Adverse Cutaneous Drug Manifestations

When we say dr didn't mention it or talked about it it doesn't mean that they are not in the slides it just mean if you do not have time it might be less imp

Objectives :

Not given

Pls before starting this lecture read more about the immune system and the hypersensitivity reactions I, II, III and IIII
https://www.youtube.com/watch?v=2tmw9x2Ot_Q&list=PLByBKxj3rXpJy07mwuc8J_-pE4qPltUce

Done by: Qusay Ajlan

Revised by: Khaled Al Jedia

Sources*: doctor's slides and notes + FITZPATRICK color atlas +433team male + 434team*

[Color index : Important | Notes | Extra]

ADVERSE CUTANEOUS DRUG REACTIONS

you have to know the serious reactions and it can come in any morphology like any dx

ADVERSE CUTANEOUS DRUG REACTIONS ICD:10: T88.7

- Adverse cutaneous drug reactions (ACDRs) are unpredictable They affect 2 to 3% of inpatients and lead to 0.1 to 0.3% of hospital fatalities.
- In the United States, adverse drug events account for up to 140,000 deaths and $136 billion in costs annually.
- Most reactions are mild, accompanied by pruritus, and resolve promptly after the offending drug is discontinued.
- Drug eruptions can mimic virtually all the morphologic expressions in dermatology and must be the first consideration in the differential diagnosis of a suddenly appearing eruption.
- Drug eruptions are caused by immunologic or nonimmunologic mechanisms and are provoked by systemic or topical administration of a drug.
- The majority are based on a hypersensitivity mechanism and are thus immunologic and may be of types I, II, III, or IV.

It should be noted that in most reactions both cellular and humoral immune reactions are involved.

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 ACDR Important to understand

Type	Pathogenesis	Pattern
Type 1	IgE mediated **(immediate type)**	Urticaria/Angioedema/Anaphylaxis
Type 2	Drug + Cytotoxic antibodies cause lysis of cells	1- Petechiae **2- ITP** (thrombocytopenic purpura) 3- Drug-induced **pemphigus**
Type 3	Immune complexes formed of **Immunoglobulins** and **drugs**	**1- Vasculitis** **2- serum sickness**
Type 4	Cell-mediated, **(delayed type)**	1- Morbilliform exanthems 2- fixed drug eruptions 3- lichenoid eruptions 4- Stevens-Johnson Syndrome 5- TEN

2- Nonimmunologic mediated ACDR

Type	Mechanism
Idiosyncrasy	1-Hereditary enzyme deficiencies 2-Idiopathic
Cumulation	Dose dependent eg:pigmentation gold, amiodarone or minocycline
Photosensitivity	Formation of toxic photo-products 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
Pseudo-immunologic:direct release of inflammatory cytokines	Mast cell degranulation, alternate complement system, cyclooxygenase inhibitors, others
Individual idiosyncrasy to a topical or systemic drug	Mechanisms not yet known

Clinical types of ACDR (will only talk about the red ones)

1. **Exanthematous drug reactions** (also called maculopapular or morbilliform) **(most common)**
2. **Drug induced Urticaria/angioedema** **(second most common)**
3. **Fixed drug eruptions** (third most common)
4. **DRESS Syndrome** (drug Reaction with Eosinophilia and Systemic Symptoms)
5. **ACDR- related pigmentation or necrosis/** alopecia/ nail changes/hypertrichosis
6. Anaphylaxis/anaphylactoid rxns most serious type
7. Serum sickness

ACDR mimicry of other dermatoses (almost all other dermatologic forms can come as a result of drug reaction)

-Acneiform Eruptions

-Bullous Eruptions

-Dermatomyositis-like

-Drug hypersensitivity syndrome

-Eczematous Eruptions

-Erythema Multiforme

-SJS

-TEN

-Erythema Nodosum

-Exfoliative dermatitis

-Erythroderma

-Lichenoid Eruptions

Lupus erythematosus-like

-necrosis

-Photosensitivity

-pigmentary

-Pityriasis rosea-like

-Pseudolymphoma

-Pseudoporphyria

-Psoriasiform eruption

-Purpura

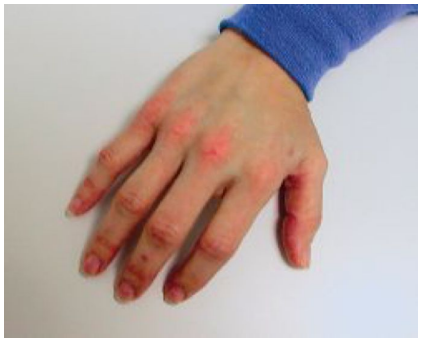
-Pustular eruptions

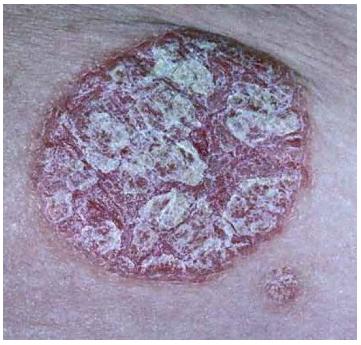
-Scleroderma-like reactions

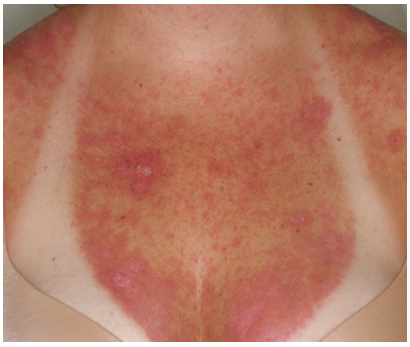
-Sweet syndrome

-Vasculitis

*Psoriasiform



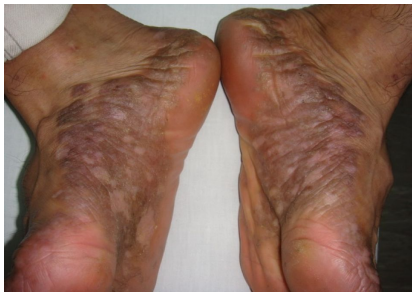


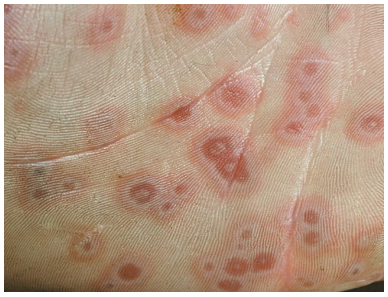


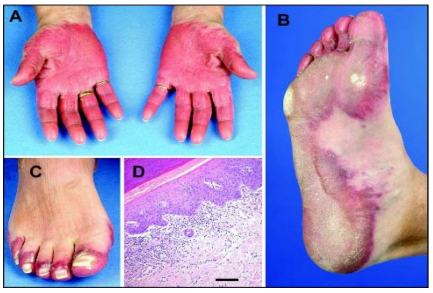
**Lichenoid

*Erythema Multiforme

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



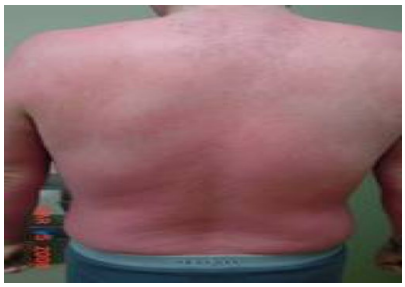


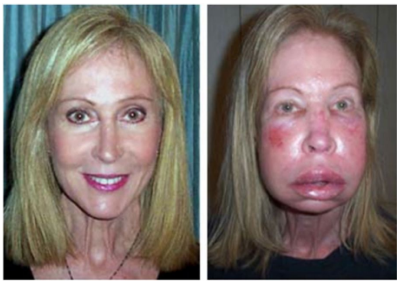


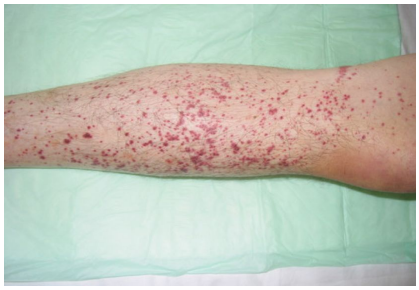
* Exfoliative Dermatitis

*Facial edema

*Vasculitis



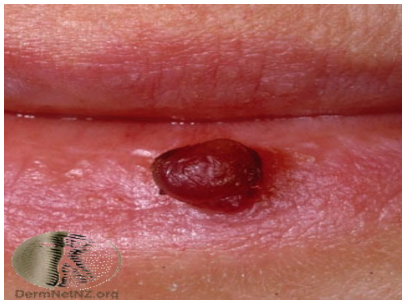


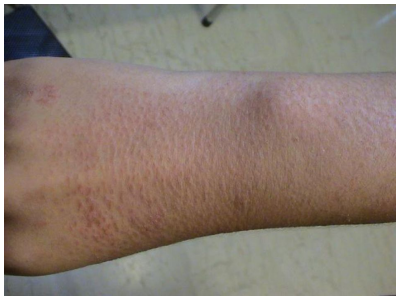


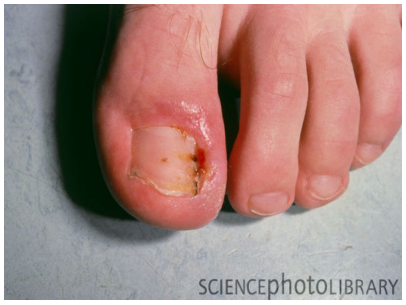
*Pyogenic granuloma

* Retinoid dermatitis

*Paronychia



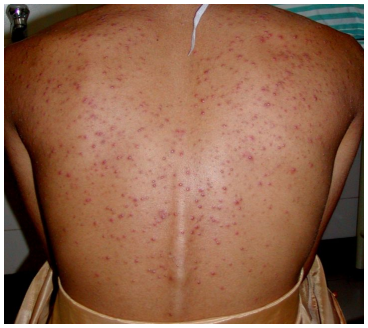


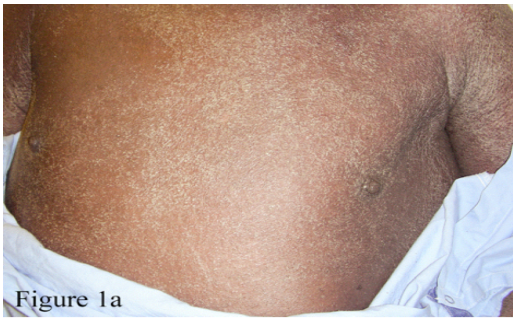


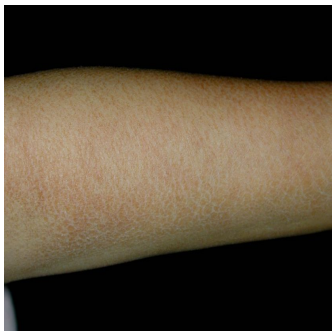
*Steroid induced acne

*Acute generalized exanthematous pustulosis

* xerosis







Guidelines for assessing possible ACDRs

- Exclude other causes especially Infections (viral mainly)
- Examine interval between introduction and induction look at when the patient started the new medication and when the symptoms first apeared (for example if the patient started a new drug a month ago and the cutaneous manifestations only appeared yesterday then its ***less likely*** caused by that drug) this is very crucial
- 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 it is similar to the ones in emergency lecture

- ★ 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
- ★ Urticaria/Angioedema

Diagnosis:

Is usually made on clinical finding

1. **Biopsy**:is helpful in defining the type of reaction pattern but **not in identifying the offending drug.**
2. **CBC**:**eosinophil count >1000/microL**Lymphocytosis with atypical lymphocytes**
3. **Chemistry**: abnormal LFT
4. **Skin Test/RAST:** helpful in IgE-mediated reaction (penicillin)

Management :

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

1-Exanthematous Drug Reactions

Definition

A cutaneous eruption that **mimics a measles**-like viral exanthem.

- (also called: Morbilliform drug rash, maculopapular drug reaction)

Most common type of cutaneous drug reaction but less common in the very young.

- Systemic involvement is low.

Pathogenesis

- mechanism unknown. Probably delayed hypersensitivity.
- Most common 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.

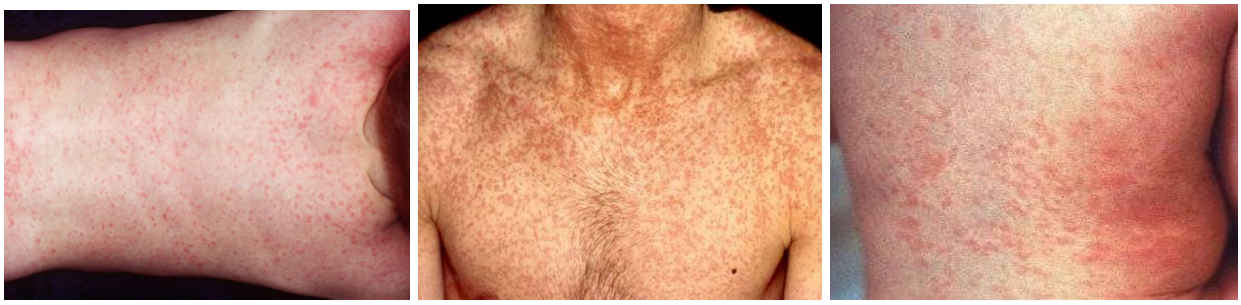
The dr didn't mention all of it

Clinical Manifestations

Onset: peak incidence at **ninth** day after administration **2-3 days** after readministration.
Symptoms: severe **pruritus** (if painful think TEN) with or without fever, chills.

Signs:

1. **Symmetrical involvement of trunk extremities** (in children face and extremities)
2. **bright red erythematous 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
   dr. skipped this part only mentioned the ones with bold dark



Maculopapular

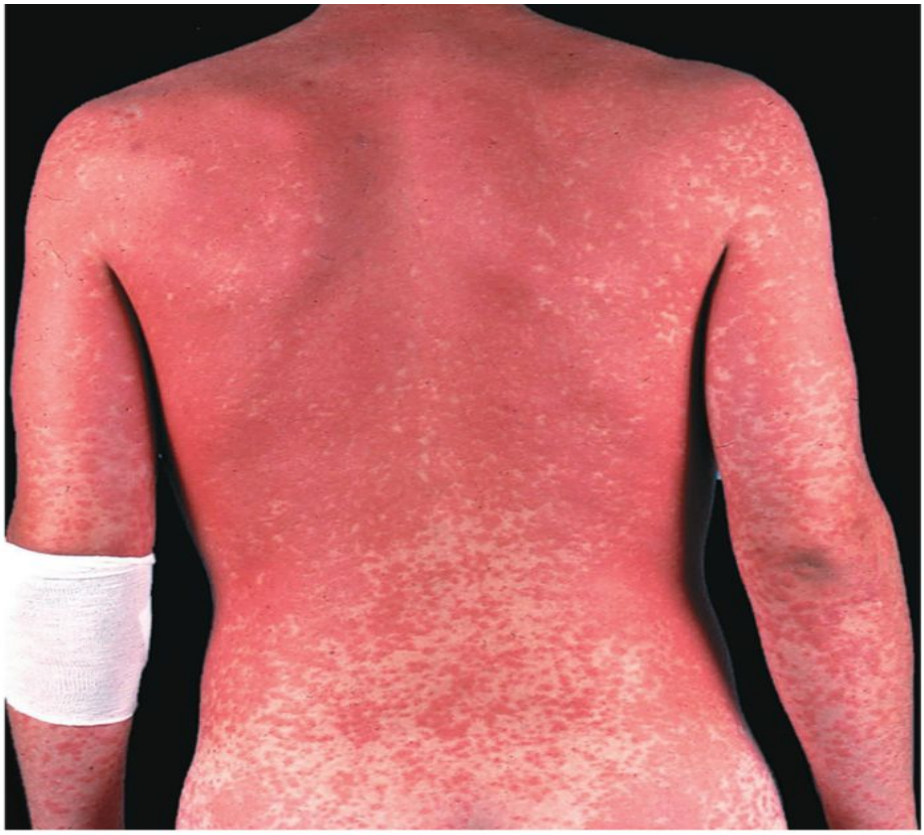


FIGURE 23-1 **Exanthematous drug eruption: ampicillin** Symmetrically arranged, brightly erythematous macules and papules, discrete in some areas, and confluent in others,

Diagnosis

Clinical Diagnosis

-Histopathology: perivascular lymphocytes and eosinophils
-Blood: eosinophilia

Differential Diagnosis

-Viral exanthems (most imp)
-Secondary syphilis
-Atypical pityriasis rosea
-Early widespread allergic contact dermatitis

Prognosis

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

Treatment: you don't treat it always sometimes it is mild and you just need to reassure or give them symptomatic 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 medical alert bracelet is advised.

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

Definition:

Characterized transient wheals and edema >> evanescent سريعة الزوال
and angioedema causing extensive tissue swelling with involvement of deep dermal and subcutaneous tissues.Angioedema is often pronounced on the face or mucous membranes
urticaria(wheals are the primary lesions) are very well defined lesions but angiooedma is ill defined because it is more deep so the borders are not clear in contrast to urticaria it is more superficial and thus you can find(feel) the borders

Pathogenesis:

Immune-mediated
(**IgE** or complement and immune complex)
Non allergic:
cyclooxygenase inhibitors, direct degranulation of mast cells, direct complement trigger, kinin metabolism inhibitors. Dr didn't talk about it

Clinical manifestation:

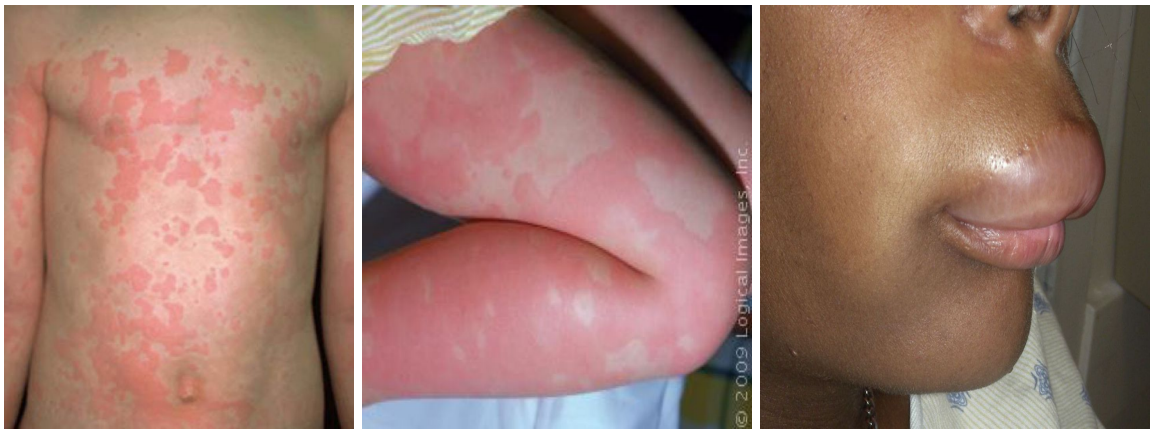
Onset:1-2 weeks after administration; minutes to hours after re-administration

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 swellings
- flushing, yawning, airway edema, sneezing, bronchospasm, laryngeal edema, hypotension, vomiting, diarrhea, arthralgia
- In case of angioedema it could cause airway obstruction people could die medical emergency



The pic with inflamed lip is angioedema the other 2 are urticaria

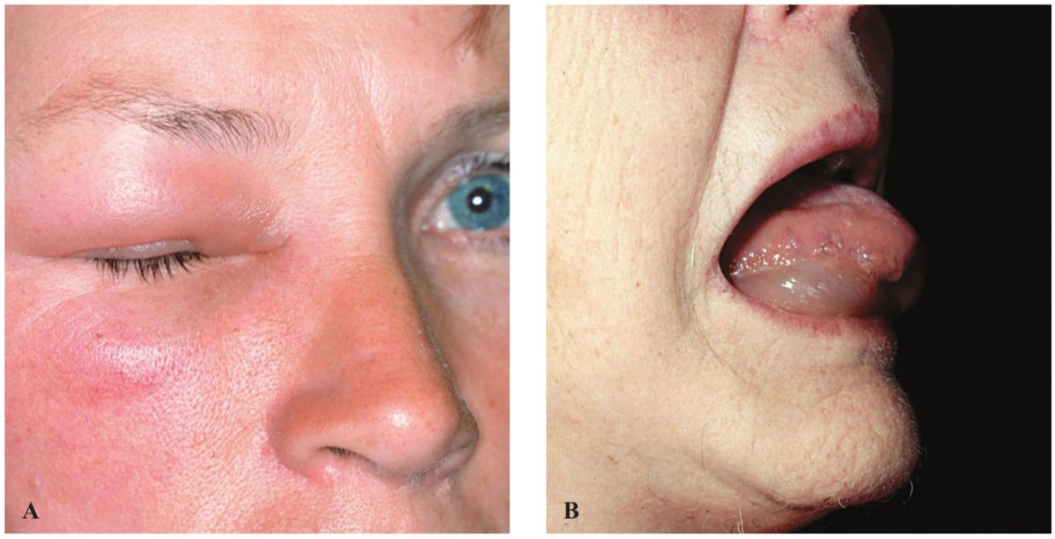


FIGURE 23-5 **Drug-induced angioedema: penicillin** **(A)** Angioedema has led to closure of right eye. **(B)** Sublingual angioedema in another patient interfered with breathing, talking, and eating and caused great concern.

Diagnosis:

Clinical Diagnosis

-Do biopsy if vasculitis suspected in case of urticaria it persists for 24 h or less but if it persists for more than 24 to 72 h suspect urticarial vasculitis

-Measure complement if vasculitis suspected

-Ultrasonography if edema of bowel suspected

chronic urticaria is mostly secondary to other dx but sometimes it is idiopathic so we need to investigate more

Differential Diagnosis:

-Acute allergic contact dermatitis

-Insect bites

-Cellulitis

Treatment

- ❖ **Definitive**
- ❖ **Symptomatic:**
  1. **subcutaneous epinephrine** (0.3-0.5ml of 1/1000) + airway/ **IV** access, (in angioedema)(also we give the pt epinephrine pen for emergencies)
  2. Anti-histamine H1/H2 blockers (in urticaria we give only anti histamine unless it is very severe with RT involved we give epi)
  3. systemic glucocorticoids
- ❖ **Prevention:**

- awareness very important for pt
- wallet card
- Bracelet
- Pretreatment

In case of angioedema, we have to give the patient epinephrine

Prognosis it resolves within hours to weeks after **drug withdrawal**

3-Fixed Drug Eruption

typically the dr talked about it for less than 3 min -_-

Definition

Identical skin lesion (could be single or multiple) that recur at the **same location.**

Thats why called fixed

Pathogenesis

Unknown Most common drugs: tetracyclines, antimicrobials phenolphthalein, oral contraceptives, NSAIDs, Salicylates, sulfonamides, metronidazole, barbiturates, food coloring (yellow), quinine dr did not mention it

Clinical manifestation

Onset:

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

Symptoms:

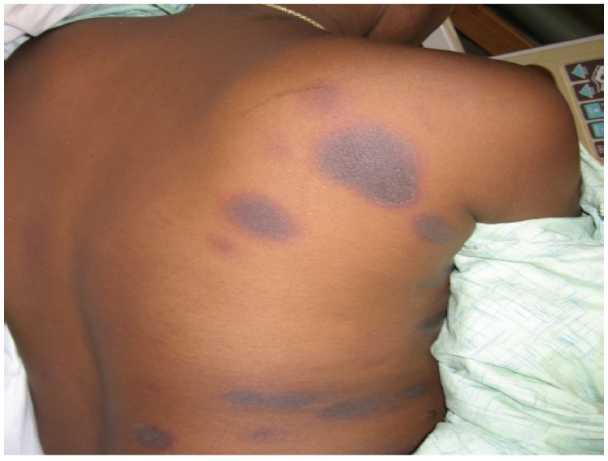
- Usually asymptomatic (painful if eroded) could come with systemic symptoms

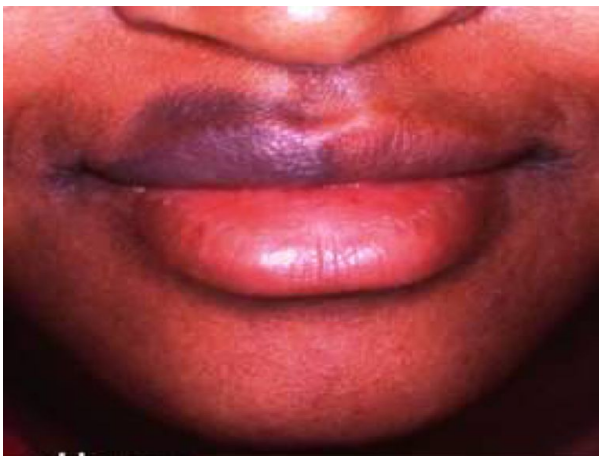
May be pruritic, pain ul, or burning.

- May be associated with headache (barbiturate analgesic), constipation (phenolphthalein laxative), Cold (OTC yellow dye) Food (yellow dye, quinine, salicylates) dr did not mention it

Signs:

- Round/oval usually solitary, sharply demarcated, erythematous macule
- dusky red/violaceous edematous plaque
- bulla/erosion
- dark brown violaceous post inflammatory hyperpigmentation. Leaves pigmentation
- Common on genitals and oral mucosa but any site including periorbital, conjunctivae and oropharynx





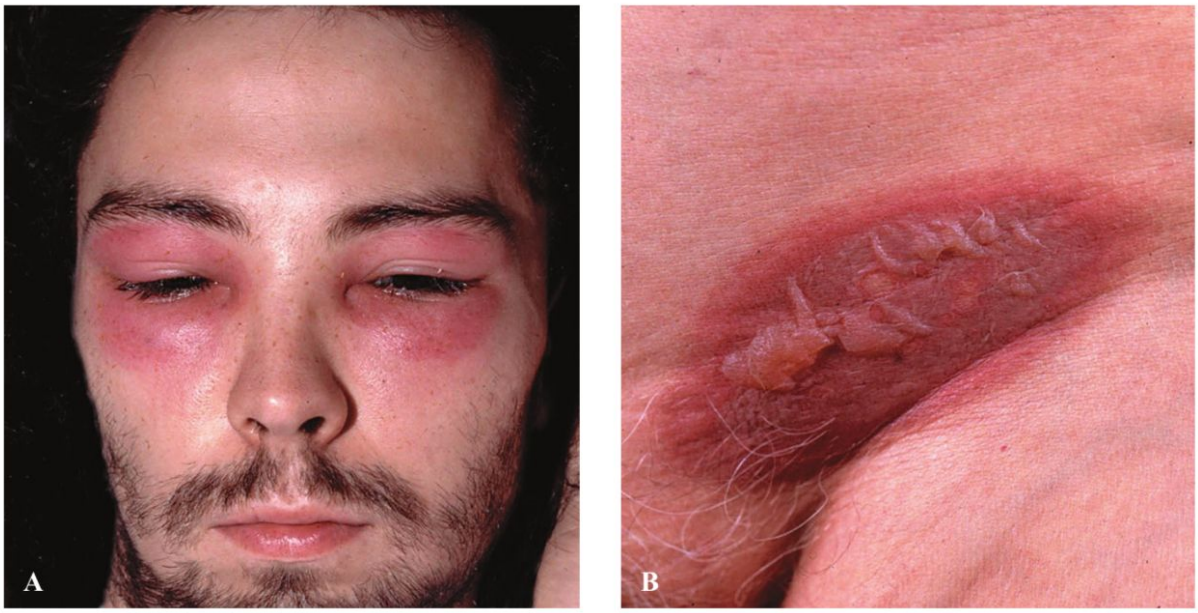


FIGURE 23-6 **Fixed drug eruption** **(A)** Tetracycline. Two well-defined periorbital plaques with edema. This was the second such episode following ingestion of a tetracycline. No other lesions were present. **(B)** Tylenol. A large oval violaceous lesion with blistering in the center. Erosive mouth lesions were also present.

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

If Eroded: antimicrobial ointment to prevent infection

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

4-Drug Hypersensitivity Syndrome (DRESS)-Drug reaction with eosinophilia and systemic symptoms

Definition

An idiosyncratic serious (could lead to death) adverse drug reaction that involves skin and other organs.

Pathogenesis

1-Hereditary (toxic areneoxide metabolites; slow N-acetylationof sulfonamides)
2-Idiopathic

Most common drugs:

Antiepileptics (phenytoin, carbamazepine,phenobarbital)
Sulfonamides (antimicrobials, dapsone, sulfasalazine).

Clinical manifestation

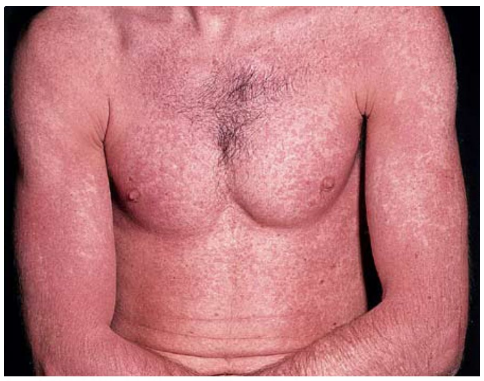
Onset: 2-8 weeks after first drug administration
Symptoms:Fever, malaise, pruritus

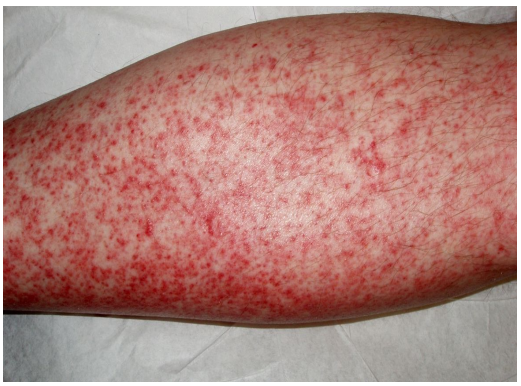
Signs:

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
Starts as mobilliform but could progress to erythroderma

Other (systemic):

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





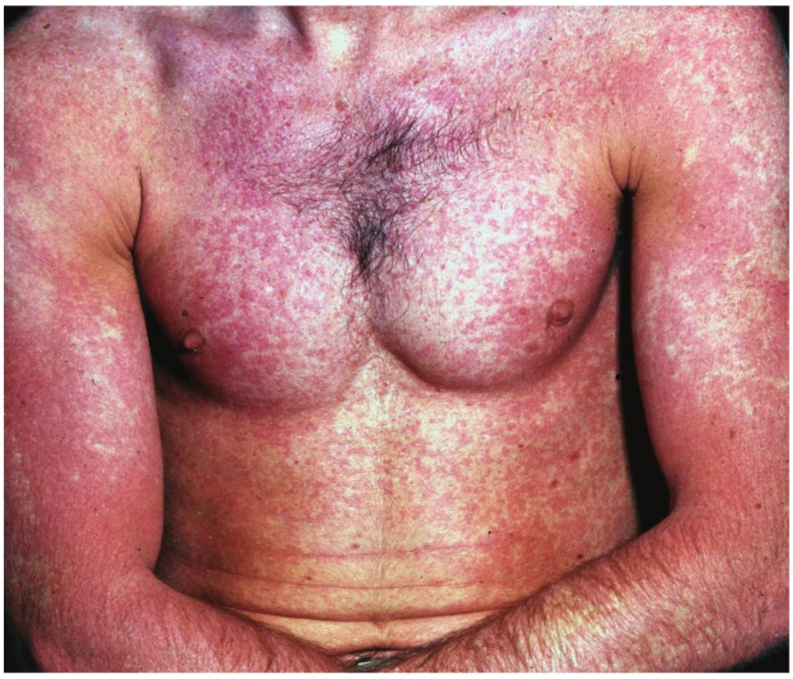


FIGURE 23-8 **Drug hypersensitivity syndrome: phenytoin** Symmetric, bright red, exanthematous eruption, confluent in some sites; the patient had associated lymphadenopathy and fever.

Diagnosis:

Proposed diagnostic criteria (three criteria required for diagnosis):

1.Cutaneous drug eruption

2.Hematologic abnormalities (***eosinophilia≥1500***/microLor atypical lymphocytes

3.Systemic involvement (adenopathies≥ 2cm in diameter or hepatitis (SGPT ≥ 2N) or interstitial nephritis, interstitial pneumonitisor 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 mononuleosissyndrome.

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

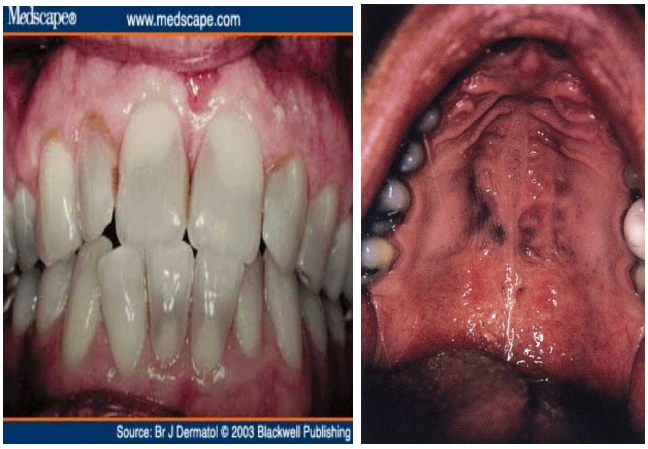
Awareness, wallet card/ bracelet

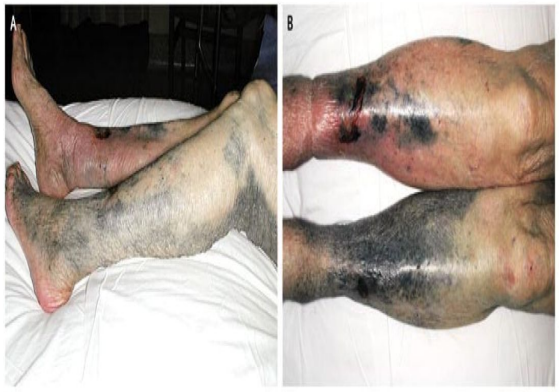
5-Drug Induced Pigmentation

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

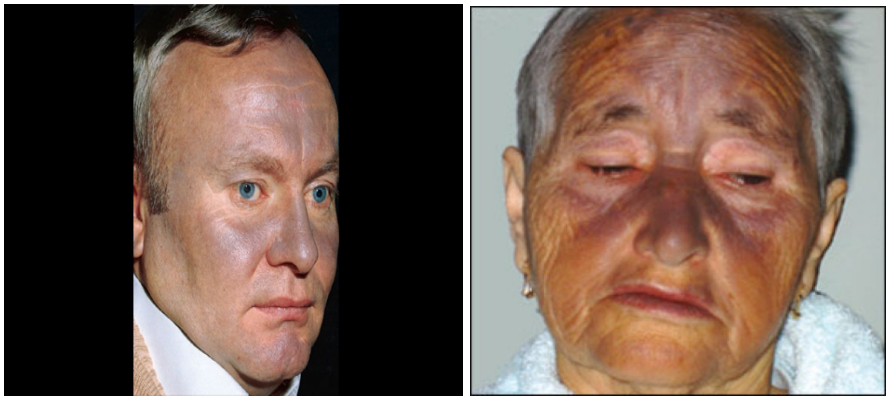
Drugs involved: the dr only talked about the red ones

- **Amiodarone**
- Antimalarial
- Antimicrobial: **minocycline**, zidovudine, **clofazimine**
- (clofazimine gives a red to orange color which is characteristic)
- Hydantoins/chlorpromazine
- Hormones: ACTH, estrogen/progesterone
- Heavy metals: silver, gold, mercury
- Cytostatic:**bleomycin**, cyclophosphamide
- -5-fluorouracil, dactinomycin,busulfan, doxorubicin, daunorubicin

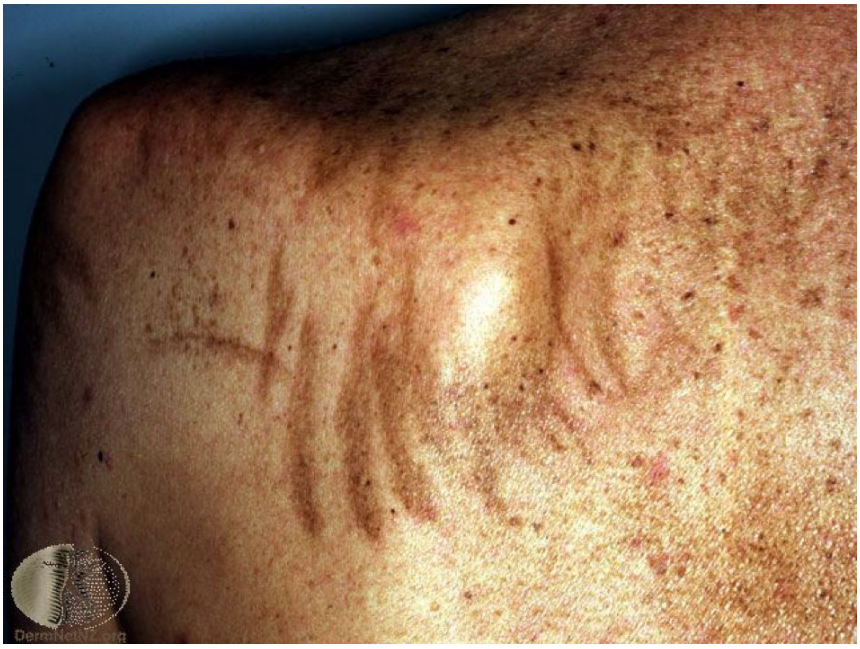




Minocycline induced pigmentation



Amiodarone induced pigmentation



Bleomycin induced pigmentation

patients taking chemotherapy (Whiplash Configuration) تشبه ضربة السوط

Minocycline didn't talk about it

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 didn't talk about it

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**

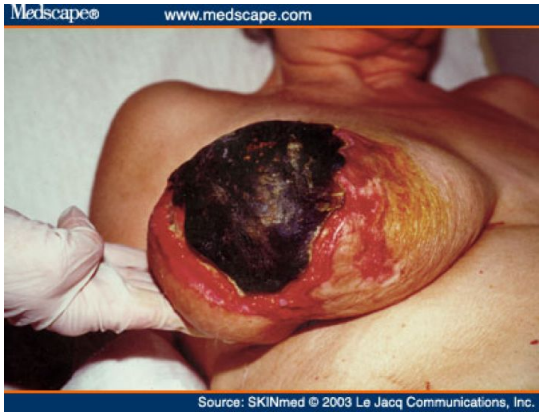
Warfarin cutaneous necrosis: Idiosyncratic
Onset: 3-5 days of anticoagulation therapy.
Due to a **transient hypercoagulable state and thrombus formation. In the beginning**
Risk factors: high initial dose, obesity, female, hereditary deficiency of protein C, protein S or antithrombin III.

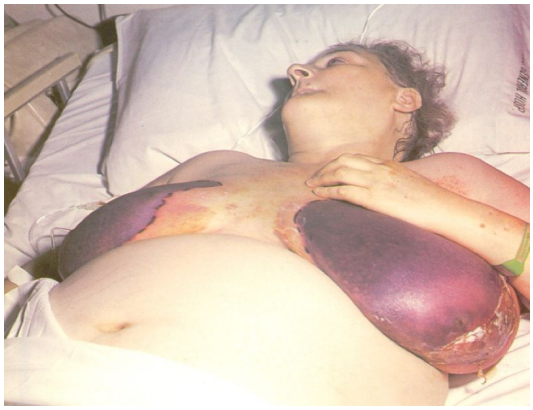
Sharply demarcated, deep purple to black necrosis.
Lesions vary with severity of reaction: petechaieto acchymosesto tender hemorrhagic infarcts to extensive necrosis
->deep tissue sloughing/ ulceration.
Usually single. On areas of abundant fat. Acral areas spared.
Coagulation studies: within normal limits

Differential Diagnosis

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

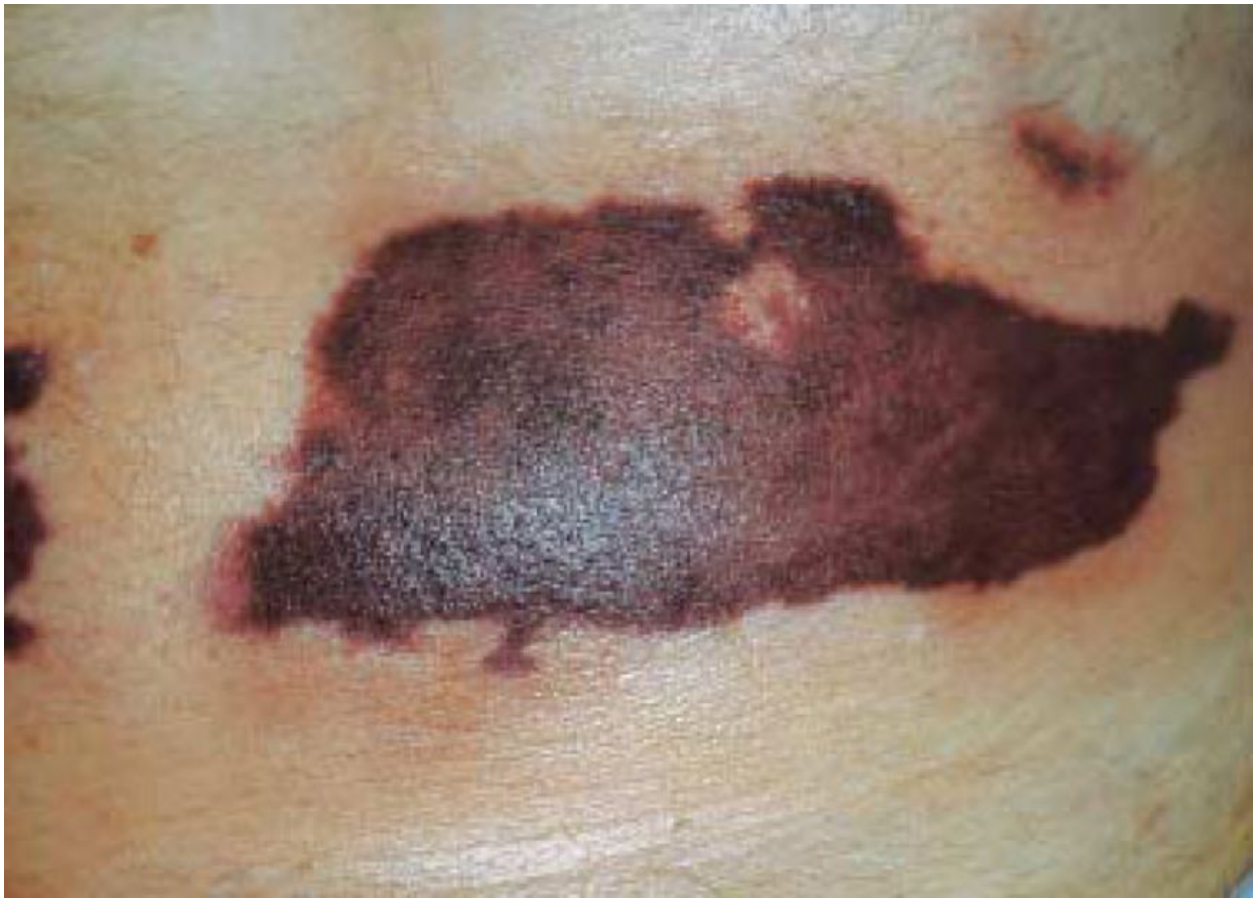
Course/ Prognosis
May subside/heal by granulation or require surgical intervention.
Life threatening if extensive in an elderly debilitated patient.





Warfarin induced cutaneous necrosis

Heparin could do the same as warfarin but not as bad



Heparin induced cutaneous necrosis