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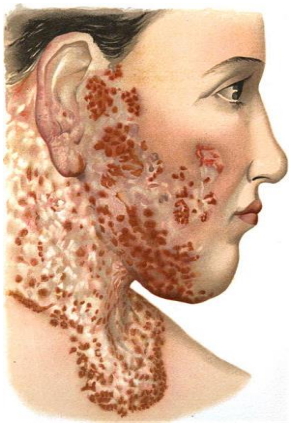
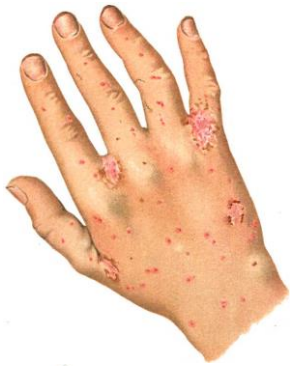
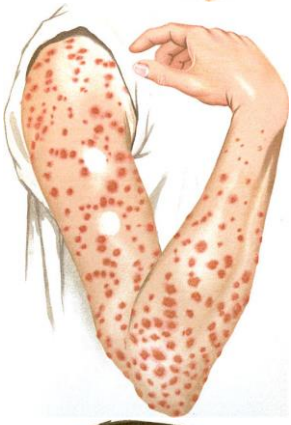
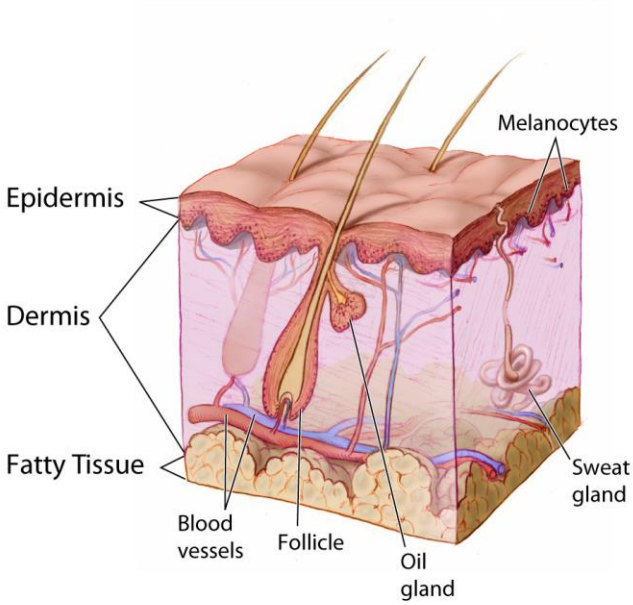






432 Teams

Dermatology



ADVERSE CUTANEOUS DRUG REACTIONS (ACDR)

Color Code: Original, Team's note, Important, Doctor's note,Not important, Old teamwork

Done by: ***Naif Alarjani***

Reviewer: ***Wael Al Saleh***

Team Leader: ***Basil Al Suwaine***

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Objectives

Not given

Introduction :

- ACDRs 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, Usually infections and other causes take time to manifest and show.
- When taking history ask about herbal remedies (أعشاب طبية), 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)

1) Immunologically Mediated ACDRs

- 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 SLE*
Type IV (the most common)	*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

2) Non-immunologic ACDRs

No genetic susceptibility except some idiosyncratic reactions

TYPE	MECHANISM
Idiosyncrasy	Hereditary enzyme deficiencies/ Idiopathic
Cumulation	Dose dependent eg: pigmentation d° gold, amiodarone or minocycline
Photosensitivity	Formation of toxic photoproducts d° 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) could be life threatening (serious) if the edema involved the respiratory pathway
- 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 readmination

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

The following findings can be placed into 4 groups:

Group 1:
Generalized wide spread rash

Group 2:
Rash + Systemic symptoms e.g. (SOB, arthralgia, hypotension, etc.)

Group 3:
Rash + Swellings, can be dangerous if they involve airway (laryngeal edema) or bowel (intussusception)

Group 4:
Bullae (blisters), sloughing of skin (necrosis), Purpura

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 :

- *Discontinue the culprit drug/drugs (cf. morbilliform vs. angioedema, SJS & TEN)*
- *Symptomatic treatment*
- *Prevention:*
  - Awareness (Use bracelets in kids & elderly indicating allergy)
  - Premedication (in certain procedure where the patients is known to be susceptible, or in certain procedure which can cause ACDR as a side effect e.g. infliximab injections)

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 :

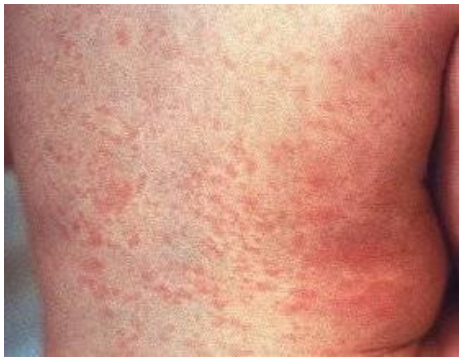
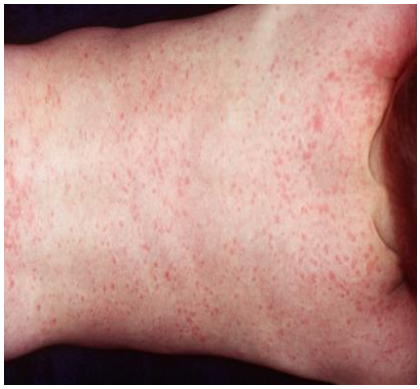
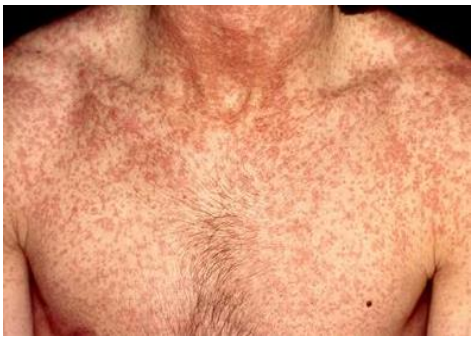
- Exact mechanism unknown. Probably delayed hypersensitivity.
- Most commonly incited drugs (10-20%): penicillins, carbamazepine, allopurinol, gold salts
- Less common (3-5%) : sulfonamides (bacteriostatic, diuretic, antidiabetic), NSAIDs, hydantoin derivatives, isoniazid, chloramphenicol, erythromycin + others (<1%).
- Special situations: Mononucleosis, HIV, Allopurinol, cross-drug hypersensitivity.

Clinical Manifestations :

❖ Onset : peak incidence at ninth day after administration (1-2 weeks),
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

Maculopapules

Diagnosis :

Clinical Diagnosis :

- Histopathology: perivascular lymphocytes and eosinophils
- Blood: eosinophilia

Differential Diagnosis :

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

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 (NSAIDs), direct degranulation of mast cells, direct complement trigger, kinin metabolism inhibitors.

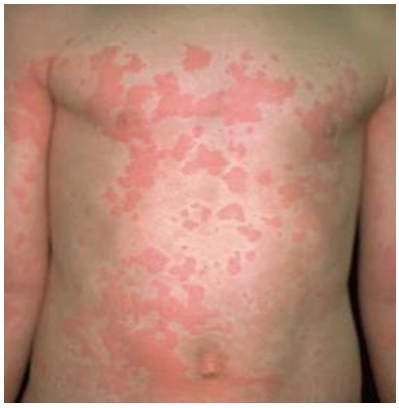
*Medication that can cause Urticari/angioedema: NSAID and Curare (used in anesthesia)

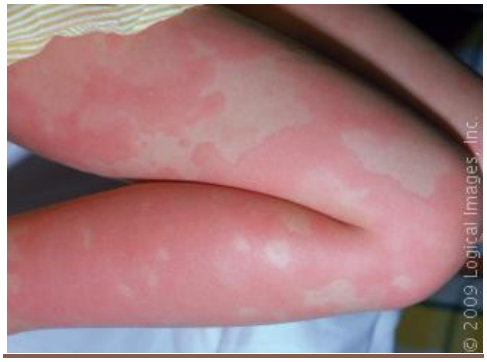
Clinical manifestation :

- Onset : 1-2 weeks after administration; minutes to hours after readministration
- 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 swellings
  - flushing, yawning, airway edema, sneezing, bronchopasm, laryngeal edema, hypotension, vomiting, diarrhea, arthralgia

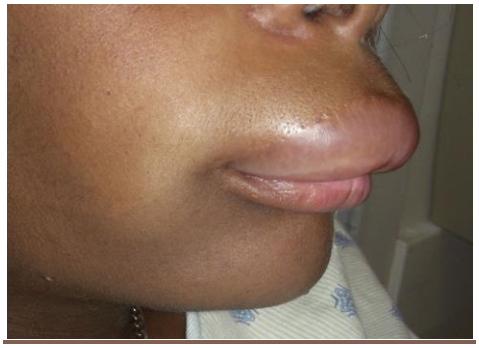
- If there is burning sensation, pinpoint bleeding, wheals last longer this is Urticaria Vasculitis

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
(unclear boarders and no erythema)

Angioedema
(It is serious if it involves the respiratory track)

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 every time you take the drug.

Pathogenesis :

- Unknown

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

Clinical manifestation :

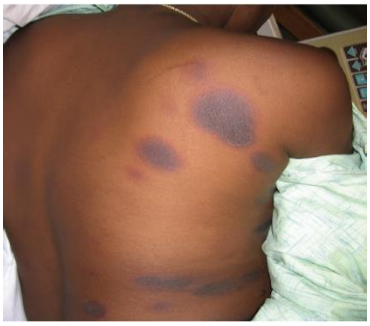
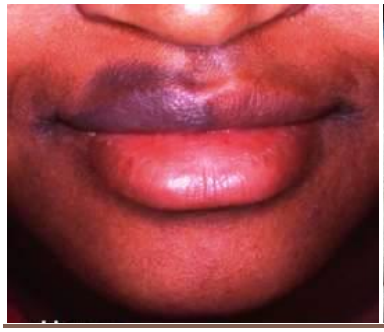
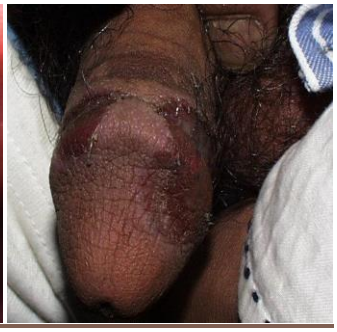
❖ Onset :Within 30 minutes to 8hours (Fast) after ingestion of drug in previously sensitized individual

❖ 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)

The patient will tell you every time I have a headache I get a rash, or every time I have constipation I get a rash.

❖ 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

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)

DRESS stands for Drug Rash with Eosinophilia and Systemic Symptoms

Definition :

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

Pathogenesis :

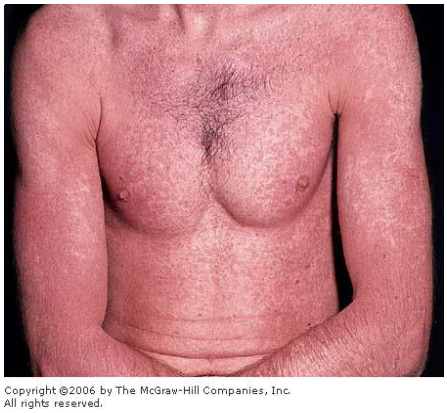
- Hereditary (toxic arene oxide metabolites; slow N-acetylation of sulfonamides)
- Idiopathic

Most common drugs:
- Antiepileptics (phenytoin, carbamazepine, phenobarbital)
- Sulfonamides (antimicrobials, dapsone, sulfasalazine).

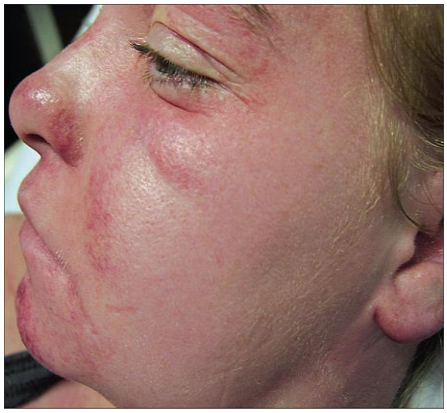
Clinical manifestation :

Onset : 2-8 weeks after first drug administration

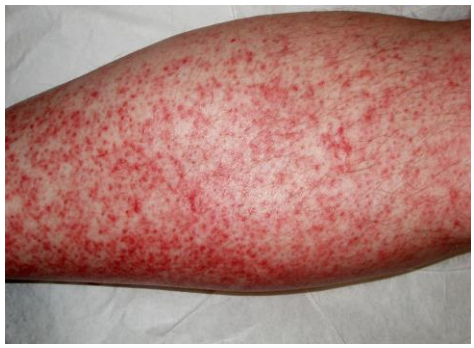
- Symptoms : Fever, malaise, ± pruritus
- Signs:
  - Morbilliform eruption on face, upper trunk and extremities with periorbital edema and mucosal involvement
    - generalized exfoliative (erythroderma) ± pustular ± bullous ± purpura on legs
    - scaling/desquamation with healing
  - Other:
    lymphadenopathy, 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 :

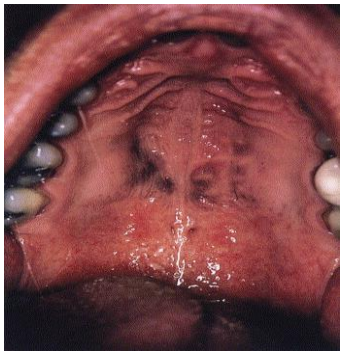
- Withdrawal
- Systemic glucocorticoids (prednisolone 0.5mg/kg/day) results in rapid improvement
- Awareness, wallet card/ bracelet

Drug Induced Pigmentation

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

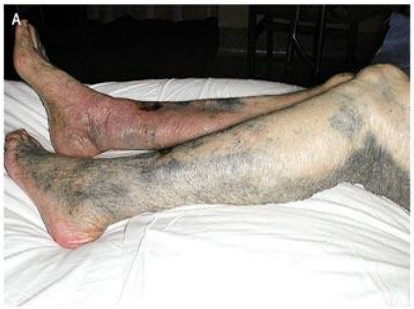
Drugs involved:

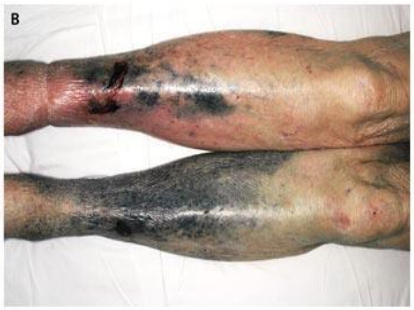
- Amiodarone
- Antimalarial
- Antimicrobial: minocycline, zidovudine, clofazimine
- Hydantoins/chlorpromazine
- Hormones: ACTH, estrogen/progesterone
- Heavy metals: silver, gold, mercury
- Cytostatic: bleomycin (Whiplash Configuration) , cyclophosphamide,
-5-fluorouracil, dactinomycin, busulfan, doxorubicin, daunorubicin.



(Minocycline induced pigmentation)

Pigmentation of teeth happens when taking medication before age 10 or during pregnancy





(Minocycline in

Dark pigmenta
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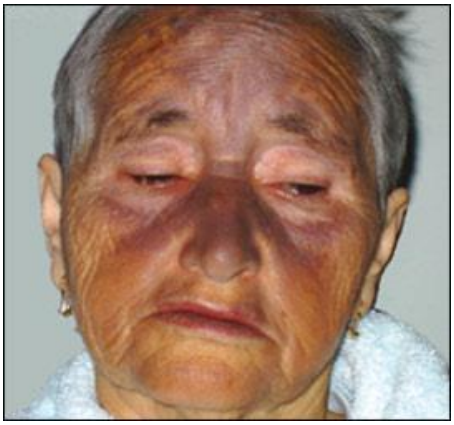
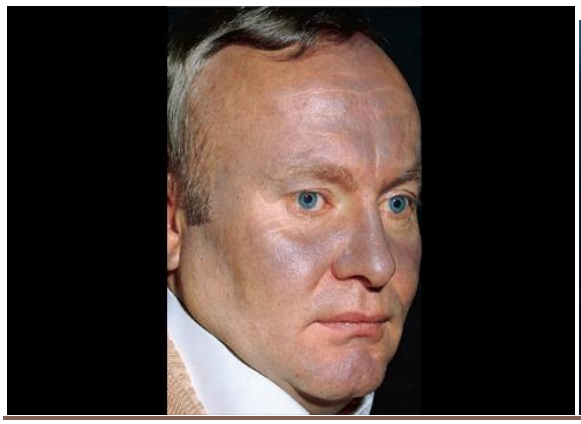
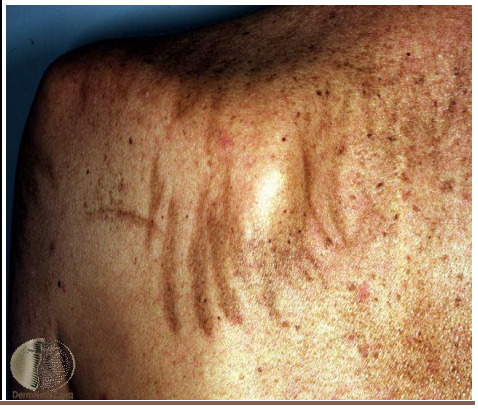


(Amiodarone induced pigmentation)





Bleomycin induced pigmentation
(Whiplash Configuration)

Minocycline :

- Usually after total dose of >50 grams (Cumulative effect)
- 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.

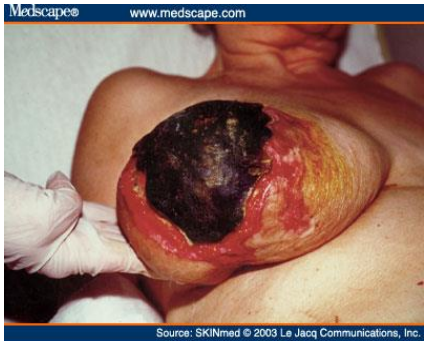
- Coagulation studies: within normal limits

Differential Diagnosis :

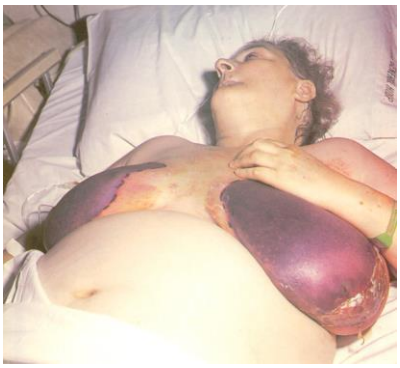
- Purpura fulminans (DIC).
- Hematoma in overly anticoagulated patient.
- Necrotizing soft tissue infection.
- Vasculitis.
- Recluse spider bite.

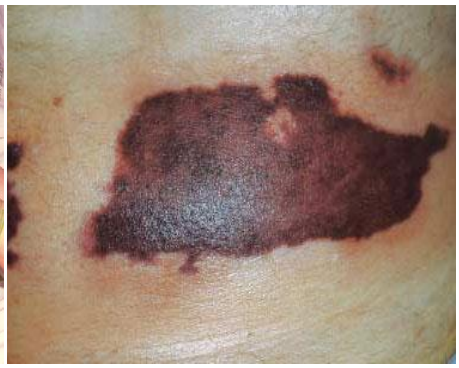
Course/ Prognosis :

- May subside/heal by granulation or require surgical intervention.
- Life threatening if extensive in an elderly debilitated patient.



(Warparin induced cutaneous necrosis)



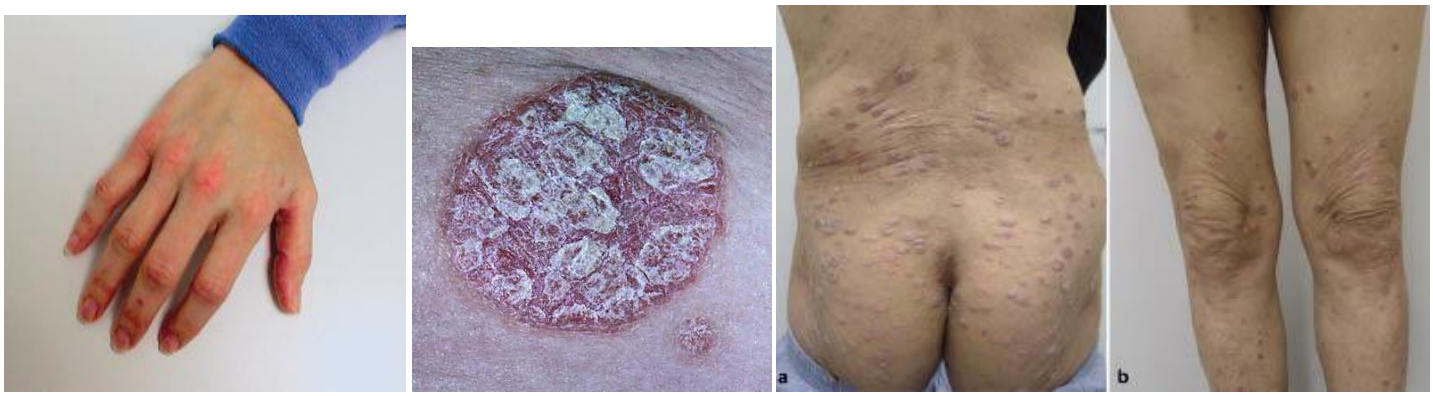


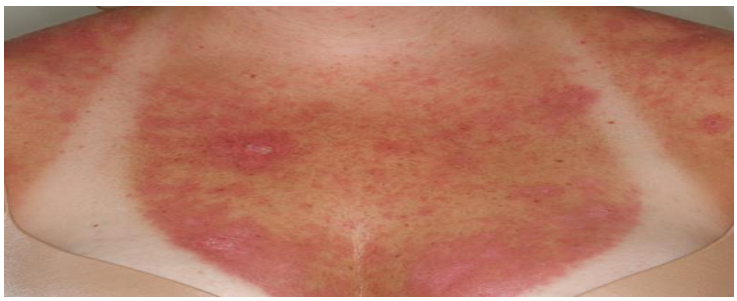
(Heparin induced cutaneous necrosis)

Other causes of ACDR-related necrosis:

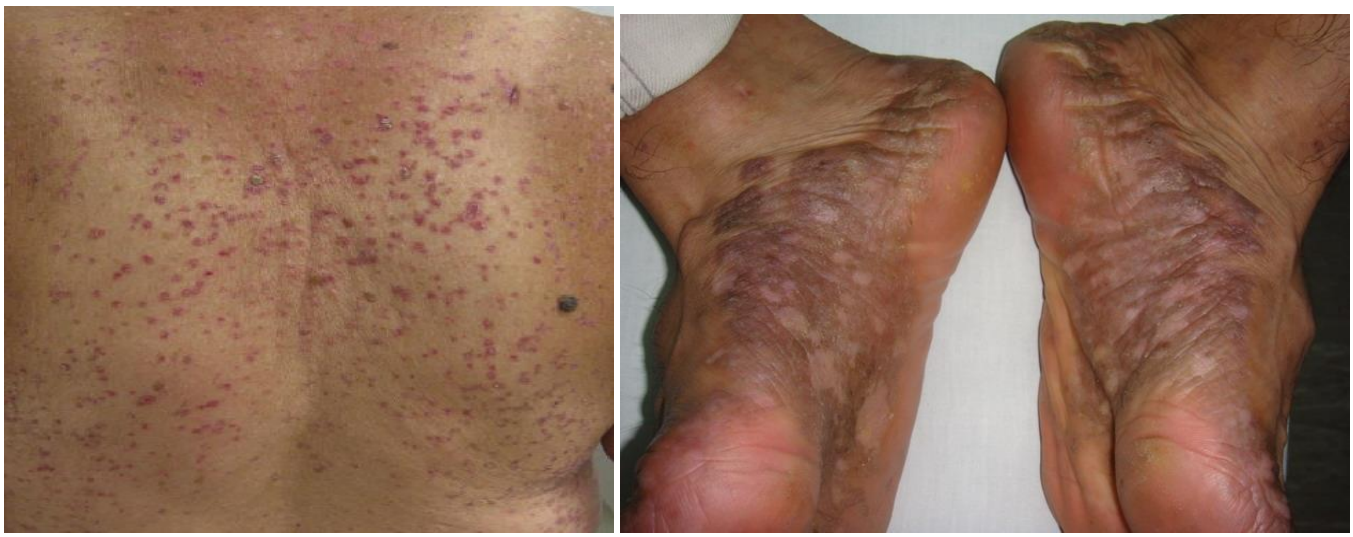
- Heparin/ Interferon-α/ embolia cutis medicamentosa at site of injection
- Ergotism: acral gangrene (suppositories perianal)
- At pressure sites in deeply sedated patients.

ACDR mimicry of other dermatoses

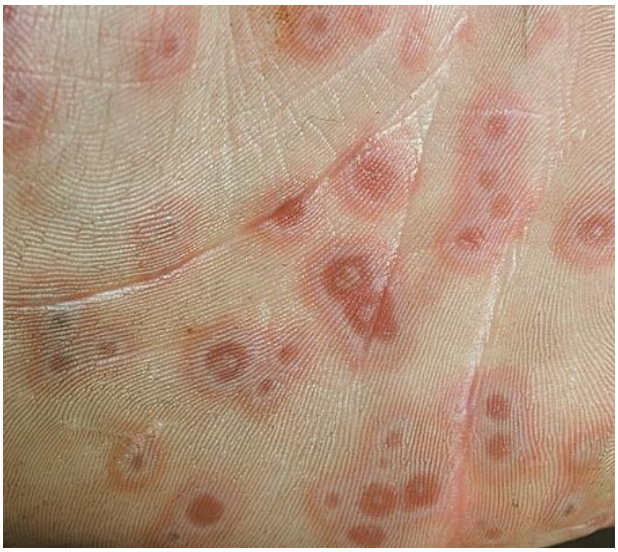


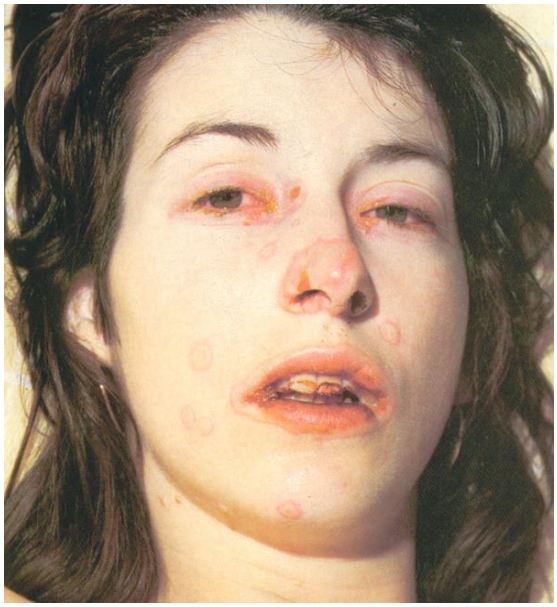


Psoriasiform

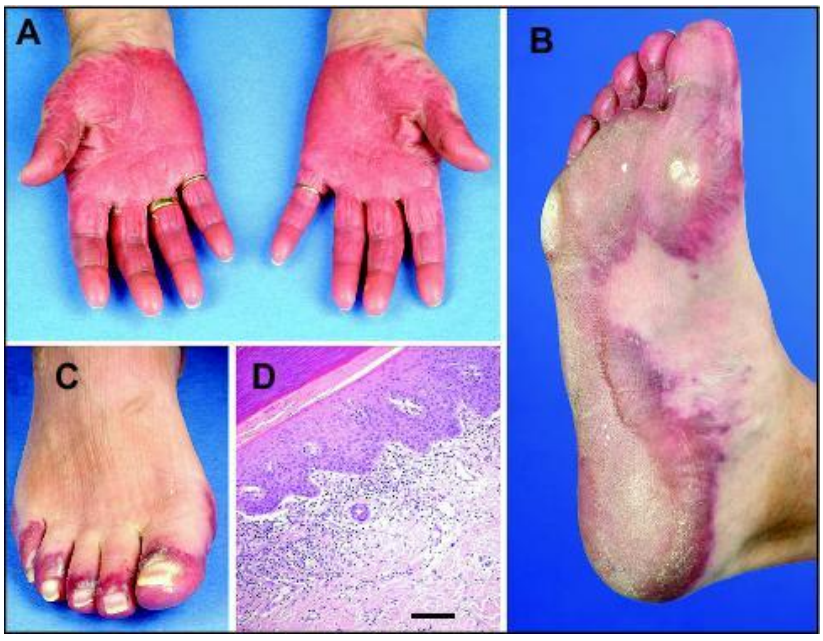


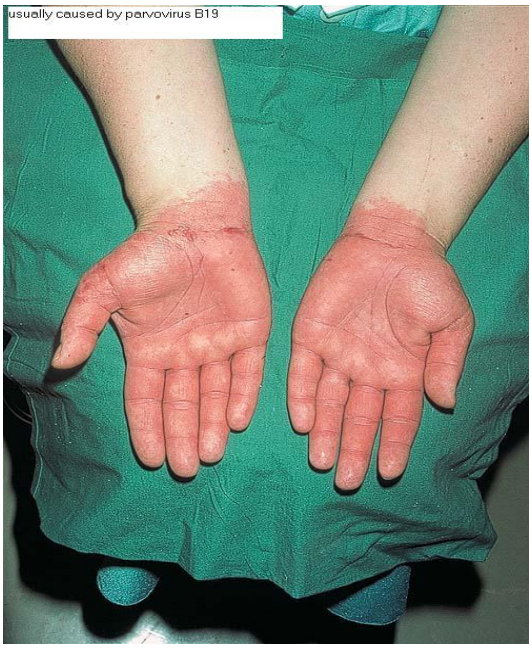
Lichenoid



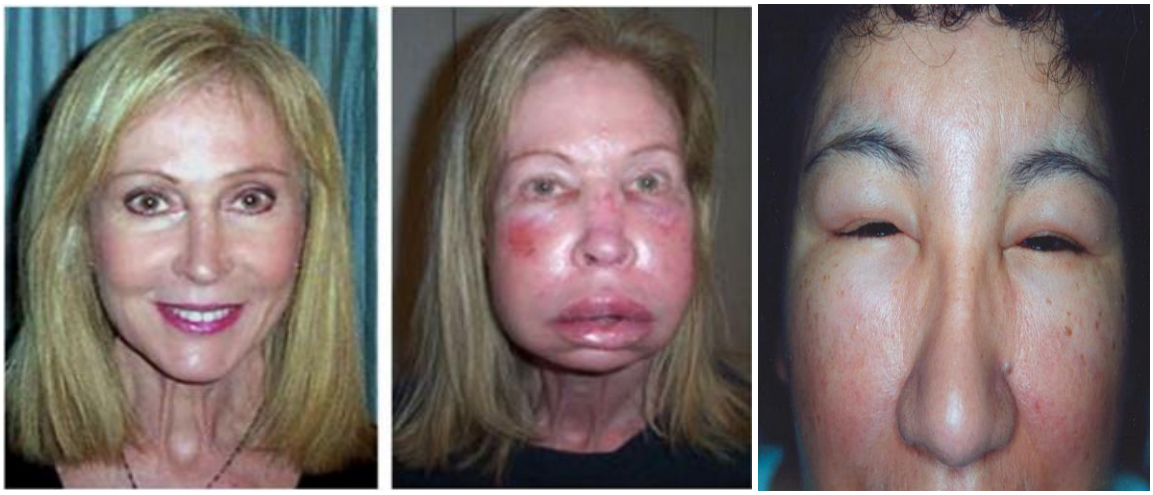


Erythema Multiforme
(Target like lesions that consist of 3 zones dark- light – dark)

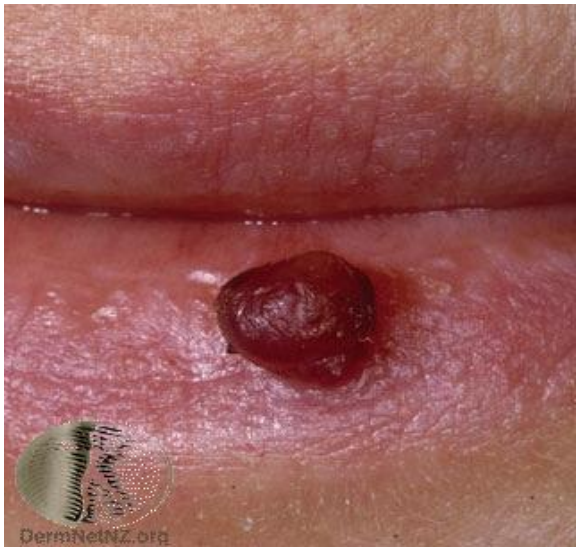




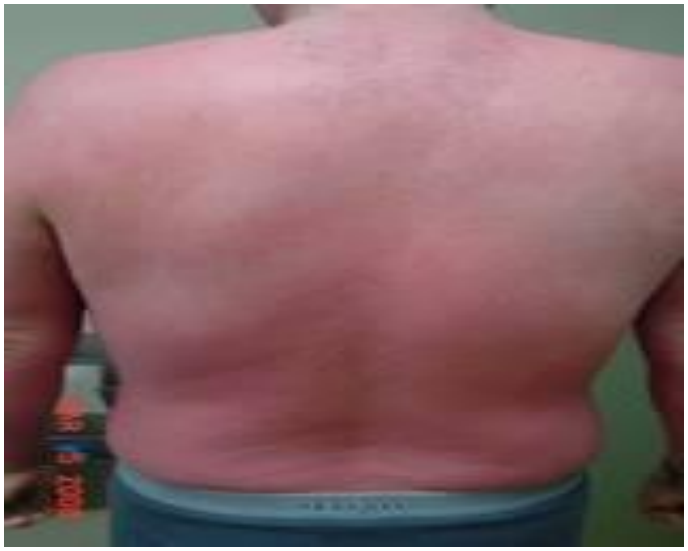
Hand-foot skin reaction
(Gloves and socks drug rash) **Caused by: Chemotherapy**



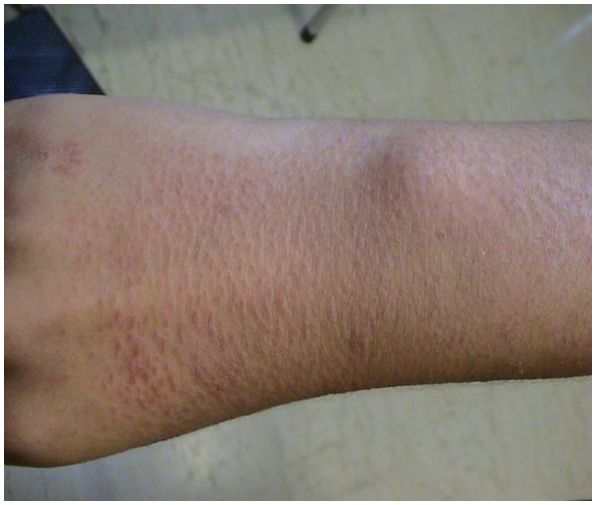
Facial edema



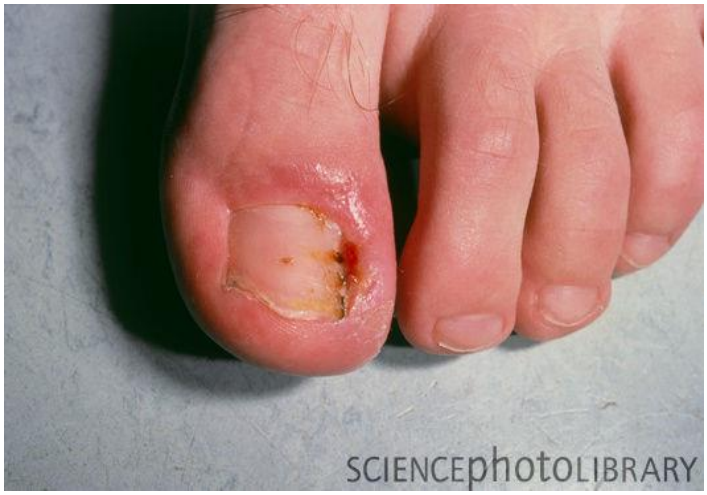
Pyogenic granuloma
Caused by: Isotretinoin)



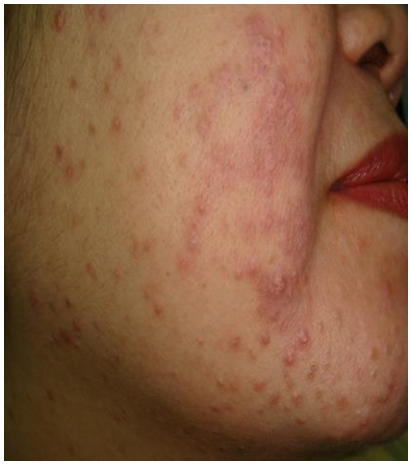
Exfoliative Dermatitis

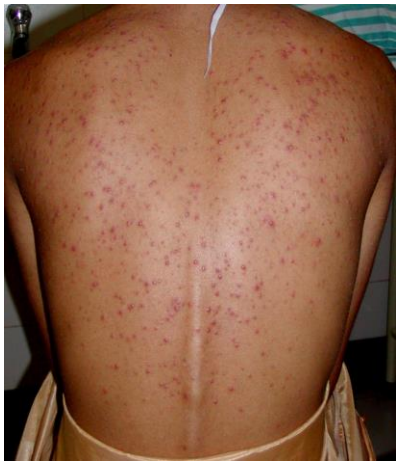


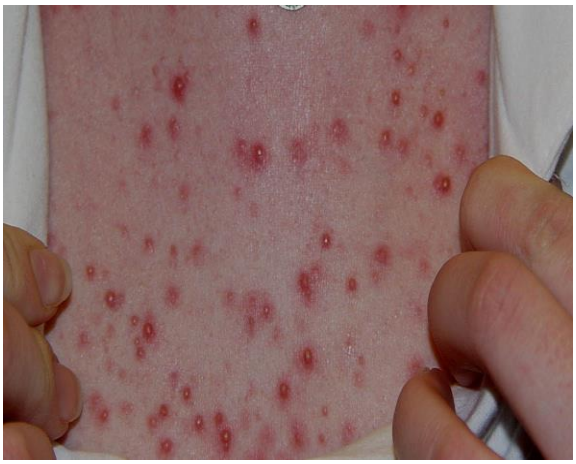
Retinoid dermatitis



Paronychia

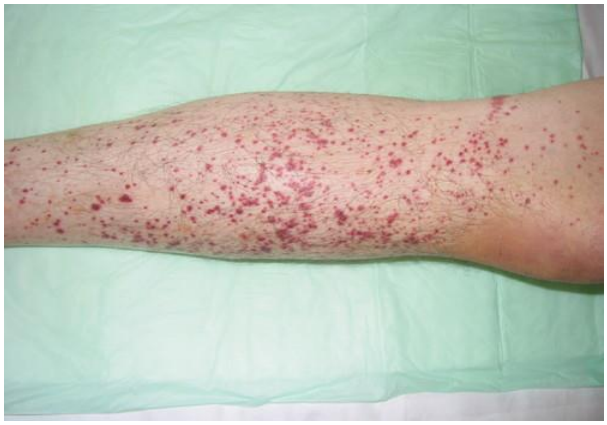


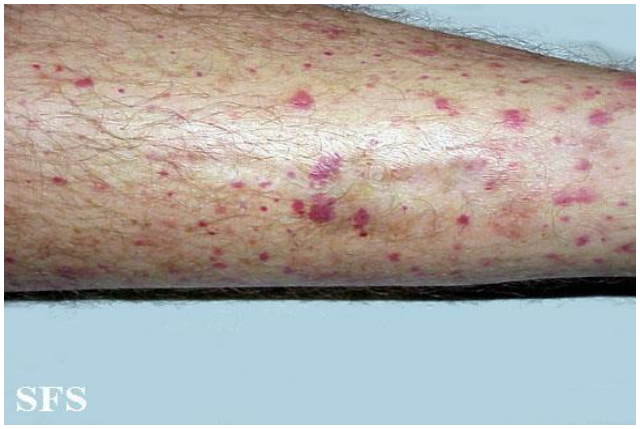




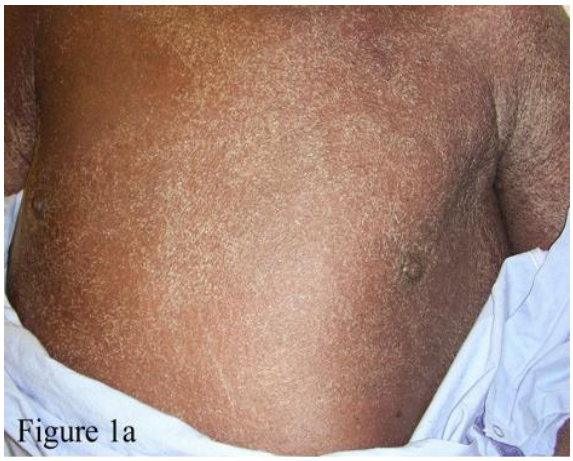
Steroid induced acne

Usually monomorphic papules and pustules BUT no comedones

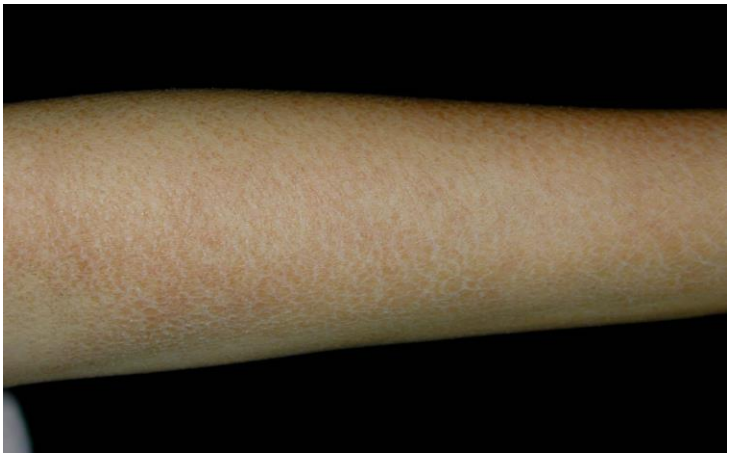




Vasculitis



Acute generalized exanthematous pustulosis



xerosis

Summary

- ACDRs are Common.
- Most ACDRs are mild, some are severe life threatening.
- They can mimic all the morphologic expressions in dermatology, and should be the first consideration in suddenly appearing eruptions.
- ACDRs are either immunologically mediated 80% or non-immunologically mediated.
- The most common clinical type of ACDRs is Exanthematous.
- ACDR is a diagnosis of exclusion.
- Pay attention to findings that indicate a life threatening ACDR.
- Diagnosis is usually made on clinical findings.
- Definitive management is discontinuing the culprit drug + symptomatic treatment.
- Anticonvulsants, Sulfonamides, NSAIDs, & Antibiotics are known to cause ACDR.
- Exanthematous drug reaction is a delayed hypersensitivity that mimics a measles-like viral exanthema, that presents with severe pruritis and the rash usually spares face & periareolar area.
- Urticaria is a Transient >24hrs, wheals and edema with pruritus caused by immune-mediated or non-allergic reaction.
- It important to differentiate between urticaria & urticaria vasculitis.
- Angioedema of the face can be serious if it involves the larynx causing asphyxiation.
- Fixed drug eruption is a fast reaction that causes identical skin lesion that recur at the same location.
- Fixed drug eruption can be associated with headaches (analgesic use), constipation (laxative use), and are Common on genitals and oral mucosa.
- DRESS syndrome is an idiosyncratic drug reaction that involves skin and other organs, & is commonly caused by Antiepileptics & Sulfonamides.
- DRESS is diagnosed based on 3 criteria, and predisposes patients to lymphoma and thyroiditis.
- Drug induced pigmentation is relatively common and is caused by: Amiodarone, Antimalarial, minocycline, & bleomycin.
- Warfarin cutaneous necrosis is an Idiosyncratic reaction that usually affects obese females on areas of abundant fat (e.g. breast)
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