Hey Doc, What Did That Pill Do To My Skin? A Review of Cutaneous Drug Reactions

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Background and Disclosures

- Completed Medical School and Dermatology Residency training at UNM
- Outpatient private practice: Albuquerque Dermatology Associates
- General Dermatology (includes adults, pediatrics, surgical and cosmetic)
- No disclosures
Why Talk About Cutaneous Adverse Drug Reactions?

- 2-3% of hospitalized patients develop cutaneous adverse drug reactions (CADR)
- Outpatient incidence is unclear
- CADR are the most frequent manifestation of drug reactions
- Cause of patient non-compliance
- Confusing and frustrating
- Requires effort and patience to sort out

How Are Cutaneous Drug Reactions Classified?

- Acneiform
- Acral erythema
- AGEP (Acute Generalized Exanthematous Pustulosis)
- Dermatomyositis-like
- DRESS (Drug Rash with Elevated Eosinophilia and Systemic Symptoms)
- Erythema multiforme (EM), including EM minor, SJS, TEN, and SJS/TEN overlap
- Erythema nodosum
- Erythroderma
- Fixed drug eruptions
- Hypersensitivity syndrome
- Leukocytoclastic vasculitis
- Lichenoid
- Lupus
- Morbilliform or exanthematous
- Pseudoporphyria
- Phototoxic/photoallergic
- Serum Sickness and serum sickness-like
- Sweet syndrome (acute neutrophilic dermatitis)
- Urticaria
- Vesiculobullous

https://emedicine.medscape.com/article/1049474-overview#a1
Case Presentations
Case 1

An 83 yo female presents with an itchy tender violaceous purple brown rash on the arms, legs and upper back for 2 months. Which medication is the most likely cause of this rash?

A) Penicillin  
B) Metformin  
C) Spironolactone  
D) Acyclovir
Case continued . . .

Started hydralazine, felodipine and spironolactone within the last few prior months

Biopsy: “compatible with lichenoid drug reaction – vacuolar to lichenoid interface change with prominent dermal melanophages and scattered eosinophils”

http://www.danderm-pdv.is.kkh.dk/atlas/3-17.html
Answer: Spironolactone

Lichenoid Drug Eruptions:

• Itchy purple brown scaly papules and plaques
• Scattered more diffusely than classic LP
• Larger and sometimes atypical lesions
• Sometimes photo-distributed
• May occur 3-6 months up to years after initiation of a medication
• Resolution ranges from a couple of weeks to a year
• Clearance with 2 weeks of topical clobetasol and discontinuation of spironolactone
Lichenoid Drug Eruptions

- β-blockers
- ACE inhibitors
  - captopril
- Antimalarials
- Gold salts
- Lithium
- NSAIDs
- Penicillamine
- Ethambutol
- Sulfonylurea
- Thiazide Diuretics
- Furosemide
- PPIs
- Spironolactone
- Sulfasalazine
- Sildenafil

http://www.dermpedia.org/dermpedia-textbook/lichenoid-drug-eruption
Pathology of Lichenoid Drug Eruptions

- Focal parakeratosis
- Spongiosis
- Eosinophils and occasional plasma cells
- Cytoid bodies/Dyskeratotic cells in the epidermis
- Exocytosis of lymphocytes into the upper epidermis
- Deep dermal perivascular infiltrate
How Do We Approach Cutaneous Drug Reactions?

- Is it life threatening?
- Does the patient need to be hospitalized? Do they have systemic symptoms?
- Is it a symmetric eruption or localized (Fixed Drug Eruption)?
- What is the timing of this rash in association with any new and old medications?
  - 1-6 weeks
- Review all prescriptions, over-the-counter drugs (NSAIDs), herbal and homeopathic remedies
- If CADR is suspected and if you are able, stop the medication(s) for at least 2 months
- Any improvement after drug withdrawal and any reaction with re-administration supports the diagnosis
- Diagnostic tests
Features of Life Threatening Cutaneous Adverse Drug Reactions

- Mucous membrane erosions
- Blisters (Bulla)
- Nikolsky sign
- Confluent erythema
- Angioedema and tongue swelling
- Palpable purpura
- Skin necrosis
- Lymphadenopathy
- Elevated liver enzymes
- High fever, dyspnea, hypotension


https://www.dermnetnz.org/topics/sjs-ten-nursing/
Drugs That Commonly Cause Serious Reactions

**TEN/SJS**
- Allopurinol*
- Anticonvulsants (Carbamazepine*, Phenobarbital* Phenytoin, Lamotrigine, Valproic acid)
- Beta-Lactams: PCN, cephalosporins
- Sulfa drugs*
- NSAIDs (Oxicams, Ibuprofen, Indomethacin)
- Nevirapine

**DRESS***
- Minocycline*
- Sulfasalazine*

* implicated in both TEN and DRESS

*Hypersensitivity syndrome patients are at risk of becoming hypothyroid, usually within the first 4-12 weeks after the reaction(* regulatory T cells>autoimmune)

https://jamanetwork.com/journals/jamadermatology/fullarticle/422535

Diagnostic Tests

- Skin Biopsy-Punch or Shave
  - Biopsy a new lesion
  - Parakeratosis, spongiosis, eosinophils, deep inflammation
- Complete blood count (CBC) with differential
  - Eosinophils
- DIF (Direct immunofluorescence)-bullous drug eruptions
- Antibody testing and patch tests usually not helpful
  - Exception: + Anti-histone antibodies in drug induced SLE and +Anti-Ro antibodies in drug induced SCLE

https://www.mayoclinic.org/tests-procedures/skin-biopsy/about/pac-20384634
What is the Pathophysiology of CADR?
Immunologic vs Non-Immunologic Mediated Reactions

**Immunologic Reactions:**

- **Type I** - immunoglobulin E (IgE)–dependent reaction, which result in urticaria, angioedema, and anaphylaxis (minutes to hours, 2\textsuperscript{nd} most common CADR)
- **Type II** - cytotoxic reaction, which result in hemolysis and purpura (ex. cytotoxic therapy and Drug Induced Pemphigus)
- **Type III** - immune complex reaction, which result in vasculitis
- **Type IV** - delayed-type reaction with cell-mediated hypersensitivity, which results in contact dermatitis, exanthematous reactions, and photoallergic reactions
  - Most common cause of cutaneous adverse drug eruptions
  - 7-20 days after exposure
  - Not dose dependent
  - Recurs if drugs chemically related to the causative agent are administered at a later point
# Immunologically Mediated Reactions

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Pathogenesis</th>
<th>Examples of Causative Drug</th>
<th>Clinical Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>IgE-mediated; immediate-type immunologic reactions</td>
<td>Penicillin, other antibiotics</td>
<td>Urticaria/angioedema of skin/mucosa, edema of other organs, and anaphylactic shock</td>
</tr>
<tr>
<td>Type II</td>
<td>Drug + cytotoxic antibodies cause lysis of cells such as platelets or leukocytes</td>
<td>Penicillin, sulfonamides, quinidine, isoniazid</td>
<td>Petechiae due to thrombocytopenic purpura, drug-induced pemphigus</td>
</tr>
<tr>
<td>Type III</td>
<td>IgG or IgM antibodies formed to drug; immune complexes deposited in small vessels activate complement and recruitment of granulocytes</td>
<td>Immunoglobulins, antibiotics, rituximab, infliximab</td>
<td>Vasculitis, urticaria, serum sickness</td>
</tr>
<tr>
<td>Type IV</td>
<td>Cell-mediated immune reaction; sensitized lymphocytes react with drug, liberating cytokines, which trigger cutaneous inflammatory response**</td>
<td>Sulfamethoxazole, anticonvulsants, allopurinol</td>
<td>Morbilliform exanthematous reactions, fixed drug eruption, lichenoid eruptions, Stevens–Johnson syndrome, toxic epidermal necrolysis</td>
</tr>
</tbody>
</table>

*After the Gell and Coombs classification of immune reactions.

**For contact sensitivity see Section 2.

Non-Immunologically Mediated Reactions

Classified Accordingly:

- Adverse effects
- Direct release of mast cell granules
- Idiosyncratic reactions
- Intolerance
- Overdosage

An example of accumulation is **Argyria** (blue-gray discoloration of skin and nails) observed with use of silver preparations or **Ochronosis** due to overuse of hydroquinone.

**Phototoxic dermatitis** is an exaggerated sunburn response caused by the formation of toxic photoproducts, such as free radicals or reactive oxygen species.

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Who is most at risk for cutaneous adverse drug reactions?

- HIV patients have a 10-fold higher risk of developing a drug eruption than the general population
- CD4 count < 200 cells/µL) have a 10- to 50-fold increased risk of developing an exanthematous eruptions to sulfamethoxazole
- Women
- Elderly
- Polypharmacy
Case Presentation

A 75 yo male presents with a recurrent rash worse in the summer located on the face, extensor arms, hands, and upper trunk. The rash is bright pink, itchy, burning, and flaking. Which medication is the most likely cause of this rash?

A) Omeprazole
B) Sertraline
C) Atorvastatin
D) Amiodarone
Case continued. . .
Answer:

Amiodarone

Skin complications of amiodarone are common!

- Phototoxic
- Photoallergic
- Hyperpigmentation

Case continued . . .

- Biopsy: “spongiotic dermatitis with intracorneal neutrophils, rare dyskeratotic cells, perivascular lymphocytic infiltrate, rare dermal eosinophils. . . Could be seen in photo-exacerbated eczematous dermatosis or drug reaction. Photoallergic dermatitis could appear similar”

- Abs. Eosinophils slightly elevated 0.4 (0-0.3)

- ANA negative

- Treatment- clobetasol bid x 2 weeks to arms, hydrocortisone 2.5% ointment to face x 10 days, Keflex bid x 10 days

- Resolved but erythema/hyperpigmentation persisted
Photosensitive Drug Eruptions (Phototoxic and Photoallergic)

- Due to the combination of a drug and ultraviolet radiation (UVR), either UVA (320–400 nm) and/or UVB (290–320 nm); however, UVA is most often implicated
- Phototoxic>Photoallergic

**Phototoxic: (can happen to anyone!)**
- Resembles exaggerated sunburn, followed by hyperpigmentation
- Occurs within a few hours after ingestion
- Release of energy absorbed by photosensitizing drugs leads to the generation of free radicals and specific cellular toxins that damage the cell
- Photo-onycholysis and pseudo-porphyria are examples of phototoxic reactions to drugs

Phototoxic Eruptions

Tetracyclines*, cipro, sulfonamides
Thiazide diuretics*
NSAIDs*
ACE inhibitors, amiodarone, amlodipine, celecoxib, chlorpromazine, diltiazem, furosemide, griseofulvin, lovastatin, nifedipine, phenothiazine, piroxicam, quinolones, retinoids

http://london-newss.ga/hytax/doxycycline-photosensitivity-rash-moj.php
Pseudoporphyria

- NSAIDs (including nalidixic acid and naproxen)*
- Tetracyclines*
- Diuretics * (furosemide, hydrochlorothiazide/triamterene)
- Retinoids
- Amiodarone
- Bumetanide, chlorthalidone, cyclosporine, dapsone, etretinate, 5-fluorouracil
- Voriconazole (photosensitizer)

https://www.dermnetnz.org/topics/pseudoporphyria/
Photoallergic Reactions

- Type IV Cell-mediated hypersensitivity
- Requires previous exposure
- 24 to 48 hours following 2\textsuperscript{nd} exposure
- Absorption of UVR enables the drug to conjugate with a carrier protein to form an antigen > cell-mediated hypersensitivity
- Erythema, edema, and desquamation
- Sulfur-moiety containing drugs – thiazide diuretics, sulfonamide antibiotics and phenothiazines

Case Presentation

• 77 yo male presents for recurrent bulla on the scalp for 2.5 months
• Red patches that enlarge> bulla with clear fluid
• Non tender
• Finished a 10 day course of topical 5-FU cream for actinic keratosis 3 months prior
• Denied any other new medications or any h/o autoimmune or blistering conditions
Case Continued.

- Biopsy: “subepidermal blister with scattered neutrophils and dermal scar compatible with bullous/cicatricial pemphigoid”
- DIF (direct immunofluorescence) - linear to granular deposition of IgG and C3 along basement membrane
- **Answer:** Topical 5FU
- **Pathophysiology:**
  - Drug haptens bind to and alters antigenic determinants in the BMZ > autoantibodies
  - Treatment - clobetasol bid x 2 weeks, topical gentamycin bid x 3 days
  - No recurrence at 6 week follow up appt
- **Treatment Options:**
  - Furosemide*
  - Penicillin*
  - Captopril*
  - Spironolactone
  - Gold
  - D-penicillamine
  - Potassium Iodide
  - Sulfasalazine
  - Terbinafine
  - Adalimumab
  - Topical 5FU
  - PUVA

Drug-Induced Bullous Pemphigoid

- Resembles classic *bullous pemphigoid* with *urticaria*
- Appears suddenly
- Rarely affects the mucous membranes
- Occurs in a younger age group
- The skin biopsy, histopathology, and direct immunofluorescence is the same as for the classic disease

https://jamanetwork.com/journals/jamadermatology/article-abstract/400271

Package insert for Efudex:

Integumentary: Alopecia, blistering, bullous pemphigoid, discomfort, ichthyosis, scaling, suppuration, swelling, telangiectasia, tenderness, urticaria, skin rash.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/016831s049lbl.pdf
Case Presentation

- 75 yo female presents with itchy bright red, and tender rash on the legs x 1 week
- Associated leg swelling and pain in the ankles
- No abdominal pain, no arthritis, no hematuria
- Started amlodipine, lisinopril, HCTZ and simvastatin within the prior few weeks
- ANA elevated and CRP elevated
Case Continued.

- Biopsy: “Pigmented Purpuric Dermatosis (Schamberg’s/Capillaritis) vs drug eruption”, DIF was negative
- **Answer**: HCTZ
- Petechiae and pigmented macules localized to the lower limbs
- Superficial lymphocytic infiltration and marked hemosiderin deposition with erythrocyte extravasation
- Treatment: Clobetasol 0.05% oint bid x 2 weeks
- Complete clearance at 6 weeks

- Nonsteroidal anti-inflammatory drugs
- ASA
- Acetaminophen
- Glipizide/glybuzole
- Furosemide
- Thiazide diuretics
- Hydralazine

- Increase association of PPD in patients on the following medications: Statins (13.2%), beta blockers (10.5%), aspirin (7.9%), thiazides (7.9%), angiotensin receptor blockers (5.3%), antiplatelet agents (5.3%), and calcium channel blockers (5.3%)

Drug Induced Vasculitis

Penicillin, Cephalosporins, Sulfonamide
Loop and Thiazide Diuretics
Phenytoin
Allopurinol
Adalimumab
Aspirin/NSAIDs, cimetidine, gold, hydralazine, indinavir, leflunomide, levofloxacin, minocycline, montelukast, propylthiouracil, proton pump inhibitors, quinolones, ramipril, tetracycline, and thioridazine


Drug Induced Vasculitis

Most common extracutaneous clinical findings:

Arthritis (51%), gastrointestinal involvement (38.1%), nephropathy (34.7%), fever (23.8%)

Laboratory findings: increased erythrocyte sedimentation rate (40.2%), serum cryoglobulins (26%), leukocytosis (24.7%), positive antinuclear antibodies (21.1%), anemia (18.8%), and a positive rheumatoid factor (17.5%).

Case Presentation

70 yo male presents with a pink, swollen, blistering, burning, and flaking rash on the face, arms, legs x 1 month

Erosions in the mouth and palms/soles

Occurred 48 hours after a complicated dental procedure and after starting azithromycin

Medrol dose packs cleared symptoms within 24-48 hours, then symptoms recurred

ANA negative, CRP 2.3

No other new medications
Case Continued.

- Biopsy: “suggestive of an eczematous process like a contact dermatitis, nummular dermatitis, an “id” reaction or a drug eruption”
- **Answer:** Azithromycin
- Treatment: wound care, prednisone 60 mg (18 day taper)
- Clobetasol to palms and soles bid x 2 weeks
- Wound care-Domeboro astringent solution (Aluminum Acetate) soaks 3 times per day to weeping or edematous areas
Eczematous Drug Eruptions

• Accounts for 75% CADR (Type IV)
• Aka: Morbilliform and maculopapular eruptions
• Onset is within 2 weeks of starting a new medication or within days of re-exposure
• May present with pruritus, low grade fever, eosinophilia
• Beta-lactam antibiotics (PCN, cephalosporins), sulfonamides, allopurinol, anti-seizure drugs and NSAIDs
• Resolves within 1-2 weeks sometimes with desquamation

http://genevadermatology.ch/drug-reactions-drug-allergy
Case Presentation

60 yo female with a several year h/o bright red scaly papules and plaques, mildly itchy, worse on the shins, sometimes on the trunk

No personal of family history

Medications: Asmanex, Lisinopril-HCTZ, Hydroxyzine, and Pro-Air

Biopsy: “Chronic spongiotic and psoriasiform dermatitis compatible with psoriasis vs drug eruption”

Abs. Eosinophil count- 0.7
Drug Induced/Exacerbated Psoriasis

- **Answer:** Lisinopril

- **3 Clinical Types:**
  - 1) Drug can cause preexisting psoriatic skin lesions to aggravate
  - 2) Drug can cause onset of new psoriasis lesions at clinically uninvolved skin in a patient with a personal history of psoriasis
  - 3) Drug can provoke psoriasis de novo in a patient without a personal or family history of psoriasis

- Even if drug is stopped, psoriasis can persist*

- Beta-blockers*
- Lithium*
- Ace Inhibitors/angiotensin receptor antagonists*
- Antimalarial drugs such as (hydroxy)chloroquine*
- Calcium channel blockers
- Interferons
- Terbinafine
- Anti-TNF alpha*/Anti PD-1 inhibitors
- Carbamazepine metformin, NSAIDs, tetracyclines, valproate sodium, and venlafaxine, GCSF, imiquimod, PCN

Case Presentation

57 yo male presents with mildly itchy scaly pink macules spreading on the face, neck, arms upper chest and back x 2-3 weeks

No other exposures, no new medications

Medications: Lisinopril-HCTZ, ASA, indomethacin

Biopsy showed: Lichenoid dermatitis>CTD

ANA+ and anti Ro(SSA)+

**Answer**: Drug Induced SCLE due to HCTZ
Drug Induces Lupus Erythematosus

- **Drug-induced SLE** - procainamide (15-20%), hydralazine (5-8%), isoniazid and minocycline
- Beta-blockers, chlorpromazine, cimetidine, clonidine, estrogens, isoniazid, lithium, methyldopa, oral contraceptives, quinidine, sulfonamides, tetracyclines, statins, HCTZ, NSAIDs and tumor necrosis factor (TNF)-alpha inhibitors
- **Drug-induced SCLE (subacute cutaneous LE)** – hydrochlorothiazide* calcium channel blockers, cimetidine, griseofulvin, leflunomide, terbinafine, and TNF-alpha inhibitors

*Antihypertensive drugs are most commonly associated with Ro-positive CLE*

### Characteristics of DILE and Drug Induced SCLE

<table>
<thead>
<tr>
<th>Classic DILE</th>
<th>Drug Induced SCLE</th>
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<tbody>
<tr>
<td>• Fever, myalgia, arthritis, serositis</td>
<td>• Rare</td>
</tr>
<tr>
<td>• &lt;5-25% have cutaneous findings</td>
<td>• &gt;99%(classic, bullous or EM like)</td>
</tr>
<tr>
<td>• ANA&gt;99%</td>
<td>• ANA&gt;80%</td>
</tr>
<tr>
<td>• Anti-Ro/SSA&lt;5%</td>
<td>• Anti-Ro/SSA&gt;80%</td>
</tr>
<tr>
<td>• Anti-La/SSB</td>
<td>• Anti-La/SSB&gt;45%</td>
</tr>
<tr>
<td>• Anti-histone up to 95%</td>
<td>• Anti-histone up to 35%</td>
</tr>
<tr>
<td>• Anti-dsDNA &lt;5%</td>
<td>• Anti-dsDNA &lt;1%</td>
</tr>
<tr>
<td>• Hypocomplementemia- &lt;1%</td>
<td>• Hypocomplementemia- 9%</td>
</tr>
</tbody>
</table>
Summary of Cutaneous Adverse Drug Reactions

- Present in many different forms
- Morbilliform/Maculopapular and Urticaria are most common
- Can mimic primary cutaneous dermatoses
- Biopsy is helpful
- Antibiotic such as PCN and sulfonamides, ASA, NSAIDs, anticonvulsants, ACE inhibitors are most common causes of CADR
- Some medications such as certain anti-hypertensive medications (HCTZ, ACE inhibitors, calcium channel blockers) are commonly a cause of multiple different cutaneous drug eruptions
- Review of the literature is imperative!
- If the rash does not resolve, think again
Thank You!