Lecture (10)
Adverse Cutaneous Drug Reactions

Objectives: not given.

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Color index: slides, doctor notes, extra explanation.

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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.
- Majority are caused by immunologic mechanisms (Gel and coombs types I, II, III and IV) and in most reactions both cellular and humoral immunity are involved.
- Provoked by systemic or topical administration including eye/ear drops, suppositories/ pessaries.

The Dr. said that it's important for every exam in your life but he didn't go through it

Immunologically Mediated ACDR:

Type I:

IgE mediated, Immediate type presented as urticaria, angioedema and anaphylaxis.

Type II:

Drug + Cytotoxic antibodies cause lysis of cells, presented as Petechiae, thrombocytopenic purpura and drug-induced pemphigus.

Type III:

Immune complexes formed of Immunoglobulins and drugs, presented as vasculitis and serum sickness.

Type IV:

Cell-mediated, delayed type, presented as morbilliform exanthems[1], fixed drug eruptions, lichenoid eruptions, Stevens-Johnson Syndrome/TEN.

Nonimmunologic ACDR:

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.

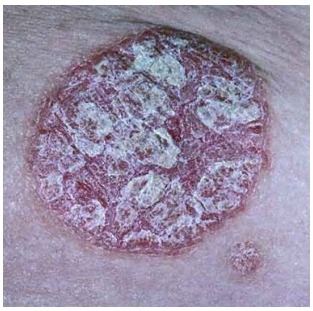
Pseudoimmunologic: direct release of inflammatory cytokines: Mast cell degranulation, alternate complement system, cyclooxygenase inhibitors, others.

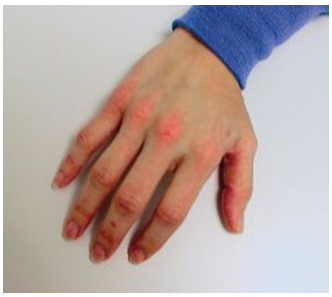
[1] Will be explained later.

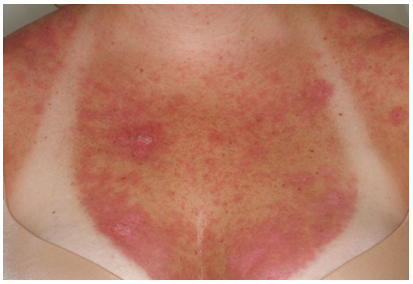
Clinical types of ACDR

1. Exanthematous (most common).
2. Urticaria/ angioedema (second most common).
3. Fixed drug eruptions.
4. Anaphylaxis/ anaphylactoid rxns[2].
5. Serum sickness.
6. DRESS[3] Syndrome.
7. ACDR- related pigmentation/ necrosis/ alopecia/ nail changes.
8. ACDR mimicry of other dermatoses:

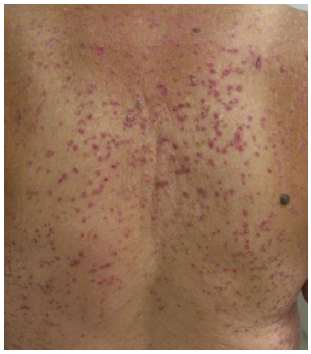
Acneiform, Bullous, dermatomyositis-like, Drug hypersensitivity syndrome, Eczematous, EM, SJS, TEN, Erythema Nodosum, Exfoliative dermatitis, Erythroderma, Lichenoid, LE, Photosensitivity, Pityriasis rosea-like, Pseudolymphoma, Pseudoporphyria, Psoriasiform eruption, Purpura, Pustular eruptions, Scleroderma-like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

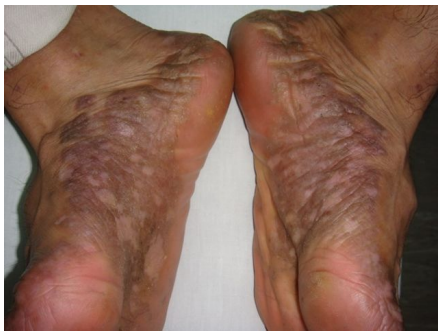






Psoriasiform



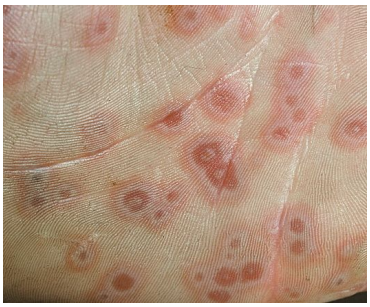


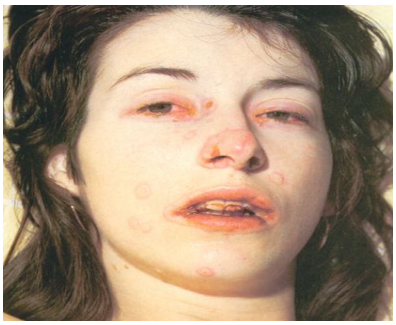
Lichenoid

5 Ps:

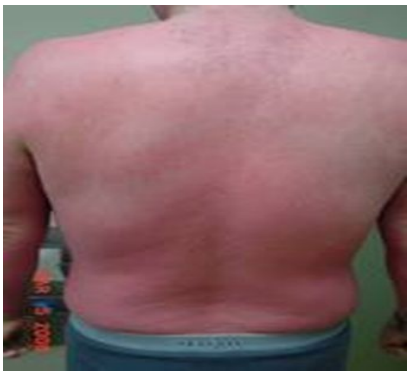
Papules
pruritus
purple
polygonal
planar

[2] reactions
[3] Drug Reaction with Eosinophilia and Systemic Symptoms

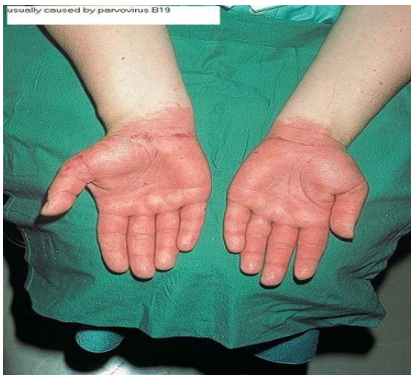




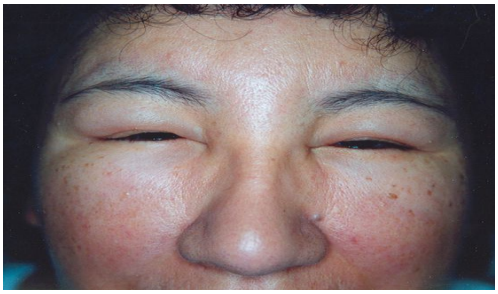
SJS Erythema Multiforme



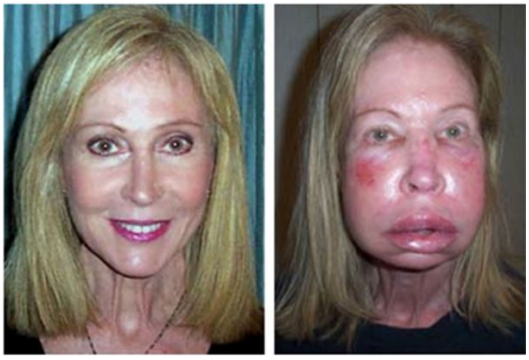
Exfoliative Dermatitis

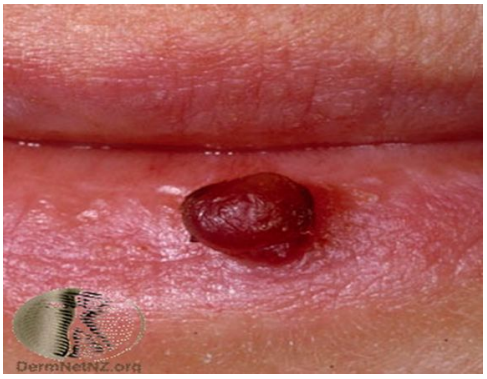


Hand-foot skin reaction
(Gloves and socks drug rash)

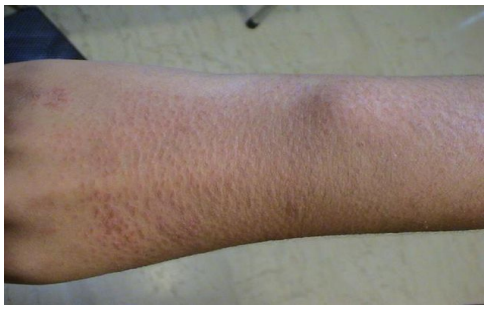


Facial edema

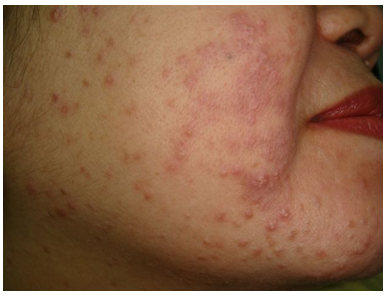


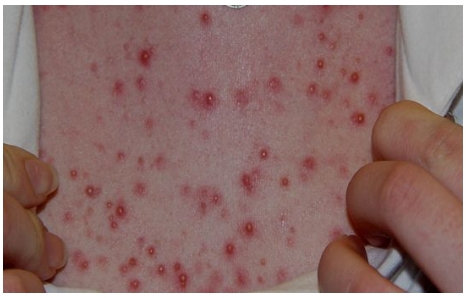


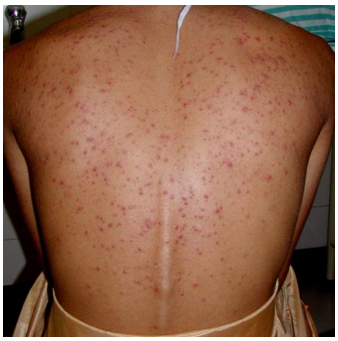
Pyogenic granuloma



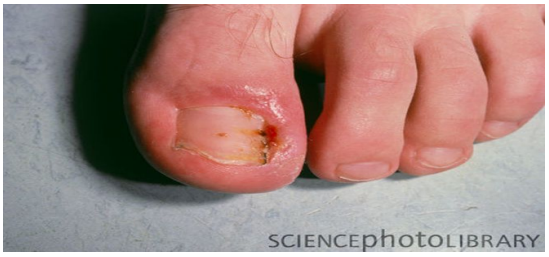
Retinoid dermatitis

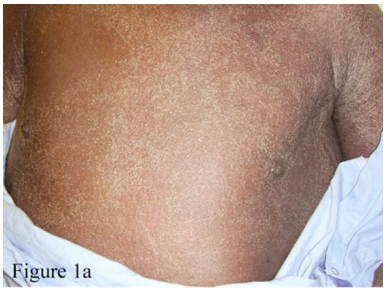






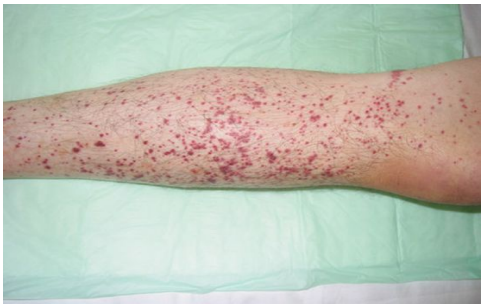
Steroid induced acne

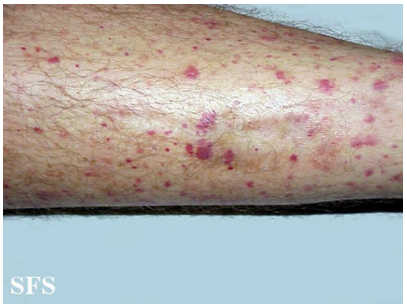




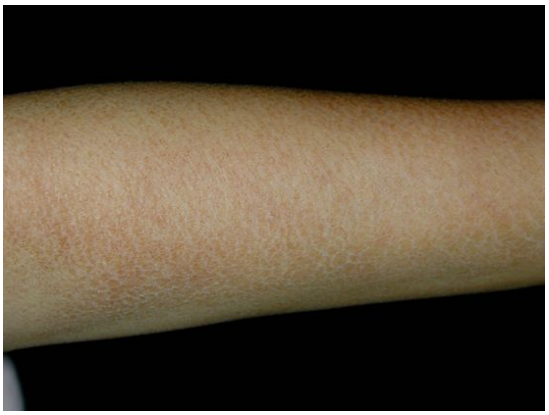
Paronychia

Acute generalized exanthematous pustulosis





Vasculitis



xerosis

Guidelines for assessing possible ACDRs

ترسم خط زمني مجدول فيه كل دواء متى بدأ وانتهى استخدامه ونستنتج أي الأدوية السبب

- Exclude other causes especially Infections.
- Examine interval between introduction and induction.
- Determine if similar reactions occurred with the same or similar compounds.
- Note any improvement after withdrawal.
- Note any reaction after readministration.

Findings indicating possible life-threatening ACDR:

- Arthralgia.
- Blisters/epidermal detachment/ positive Nikolsky sign.
- Confluent erythema
- Enlarged lymph nodes.
- 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.

Skin Test/RAST[4]: helpful in IgE-mediated reaction (penicillin).

Management:

- Discontinue the culprit drug/drugs (cf. morbilliform or. angioedema, SJS and TEN)
- Symptomatic treatment

Prevention: awareness; premedication.

[4] A radioallergosorbent test is a blood test using radioimmunoassay test to detect specific IgE antibodies

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.

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 pruritus (if painful think TEN) ± fever, chills.

Signs:

- symmetric trunk + extremities (in children face and extremities).
- bright red macules/papules -> confluent: sheet-like / polycyclic/ reticular patches -> erythroderma, ->scaling/desquamation with healing.
- usually spare face, periareolar area and surgical scars. Enanthem 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.

Prognosis:

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

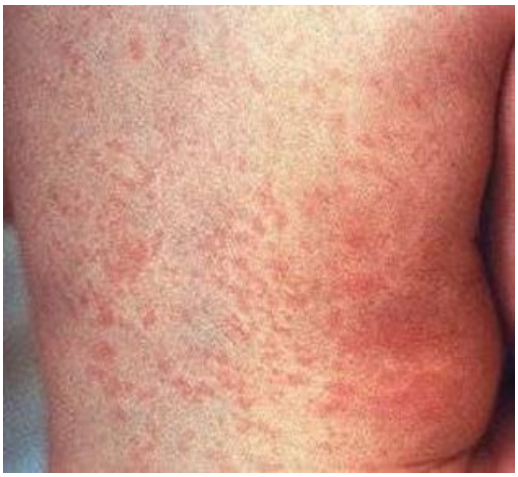
Treatment:

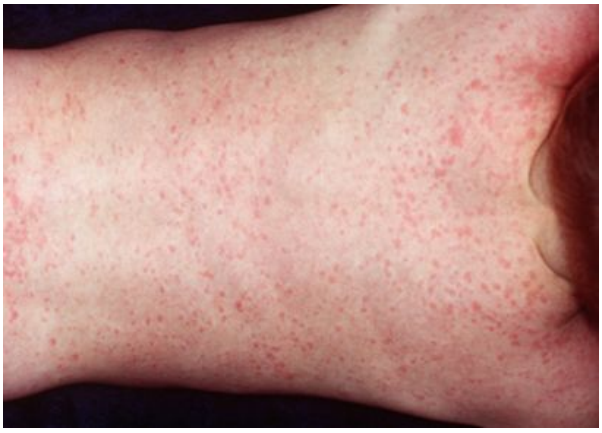
Definitive: (cf. indications for discontinuation of a drug).

Symptomatic: Oral antihistamines, topical and systemic corticosteroids.

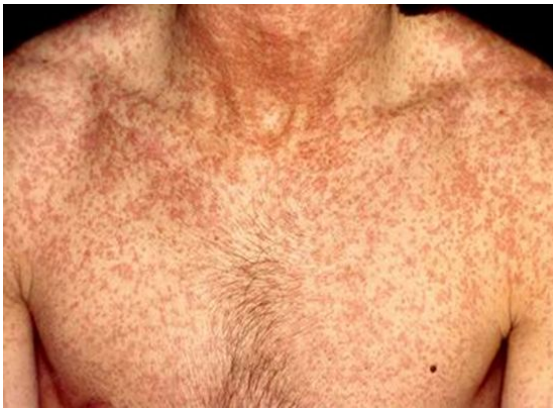
Prevention:

- Awareness of specific drug and cross-reactants.
- wearing a bracelet.





Maculopapules



Drug-Induced Acute Urticaria/Angioedema, Edema and Anaphylaxis

Definition: transient wheals and edema.

Pathogenesis:

1. Immune-mediated (IgE or complement and immune complex).
2. Non allergic: cyclooxygenase inhibitors, direct degranulation of mast cells, direct complement trigger, kinin metabolism inhibitors.

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, bronchospasm, laryngeal edema, hypotension, vomiting, diarrhea, arthralgia.

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.

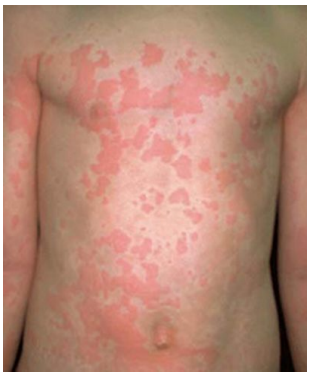
Treatment:

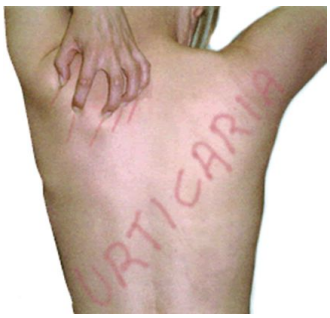
Definitive

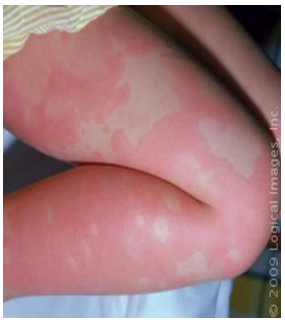
Symptomatic: subcutaneous epinephrine (0.3-0.5ml of 1/1000) + airway/ IV access,

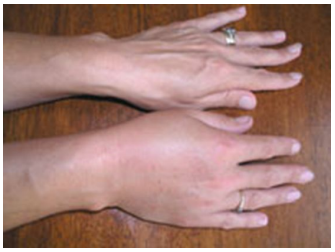
H1/H2 blockers, systemic glucocorticoids,

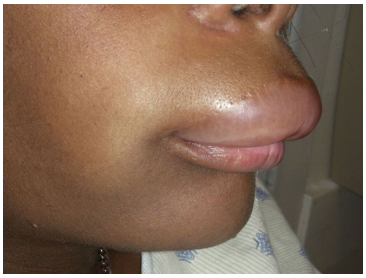
Prevention: awareness/ wallet card/ bracelet/ pretreatment.











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 8 hours 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, conjunctiva 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:

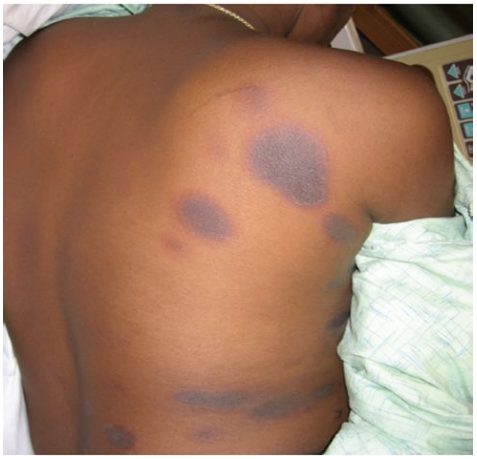
- Resolves within weeks of withdrawal
- Recurs within hours after a single dose

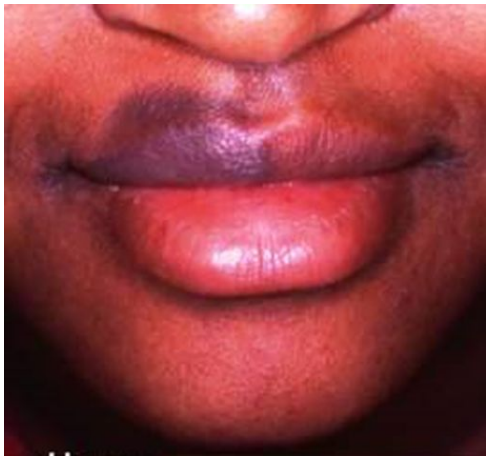
Treatment:

Non-eroded: potent topical glucocorticoid.

Eroded: antimicrobial ointment.

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





Drug Hypersensitivity Syndrome

(DRESS)-Drug reaction 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 manifestations:

lymphadenopathy, hepatitis, carditis, nephritis, pneumonitis, hematologic, joints, muscles, thyroid, brain manifestations.

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 ≥ 2 cm in diameter or hepatitis (SGPT ≥ 2N) or interstitial nephritis, interstitial pneumonitis or carditis)

Histopathology: variable lymphocytic infiltrate ± eosinophils/dermal edema (may simulate CTCL[5]).

Differential diagnosis:

Early: morbilliform eruptions.

Later: serum sickness, vasculitis, collagen vascular disease.

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

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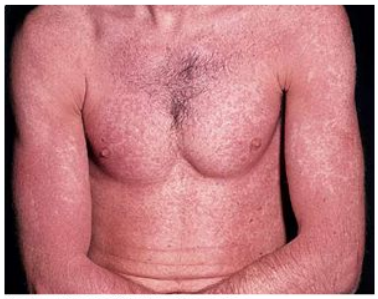
[5] Cutaneous T-Cell Lymphoma

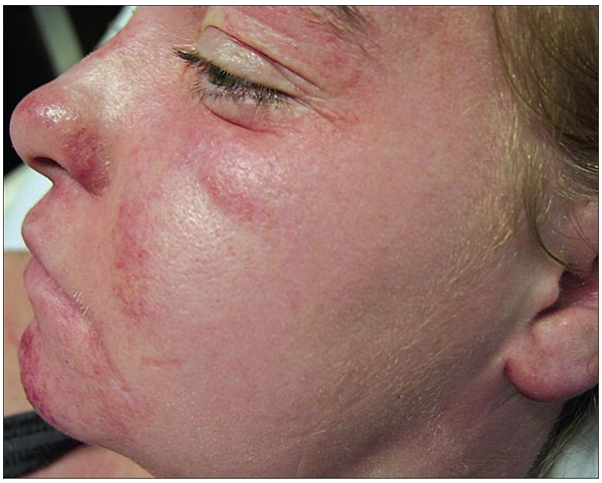
Prognosis:

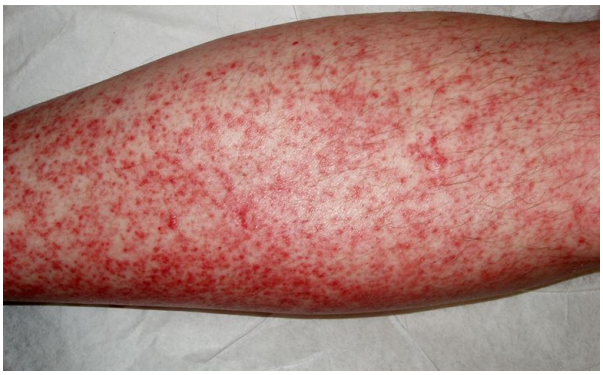
- Rash and hepatitis may persist for weeks after withdrawal.
- Mortality 10% from systemic hypersensitivity eg. eosinophilic myocarditis.
- Rare progression to lymphoma.

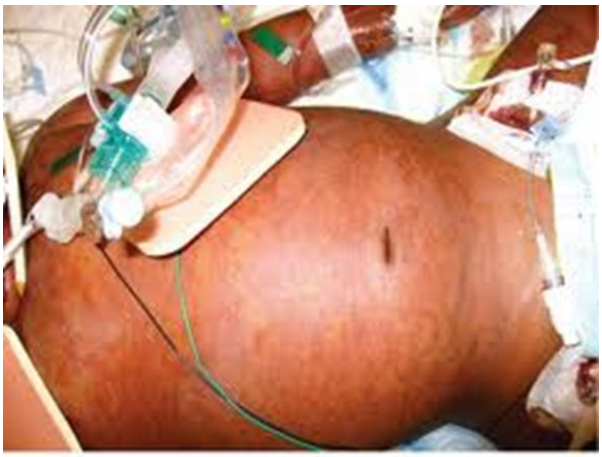
Treatment:

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









Drug Induced Pigmentation

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

Drugs involved:

1. Amiodarone.
2. Antimalarial.
3. Antimicrobial: minocycline, zidovudine,clofazimine.
4. Hydantoins/chlorpromazine.
5. Hormones: ACTH, estrogen/progesterone.
6. Heavy metals: silver, gold, mercury.
7. Cytostatic: bleomycin, cyclophosphamide, 5-fluorouracil, dactinomycin, busulfan,doxorubicin,daunorubicin.

Minocycline:

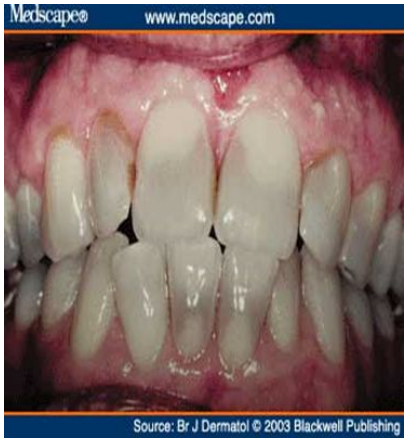
Usually after total dose of >50 grams.

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

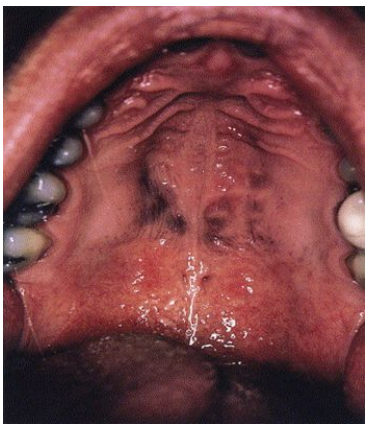
Stippled/ diffuse, blue-/slate-grey.

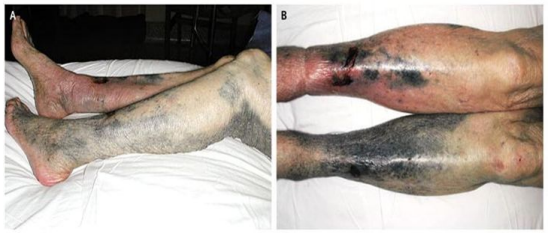
Extensor legs, face (esp. periorbital), sites of trauma or inflammation, hard palate, nails, teeth, bones/cartilage/thyroid.

Disappears within months after discontinuation.



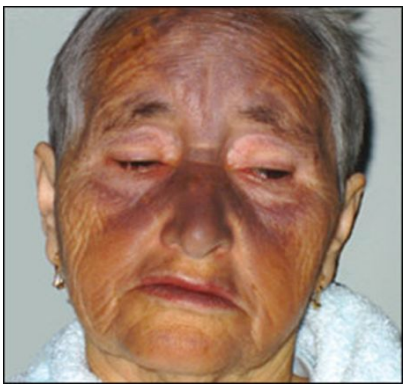
Minocycline induced pigmentation

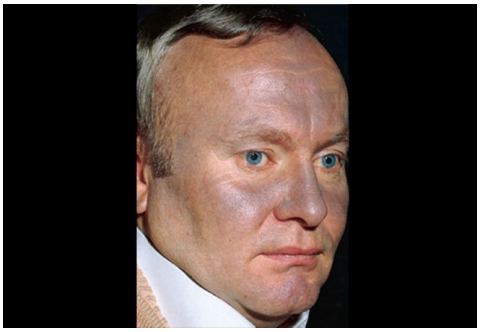




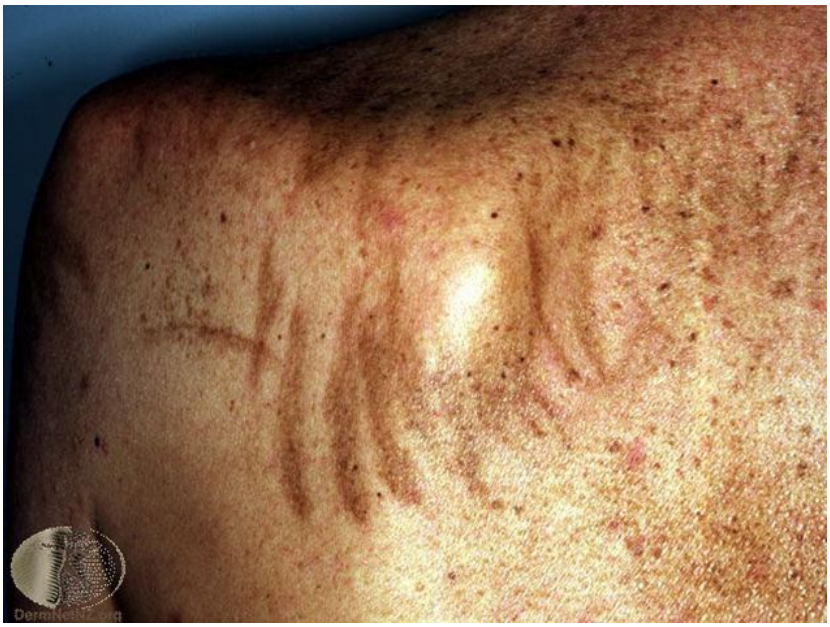
Antimalarials:

- 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.





Amiodarone induced pigmentation



Bleomycin induced pigmentation
(Whiplash Configuration)
مثل ضربات السوط

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.

Morphology:

- Sharply demarcated, deep purple to black necrosis.
- Lesions vary with severity of reaction: petechiae to ecchymoses 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.

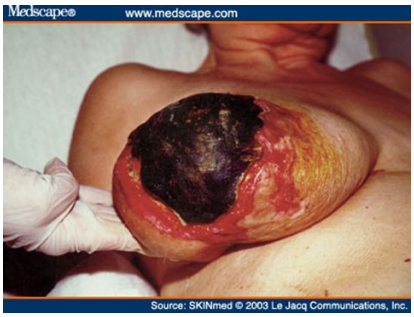
Differential Diagnosis:

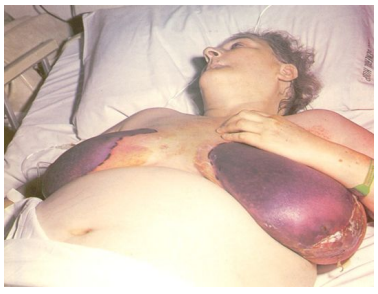
- Purpura fulminans (DIC).
- Hematoma in overly anticoagulated patient.
- Necrotizing soft tissue infection.
- Vasculitis.
- Recluse spider bite.

Course/ Prognosis:

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

Warparin induced cutaneous necrosis
Usually in fatty areas in women (ex:breast)





Heparin induced cutaneous necrosis
Less severe compared to warfarin