Dermatology Team 441

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Drug eruptions

Objective: were not given

Note: cover the following: timeline, clinical presentation, most common drugs & how to deal with it.

Color index:

- Main text
- Important
- Dr's explanation
- Golden notes
- Extra

Dermatology Team 439

DERMATOLOGY TEAM 438

This lecture was originally done by both 438 & 439 teams.
So great thanks to them

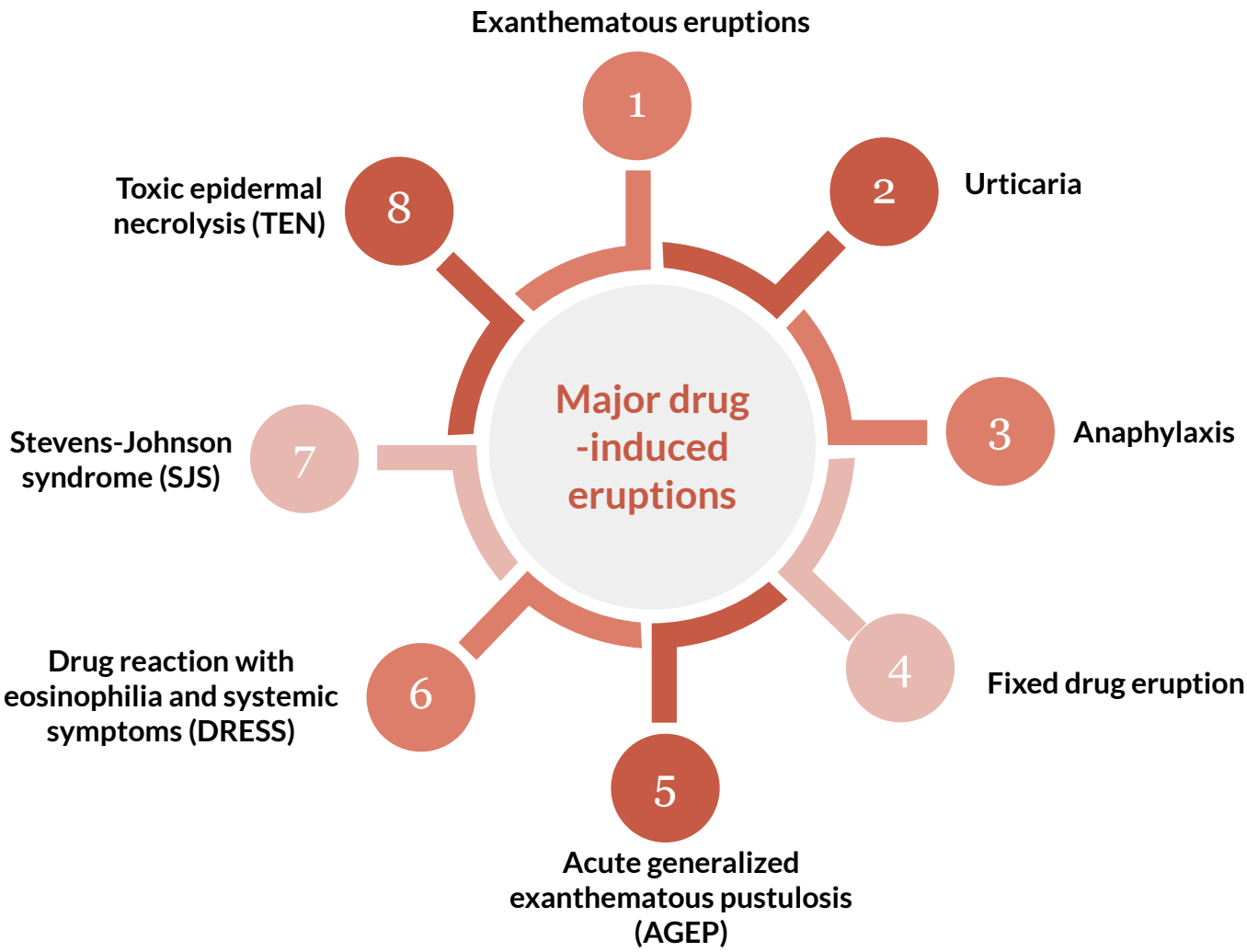
Drug Eruptions

Introduction:

- The skin is one of the most common targets for adverse drug reactions.
- 1-5% of patients receiving antibiotics and anticonvulsants may develop a drug eruption.
- ~2% of all drug-induced skin reactions are considered ''serious''.
- Skin reactions to drugs are responsible for ~3% of all disabling injuries that occur during hospitalizations.
- Either due to:
  - **Immunologic response.**
  - Non-immunologic (Overdose, side effect, drug-drug interaction, metabolism…etc).

Diagnostic approach for drug eruptions:

1. **Clinical characteristics:** (history, Examination)
   - Type of primary lesion.
   - Distribution and number of lesions (each drug have different distribution and lesions).
   - Mucous membrane involvement (to determine a benign vs. non benign skin reaction), facial edema.
   - Associated signs and symptoms fever , SOB, arthralgia
2. **Chronological factors:**
   - Document all drugs to which the patient **has been exposed**.
   - Date of eruption, time interval.
3. **Literature search:** (to be updated because all kinds of new drug reactions are published on a daily basis).



Exanthematous Drug Eruptions and Urticaria

Exanthematous Drug Eruptions

Clinical features

- The most common drug reaction affecting the skin.
- Classically begins **7 to 14** days after the start of a new medication.
- Begins as **erythematous macules** (symmetric) that sometimes becomes palpable (maculopapular eruptions).
- Begins on the trunk and upper extremities and progressively becomes confluent (start as multiple separated lesions and merge together to one big lesion).
- Mucous membranes are usually **spared.**
- Pruritus and low-grade fever(due to cytokines) and often present.
- The eruption disappears spontaneously after **1-2 weeks** without complications (it is not serious drug reaction).
- The following classes of drugs have a significantly higher incidence: **Aminopenicillins, Sulfonamides, Cephalosporins and anticonvulsants,** allopurinol, NSAIDs**.** names of the drugs will come in the exam
- **Always look for the following:**
  - Edema of the face + blood eosinophilia (DRESS).
  - Mucous membrane lesions or painful dusky skin (SJS, TEN) (usually spared in exanthematous drug eruptions).

Histology

- Nonspecific changes, eosinophils may be present.

The major DDx

- Viral exanthem (often indistinguishable) (history of respiratory tract infections).
- Drug etiology favored in adults, viral favored in pediatric patients.
- The presence of peripheral blood eosinophilia favors a drug reaction. Drug allergy

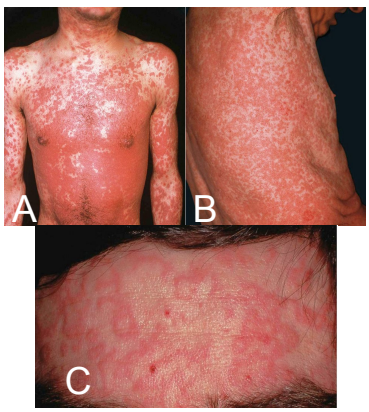
If a child came ddx —> viral

Treatment

- **Supportive** (Mostly). Depending on the symptoms
- Discontinue the offending drug. (risk vs benefit).
- Topical antipruritics and corticosteroids may help to alleviate pruritus.
- Systemic glucocorticoids

Pictures

- **(A)** Numerous pink erythematous maculopapular eruption on the trunk that is scattered and as we go down it coalesce and become confluent. (may be due to cephalosporin). major DDx: viral infection but it is more common in children unlike Drug eruption which is more in adult.
  Female note: diffuse numerous erythematous macules and patches over the trunk and extremities
- **(B)** Confluence of lesions on the trunk.
- **(C)** annular plaques on the forehead may be secondary to phenobarbital. Palpable plaque bright pink erythema



Urticaria

Clinical features

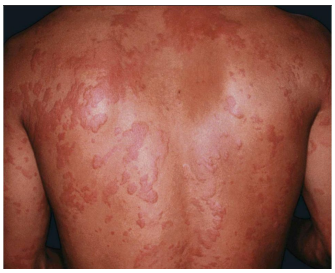
- **Transient erythematous and edematous papules and plaques that are usually associated with pruritus.**
- They can appear anywhere in the body including palms, soles and scalp.
- Duration is usually a few hours to 24 hours (sometimes stays for minutes)
- Skin is normal after they resolve.
- Acute: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

(Don't get confused, in acute case, the condition lasts 6w, the duration of the episode is 24h)

Urticaria, Angioedema, Anaphylaxis and Photosensitivity

Urticaria (cont')

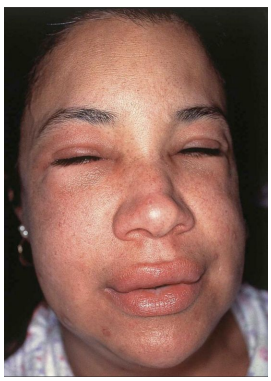
Pictures



- Erythematous Raised edematous papules or plaques (also we can call it hives or wheels). Diffuse numerous erythematous edematous ill defined blanchable plaques over the back , after few minutes this will appear as normal back
- Urticaria secondary to penicillin.
- Several of the lesions have a figurate appearance.

Angioedema

Clinical features



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

Anaphylaxis

Clinical features

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

Treatment

- Discontinue drug and strict avoidance in the future.
- Systemic steroids.
- **SubQ**(Subcutaneous) **epinephrine** in cases of life-threatening angioedema or anaphylaxis. Must go to the ER

Photosensitivity

INFO

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

- The photosensitivity drug reactions are classically divided into 2 major types:
  i. Phototoxic (more common).
  ii. Photoallergic.

Photosensitivity and vasculitis

Photosensitivity

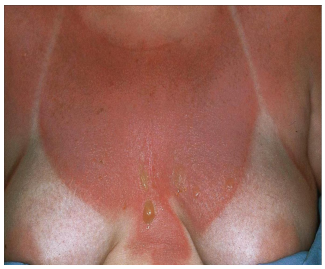
Phototoxicity

"to happen you need medication (sufficient) + light exposure"

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

Phototoxicity Picture

- Erythema and bullae are obviously limited to sun-exposed sites and resemble an exaggerated sunburn. Female notes: Diffused tensed moderate so severe it's showing blisters . V neck , photo distribution
- Phototoxic reaction in a patient receiving methotrexate. Patients on methotrexate can also experience a "sunburn-recall" phenomenon.

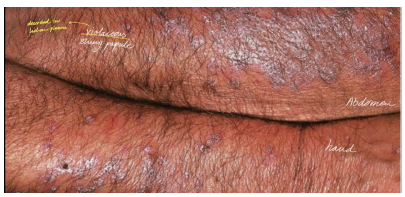


Photoallergy

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

Photoallergy Picture

- resemble lichen planus or eczematous reaction.
- Photolichenoid drug eruption due to Hydrochlorothiazide. The lesions favored the extensor surfaces of the forearms.

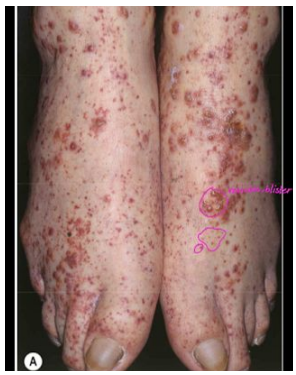


Vasculitis

Clinical features

Type 3 sensitivity can be caused by infection, drugs, or autoimmune. Examples : small —> HSP , medium—> polyarthritis nodusa

- ~10% of the cases are due to drugs.
- Clinically: Purpuric papules on the lower extremities.
- Systemic involvement is very unusual.
- Occurs 7-21 days (almost all the durations mentioned in this lecture are **important**) after drug administration and less than 3 days following re-challenge (if you give the drug again).
- Most common drugs: Penicillins, NSAIDs, Sulfonamides and cephalosporins.



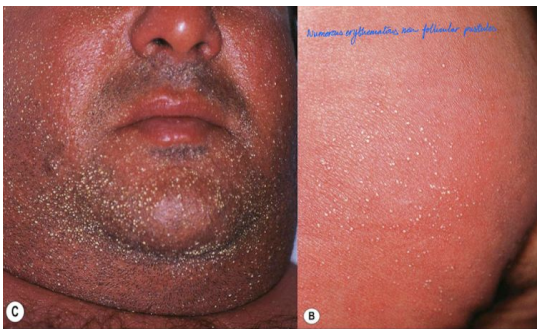
Neutrophilic drug eruptions and DRESS

Neutrophilic drug eruptions

Acute generalized exanthematous pustulosis (AGEP)

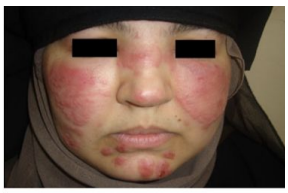
- Acute febrile drug eruption.
- Numerous small, non-follicular, sterile pustules (neutrophils are attracted to pustules) (Non-infectious), arising within large areas of edematous erythema.
- More than 90% of cases are drug-induced. imp for you
- The onset is usually within 2 days (very fast) of starting the medication.
- Lesions begin on the face or intertriginous zones (groin, axillae) and then disseminate within a few hours.
- The lesions last for 1 to 2 weeks and are followed by a superficial **desquamation**.
- Lab: leukocytosis with high neutrophils
- **DDx**: Acute pustular psoriasis.
- Drugs: **Antibiotics** (Beta-lactam and macrolides), **CCB** and **Antimalarials**.

AGEP Picture



- Hundreds of tiny 1-2 mm sterile pustules in background of erythema.
- positive patch test result 4 days following the application of 0.75% metronidazole in a patient with a previous pustular drug eruption to that medication.
- Diffuse erythema of the buttock (due to cephalosporin, **B**) and face (due to metronidazole, **A**) studded with sterile pustules.
- Spongiform pustules are seen within the epidermis of lesional skin.

Sweet's syndrome (Acute febrile neutrophilic dermatosis)

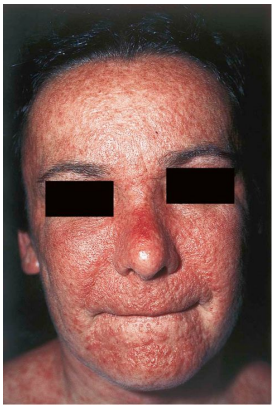


- This syndrome is characterized by fever,
- peripheral blood neutrophilia, and painful erythematous plaques that favor the face and upper extremities.
- Neutrophils migrate from the bone marrow to the skin
- Drugs represent <5% of all cases
- It starts about a week after the onset of drug administration.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

INFO

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



Multiple erythematous and edematous facial papules are present.

DRESS and Bullous Eruptions

Drug reaction with eosinophilia and systemic symptoms (DRESS) (Cont')

Clinical features

- Starts **2-6 weeks** after drug initiation.
- Fever (85%) and a cutaneous eruption (75%) are the most common symptoms.
- Begins as a morbilliform eruption, which later becomes edematous, with follicular accentuation (Prominence).
- The face, upper trunk and extremities are the initial sites of involvement.
- **Edema of the face is the hallmark of DRESS.**
- Lymph nodes are often enlarged.
- **The most common and most severe site of visceral involvement is the liver** (majority of deaths associated with this syndrome). Worst kind of hepatitis occurs with DRESS
- Other organs involved: Heart, lungs, kidneys and thyroid.
- Prominent eosinophilia is a very characteristic feature. Serious reaction

Treatment

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

Bullous Eruptions

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

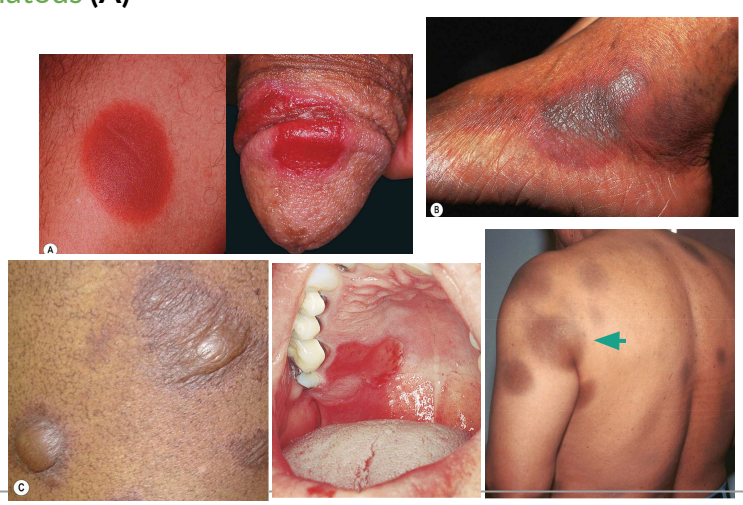
Fixed drug eruption

- Lesions develop **1-2 weeks** after a first exposure and within **24 hours within subsequent exposures.**
- **One or a few round, sharply demarcated, erythematous and edematous plaques are seen.**
- Sometimes a dusky, violaceous hue and a central blister may be seen. (violaceous = purple)
- Favors the lips, face, hands, feet and genitalia.
- The lesions progressively fade over several days (**leaving** Post inflammatory hyperpigmentation **(PIH) behind**). (not painful or itchy)(not necessarily permanent)
- **Lesions recur at exactly the same sites upon re-administration of the drug.**
- There is a generalized form of FDE (similar clinically to EM/SJS).(rare)
- A non-pigmenting variant of FDE occurs mainly with pseudoephedrine.
- Drugs: Sulfonamides, NSAIDs, Barbiturates, Tetracyclines and Carbamazepine.

Fixed drug eruption Pictures

"It's easy to remember because it is a single lesion"

- Round oval Well-demarcated erythematous **(A)** to violet–brown plaques that can develop a detached epidermis **(B)**, Bulla or blister **(C)** or erosion **(D)** centrally. As lesions heal, circular or oval areas of hyperpigmentation are commonly seen **(E).**
- Histologically, serous crust, a few necrotic keratinocytes, mild vacuolar changes at the dermo–epidermal junction, papillary dermal edema and melanophages can be seen as well as a mononuclear infiltrate.

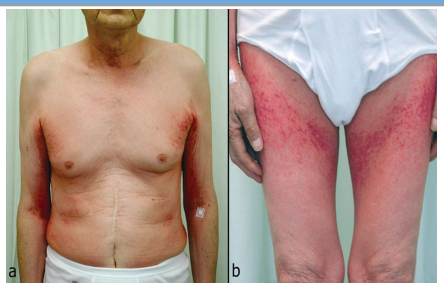


Bullous Eruptions and Other Drugs Eruption

Bullous Eruptions

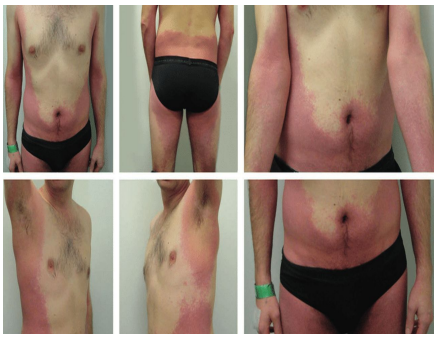
Symmetrical drug-induced intertriginous and flexural exanthema (SDRIFE)
skipped by the doctor

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



SYMMETRICAL DRUG-RELATED INTERTRIGINOUS AND FLEXURAL EXANTHEMA (SDRIFE) – CLINICAL CRITERIA

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



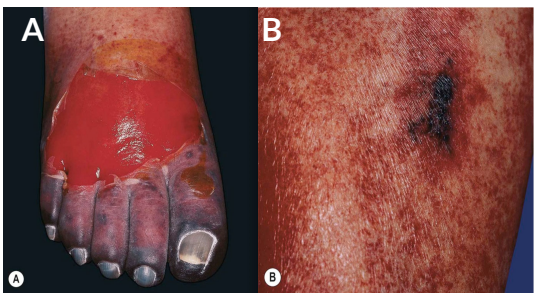
Other Drug Eruptions

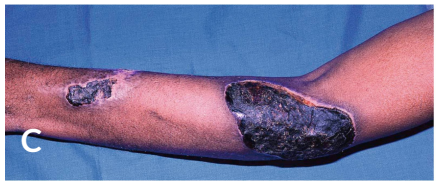
- **Anticoagulant-induced skin necrosis.**
- **Serum sickness-like eruption.**
- **Drug-induced lupus.**
- **Drug-induced psoriasis.**
- **Acneiform eruptions.**
- **Pigmentary changes.**
- **Pseudolymphoma.**
- **Chemotherapy reactions.**

Anticoagulant -induced skin necrosis

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

- Heparin-induced thrombocytopenia with thrombosis syndrome.
- **(A)** Ischemia and necrosis of the foot.
- **(B)** Petechiae due to thrombocytopenia and an irregular area of cutaneous necrosis due to thrombosis.
- **(C)** Painful necrotic ulcer.





Other Drugs Eruption

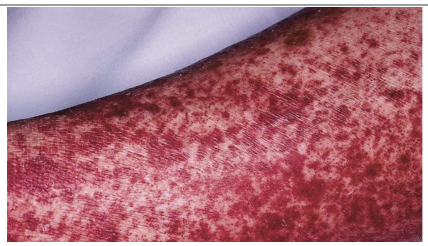
Other Drug Eruptions

Serum sickness-like eruption

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

Serum sickness-like eruption Pictures

- Serum sickness due to antithymocyte globulin.
- The purpuric lesions are due to small vessel **vasculitis** in this patient with aplastic anemia.



Drug-induced Lupus Involvement 75% Joints 90% Skin

Drug-induced systemic lupus:

- Fever, weight loss, pericarditis, pulmonary inflammation.
- Skin involvement is rare but includes: malar-erythema, photo eruption and discoid lesions.
- Vasculitis, renal and neurologic involvement is rare.
- Starts **over a year** after the medication is initiated (the time here is variable).
- +ve anti-histone Abs in 95% of cases (-ve DsDNA). MCQ
- Clinical symptoms resolve within 4 to 6 weeks.
- **Procainamide, hydralazine, chlorpromazine, isoniazid, methyldopa, quinidine, D-penicillamine and Minocycline**. (It's very important to know the medications)

Drug-induced subcutaneous Lupus:

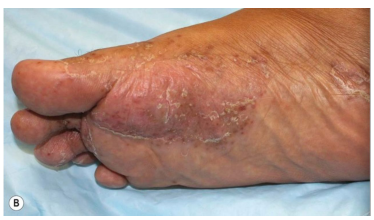
- Psoriasiform and annular lesions on the upper trunk and extensor arms.
- Hydrochlorothiazide, CCBs, Terbinafine (commonly used antifungal), NSAIDs, Griseofulvin (antifungal).
- Resolution of the rash may or may not occur after discontinuation of the responsible drug.

Drug-induced Psoriasis

- Drugs can affect a patient in 3 different ways: (no need to know about this)
  1. Exacerbation of **pre-existing** psoriasis
  2. Induction of lesions of psoriasis in clinically **normal skin in a patient w psoriasis.**
  3. De novo psoriasis.
- **Terbinafine** (antifungal), **NSAIDs**, **Antimalarials used for lupus**, ACE inhibitors, **Lithium (very common) and B-blockers.**
- Common treatment of Psoriasis can also cause it.
- Lesions of drug-induced psoriasis usually regress within weeks to a few months of discontinuing the inciting drug.

Drug-induced Psoriasis pictures

- Psoriasiform eruptions due to TNF-α inhibitors.
  -usually in palms & soles-.
- A Widespread papulosquamous lesions in a patient being treated with infliximab for gastrointestinal GVHD. Histologically, there was no evidence of cutaneous GVHD. this is Sterile pustulosis of the plantar surface developed in this patient with rheumatoid arthritis who had received infliximab for the previous 5 years. Neither patient had had a reduction in immunosuppression prior to the onset of the psoriasiform eruption.

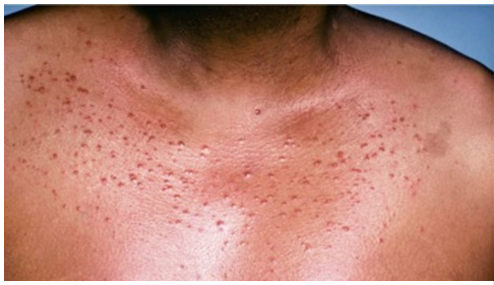


Other Drugs Eruption

Other Drug Eruptions

Acneiform eruptions

- Represent ~1% of drug-induced skin eruptions.
- Clinically, just like acne but comedones are absent.
- **Corticosteroids**, **Androgens** (male bodybuilders), hydantoins, lithium, progestin-containing OCPs.
- Tx: stop the offending agent (benefits > risk) and treat the like acne (with antibiotics)



Monomorphic, and it involves the trunk more commonly, unlike the usual acne

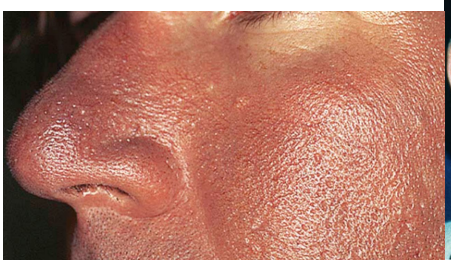
Pigmentary changes

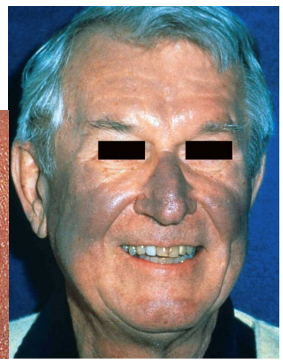
Hyperpigmentation:

- Usually more pronounced in sun-exposed areas (each one has a different type of pigmentation reaction).
- Minocycline (brown-black photosensitive) → subacute lupus.
- Antimalarials (hydroxychloroquine = grey-blue) used for SLE.
- Amiodarone (blue-grey).
- Silver, gold and arsenic.
- Bleomycin chemotherapy.

Hypopigmentation:

- Chronic use of topical steroids.





Pigmentary changes Pictures

- Gray–violet discoloration of the face due to amiodarone.
- Biopsy specimens demonstrate yellow–brown granules within dermal macrophages. Note sparing of the lower eyelid.
- Gray–violet Amiodarone induced pigmentation.

Lecture Summary (436 team)

Type of eruptions	Onset	Clinically	Causes
Exanthematous Drug Eruptions	7 to 14 days	erythematous macules (symmetric), sometimes palpable on the trunk and upper extremities, Pruritis	Aminopenicillins, Sulfonamides, Cephalosporins and anticonvulsants
Urticaria	few hours to 24 hours	Transient erythematous and edematous papules and plaques associated with pruritis. palms,soles and scalp.	antibiotics (Penicillins, cephalosporins)
Angioedema	ACE inhibitors (1 day to several years after starting)	Transient edema of the dermal, subcutaneous and submucosal tissue. on the face (eyelids, lips)	ACE inhibitors, Penicillins and NSAIDs
Anaphylaxis	within minutes	Combines skin with systemic manifestations (hypotension, tachycardia).	Penicillins
Phototoxic	sunburn in a shorter than expected time.	The erythema and bullae are obviously limited to sun-exposed sites and resemble an exaggerated sunburn	Tetracyclines (doxycycline), NSAIDs, Fluoroquinolones.
Photoallergy	-	Pruritic and resemble dermatitis or lichen planus	Thiazide diuretics, Sulfonamides antibiotics, Sulfonylureas and phenothiazines
Vasculitis	7-21 days	Purpuric papules on the lower extremities	Penicillins, NSAIDs, Sulfonamides and cephalosporins.
AGEP	2 days	Numerous small, non-follicular, sterile pustules, arising within large areas of edematous erythema	Antibiotics (Beta-lactam and macrolides), CCB and Antimalarials.
Sweet's syndrome	1 week	fever, peripheral blood neutrophilia, and painful erythematous plaques that favor the face and upper extremities	-
DRESS	2-6 weeks	morbilliform eruption, which later becomes edematous, with follicular accentuation. The face, upper trunk and extremities are the initial sites of involvement. Edema of the face is a hallmark of DRESS.	Anticonvulsants (phenobarbital, Carbamazepine and phenytoin) and sulfonamides.
FDE	1-2 weeks	One round, sharply demarcated, erythematous and edematous plaques. Sometimes a dusky, violaceous hue and a central blister.	Sulfonamides, NSAIDs, Barbiturates, Tetracyclines and Carbamazepine.
SDRIFE	-	Sharply demarcated, symmetrical areas of erythema over the anogenital region	Aminopenicillin & Cephalosporin
Anticoagulant-induced skin necrosis	2 to 5 days	Erythematous, painful plaques evolve into hemorrhagic blisters and necrotic ulcers. Mainly over the breasts, thighs and buttocks	Warfarin or Heparin
Serum sickness-like eruption	1 to 3 weeks	Mainly in children. Fever, Arthralgias, arthritis, rash and lymphadenopathy.	Cefaclor
Drug-induced Lupus	4 to 6 weeks	Fever, weight loss, pericarditis and pulmonary inflammation	Procainamide, hydralazine, chlorpromazine, isoniazid, methyldopa, quinidine, D-penicillamine and Minocycline
Drug-induced Psoriasis	weeks to a few months	-	erbinafine, NSAIDs, Antimalarials, ACE inhibitors, Lithium and B-blockers. TNF-induced Psoriasis.
Acneiform	-	Acne but comedones are absent.	Corticosteroids, Androgens, hydantoins, lithium, progestin-containing OCPs.
Hyperpigmentation	-	-	Minocycline, Antimalarials, Amiodarone, Silver, gold and arsenic, Bleomycin
Hypopigmentation	-	-	Chronic use of topical steroids

Quiz!

1- A 22-old-year female presented to dermatology clinic with an oval red patch with central blister on upper back 2 days after using NSAID. She had a similar lesion in the same location 4 months ago after using the same treatment. Which one of the following is the most likely diagnosis?

A) Pemphigus Vulgaris

B) Fixed Drug Eruption

C) Erythema Multiforme

D) Recurrent Discoid Eczema

2- A 60-year-old female with multiple medical problems has been admitted to the hospital 7 days ago. She was started on several medications. She developed black necrotic patches over both breasts for the last 3 days. Which one of the following drugs is most likely the cause?

A) Insulin

B) Warfarin

C) Gentamicin

D) Carbamazepine

3- An ER doctor admits a 70 years old patient with fever, sore throat, malaise and fatigue- The patient was treated at home with an antibiotic and antipyretic- The family was alarmed when he developed acute, itchy exanthematous rash and brought him to hospital- On examination his oral mucosa was free- No past history of systemic disease. What is the most probable cause of the rash in this patient?

A)Viral infection

B) Malignant neoplasm

C) Drugs

D) Streptococcal throat infection

4- A known epileptic patient on phenytoin presented with a morbilliform rash that started on the face. On examination he looks sick and has periorbital edema, fever with tender right hypochondrium and lymphadenopathy. His lab showed eosinophilia, atypical lymphocytes and raised liver enzymes. What is the probable diagnosis?

A) Infectious mononucleosis

B) Steven Johnson syndrome

C) Red man Syndrome

D) Dress Syndrome

5- A 25 years old male come the dermatology clinic complaining of 4 months history of itchy eruption, which waxes and wanes that is triggered by exercise he described the lesion as small punctuated and monomorphic wheels that last for less than half an hour?

A) Solar urticaria

B) Cholinergic urticaria

C) Dermatographism

D) Cold urticaria

Answers:
1: B, 2: B 3: C, 4: D 5: B

DERMATOLOGY TEAM 438

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