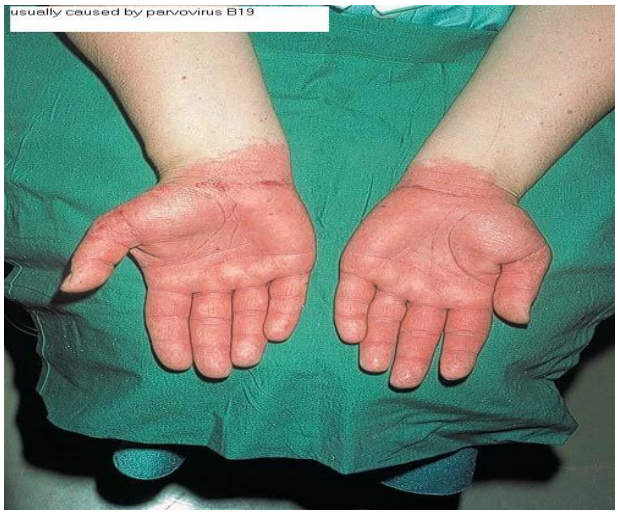



Erythema multiforme

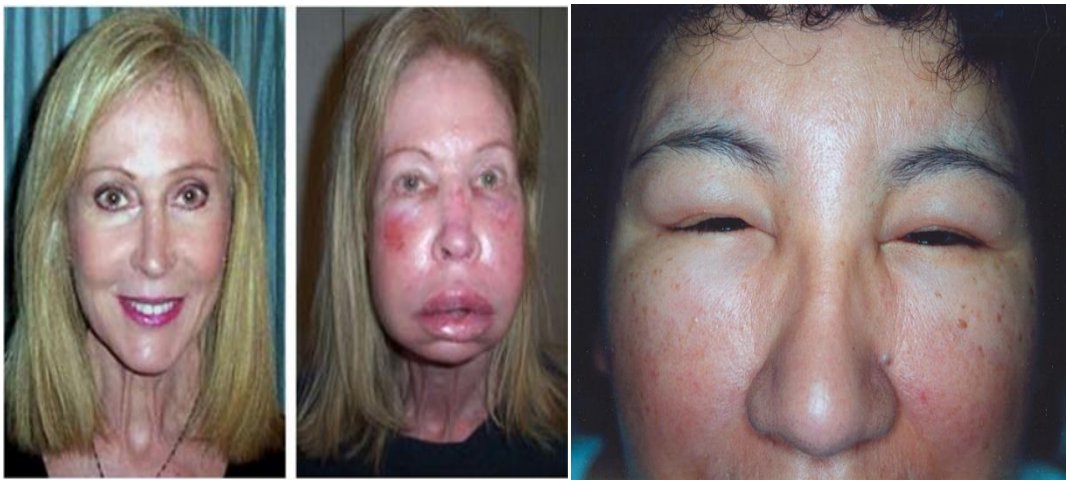


Exfoliative Dermatitis

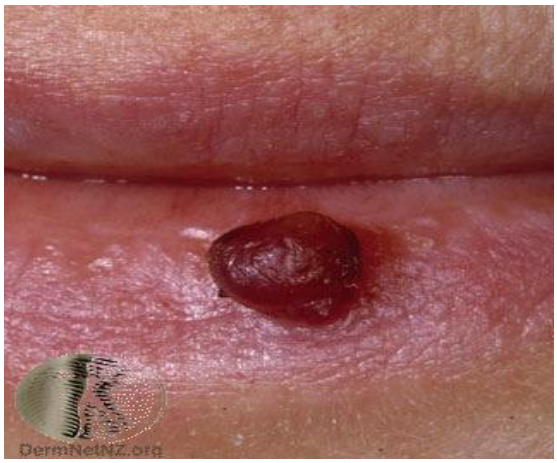




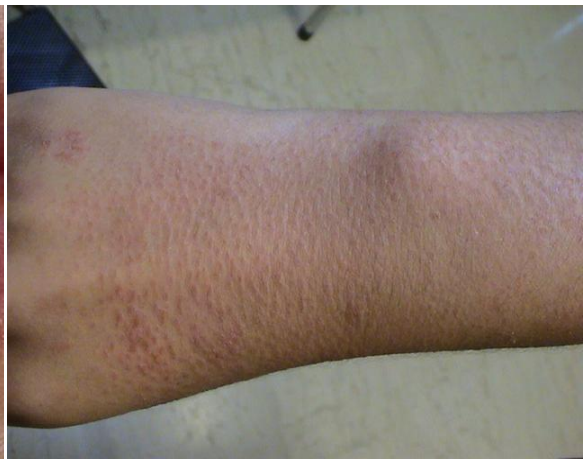
Hand-foot skin reaction (Gloves and socks drug rash)



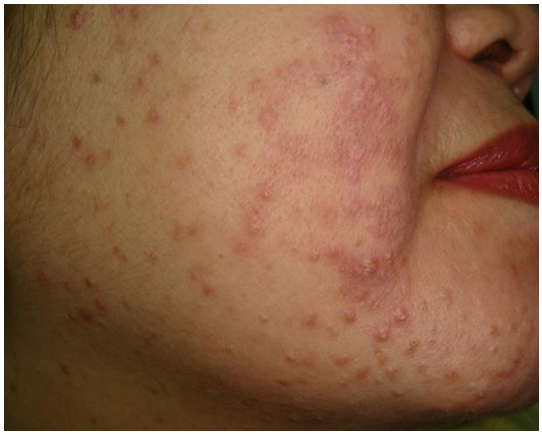
Facial edema

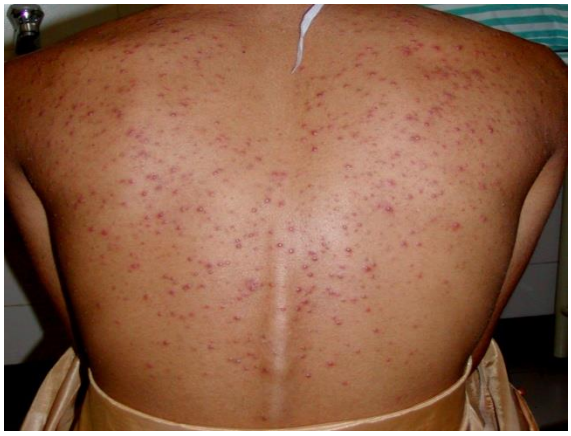


Pyogenic granulouma

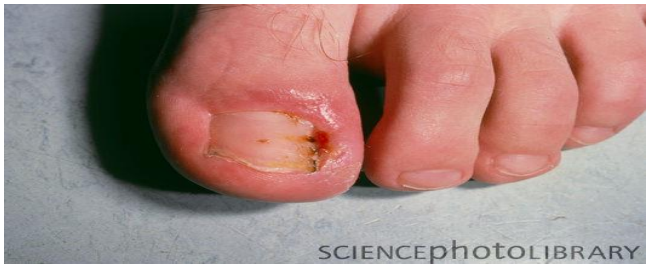


Retinoid dermatitis

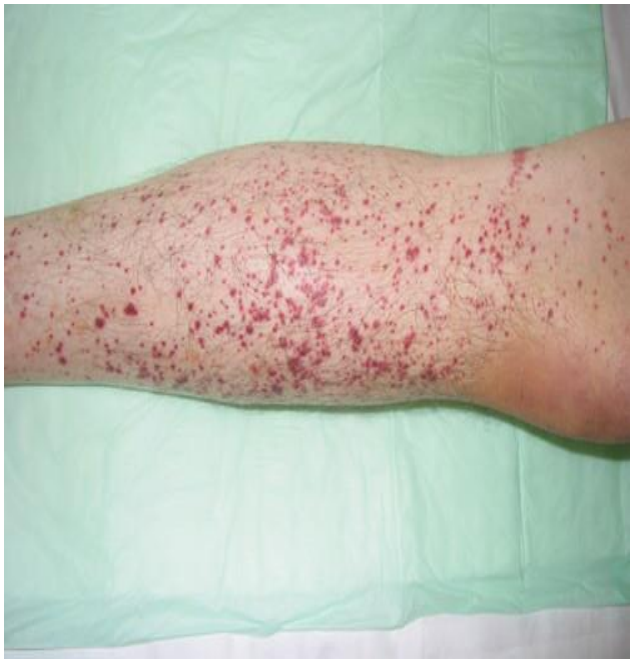


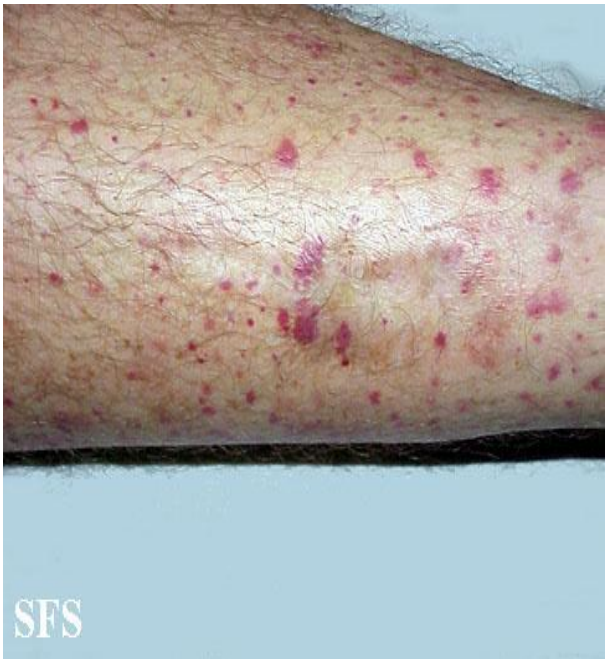


Steroid induced acne (no comedones)

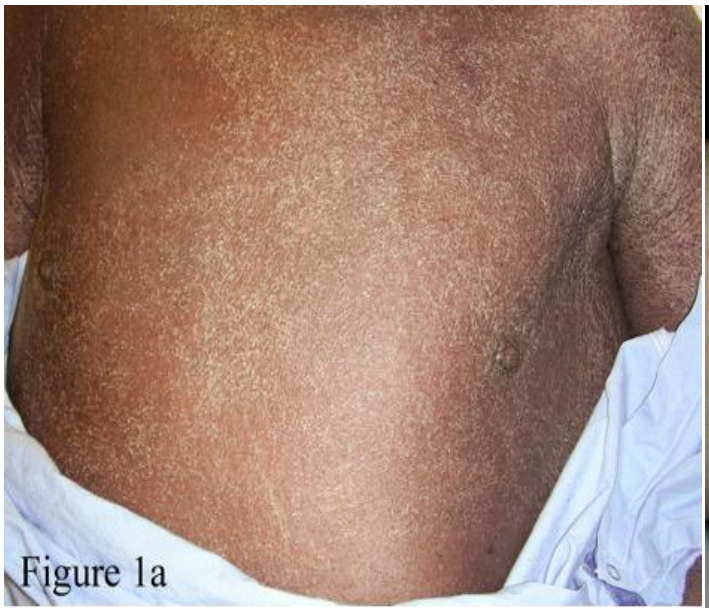


Paronychia

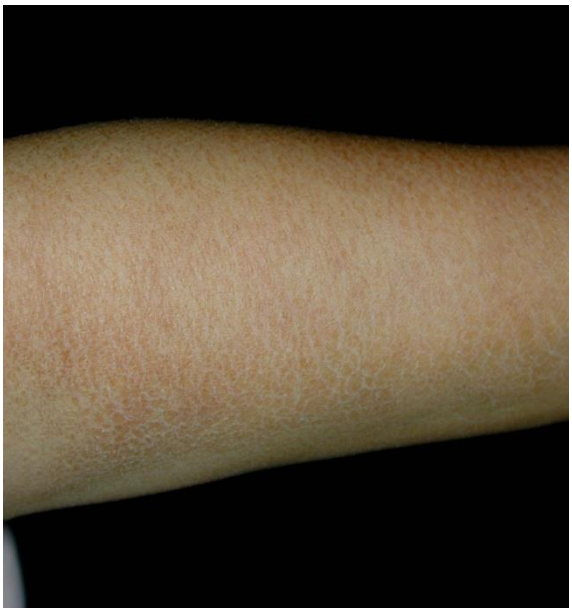




Vasculitis



Acute generalized exanthematous pustulosis



Xerosis

Mcq

Done By: