Go Ahead---Judge a Book by its Cover!

Skin Manifestations of Systemic Disease

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Objectives

• Compare diseases of the skin with reactions of the skin to diseases (30 minutes)
• Review some cutaneous manifestations of internal malignancies, and cardiovascular and pulmonary disease (30 minutes)
• Evaluate some cutaneous reactions to medications (30 minutes)

Approach to Dermatologic Diagnosis
There are 2 Ways to Think About Your Skin…

Clue to what’s going inside

Common Skin Disorders
One of the most common adverse reactions to drugs is CUTANEOUS!

DISEASE VS REACTION

What’s going on INSIDE?

Pruritic, edematous

Urticaria = Hives
True Allergic Reaction

- *IgE mediated* (type 1 hypersensitivity reaction)
- IgE reactions are manifested by bronchospasm, abdominal distress: diarrhea and emesis; angioedema, hypotension, urticaria, or a pruritic rash

Urticaria or “Hives”

- *Allergic Reaction!*
- Usually caused by medication or food
- Occasionally by infection

Urticaria = “Hives”

- Wheals resolve within 24 hours
- Identify the cause!
- Treat with H1 (?) and H2 blockers
Clinical Case

A 24 year-old college student who presents with suspected *Mycoplasma pneumonia* receives a prescription for azithromycin. She returns the next day with this non-pruritic skin eruption.

The rash is Not IgE-mediated if neither urticarial nor pruritic and there is NO increased risk of the same rash recurring with repeated courses of the same antibiotic.

Erythema Multiforme

- Usually caused by infection (herpes simplex virus or *Mycoplasma pneumoniae*); sometimes meds

Cutaneous Hypersensitivity Reaction
Erythema Multiforme

- Usually on extremities ("acral distribution")
- Self-limited; resolves in 2-4 weeks

*Common is a targetoid or iris appearance*

*Also papules, macules, plaques, vesicles*

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35 year old Female

Presents with painful, erythematous, deep nodules on the shins and posterior lower legs. She has fever, malaise, and complains that her joints ache.

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Erythema Nodosum

- Panniculitis: inflammation of the subcutaneous adipose tissue
- Occurs mostly in females 20-40 y/o
**Erythema Nodosum**

- Painful, erythematous nodules (1-5 cm in diameter) develop on the anterior surface of both legs
- Evolve into bruise-like lesions (easier to palpate than see)
- Accompanied by fever, malaise, arthralgias, arthritis

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**Erythema Nodosum**

- *Streptococcus* infection is most common cause

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**Erythema Nodosum**

- Variety of systemic diseases (IBD), some infectious causes (Salmonella, Shigella, systemic fungal infections)
- Appearance parallels intestinal disease activity (sometimes ahead of activity)
Evaluation of Erythema Nodosum

- CBC with differential
- LFTs and Cr/BUN
- ASO titer (now and in 2-4 weeks)
- Chest x-ray (evidence of sarcoidosis, TB, or fungal infection)
- TB skin test
- Stool for occult blood
- Biopsy if lesions persist

Erythema Nodosum

- Treat with NSAIDs (or prednisone), rest, elevation
- No scarring
- Resolves in 2-8 weeks

Cutaneous Manifestations of Malignancies
Cutaneous Manifestations of Internal Malignancy

- The skin reflects many internal malignancies

Cutaneous Manifestations of Internal Malignancy

- Any malignancy can metastasize to the skin

Cutaneous Manifestations in Men

- Most common from the lung, large intestine, and kidney
Cutaneous Manifestations

• Cancers of the *breast and large intestines* are most likely primary tumors to metastasize to the skin.

Cutaneous Manifestations

• Metastases usually flesh colored to violaceous nodules that appear in close proximity to the primary neoplasm.

Cutaneous Manifestations

• Most common sites are the head (scalp), neck, and trunk.
Cutaneous Manifestations of Internal Malignancy

• Skin may be infiltrated by products of malignancy and represent metastasis (Paget’s disease or metastatic lung cancer) Uncommon: Up to 10%

Cutaneous Manifestations of Internal Malignancy

• May be the site of primary malignant disease (Kaposi’s sarcoma)

Cutaneous Manifestations of Internal Malignancy

• Skin lesions related to underlying malignancy (paraneoplastic dermatologic syndromes)
Acanthosis Nigricans

- Disorder of keratinization
- Reactive skin pattern
- Velvety hyperpigmented plaques in intertriginous areas
- Benign and associated with obesity, insulin resistance

Acanthosis Nigricans

- Associated with GI malignancies (gastric and hepatocellular)
- Associated with lung malignancies
- Precede or follow diagnosis of cancer

Clinical Clues to AN as Malignancy

- Patient is older
Clinical Clues to AN as Malignancy

• NOT obese

Clinical Clues to AN as Malignancy

• Lesions develop in unusual locations or in combination with multiple skin tags (face, palms, and trunk)

Clinical Clues to AN as Malignancy

• Sudden onset; extensive distribution
Evaluation of AN

• Age of onset
• S/S of hyperinsulinemia
• New medications (glucocorticoids, niacin, OCs)
• Fasting glucose; consider insulin levels
• If normal….

Acanthosis Nigricans

• Screening tests for GI cancers

Acanthosis Nigricans

• Look for unexplained anemia
Acanthosis Nigricans

• When malignancy is treated, 
  *skin manifestations resolve!*

The MOST miserable patients I take care of…….

Generalized Pruritis

• Generalized pruritis is worrisome!
• Is there jaundice?
If Jaundice…

- Medications
- Drugs/Herbs
- Alcohol
- Hepatitis
- Liver diseases; hemolytic diseases
- Travel history
- Exposure to toxic substances

Pruritis without Jaundice

Search for Systemic Disease

- Iron deficiency anemia
- Thyroid disease
- Hepatic and renal insufficiency
- Malignancy

Evaluation of Pruritis

- History and physical exam
- CBC
- LFT
- CMP
- TSH
Malignancies associated with Pruritis

• Lymphoma (Hodgkin lymphoma)
• Leukemia
• Carcinoids of the stomach

Hodgkin Lymphoma

• Asymptomatic, enlarged lymph node (most common presentation)
• Mass on chest x-ray (2nd most common presentation)
GI Malignancies

- Primary gastric carcinoids produce histamine
- Responsible for atypical flushing and pruritis

GI Malignancies

- Malignancies of the intestines (lower GI) produce cutaneous flushing

GI Malignancies

- Malignancies of the upper GI tract produces “histamine” flush that is pruritic
GI Malignancies

- Episodic flushing is the clinical hallmark of carcinoid syndrome

GI Malignancies

- Flushing begins suddenly and lasts from 30 seconds to 30 minutes
- Involves the face, neck, and upper chest

GI Malignancies

- Severe flushing accompanied by decrease in BP and rise in pulse rate
Flushing Differential

**Diseases**
- Carcinoid syndrome
- Pheochromocytoma
- Thyroid and renal cell carcinoma

**Physiologic**
- Menopause
- Hot drinks
- Emotional distress

**Drugs**
- Alcohol (Asians)
- Diltiazem
- Niacin
- Amyl nitrate
Cardiovascular Disease

Xanthelasma
- Cholesterol filled plaques on the medial aspect of the eyelids
- Common in middle and older adults
- 50% have hyperlipidemia

Xanthelasma
- Lesions associated with hypercholesterolemia
**Xanthelasma**

- Common in disorders of LDL metabolism
- Occur in 75% of older patients with familial hypercholesterolemia

**Xanthomas**

- Yellowish-reddish macules in the head and neck area

**Xanthomas**

- Compared to xanthelasma, xanthomas are not as infiltrated and are unusual in the periorbital area
- Common in patients with myeloma
Xanthomas

- Common in primary biliary cirrhosis

- In palmar area, follow the creases of the palms and soles

- Myeloma proteins interfere with lipid metabolism with subsequent cutaneous deposition in the palms and soles
- Diagnostic work up when identified

- Diagnostic work up when identified
Pulmonary Disease

Sarcoidosis
• Multisystem, granulomatous disease of the lungs, bones, CNS, lymph nodes, eyes, and skin

Sarcoidosis
• Skin disease affects 25-35% of patients
**Sarcoidosis**

- Red to purple plaques and annular plaques on trunk or extremities

**Erythema Nodosum**

- Most common non-specific cutaneous manifestation of sarcoidosis

**Lupus Erythematosus**

- Autoimmune *photosensitive* dermatosis
- 80% of patients have skin and mucous membranes involved
Lupus Erythematosus

- Tremendous variability in skin involvement/lesions
- Lesions worsen with exposure to UV light

Butterfly Rash

- Appears in about 50% of patients, usually after UV exposure
- Rash may precede symptoms by months or years
- Rash lasts for hours or days

Differential

- *Rosacea* presents as malar erythema
- Others: *seborrheic, atopic, contact dermatitis*
- *Glucocorticoid-induced dermal atrophy, flushing*
More Rheumatic Disease

Scleroderma

- Autoimmune skin disease
- Can be localized or generalized

Scleroderma

Localized: known as “morphea”
Scleroderma

- Erythematous patches that evolve into violaceous borders, often on the trunk

Hematologic Disease

Petechiae and Purpura

*Petechiae:*
Due to extravasation of red cells from capillaries
**Petechiae and Purpura**

*Purpura*: purplish discoloration of the skin from confluent petechiae

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**Petechiae and Purpura**

Non-tender and **DO NOT** blanch

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**Clinical Pearl**

Patients with coagulation disorders don’t have petechiae!
What’s the Etiology?
Do we have decreased platelet production?
OR
Increased destruction?

Thrombocytopenia
- Drug Reaction
- Vasculitis
- Leukemia
- Alport’s syndrome (hereditary nephritis)
- Many others

DISEASE
VS
REACTION
Pattern of Distribution

*Thrombocytopenia*
- Asymptomatic
- Localized to dependent portions of the body (feet and ankles)

Pattern of Distribution

*Thrombocytopenia*
- Areas with firm sub-q tissue (soles of feet) are protected from purpura
- Areas with minimal sub-q support have large bullous hemorrhagic areas

Cutaneous Drug Reactions
Drug Eruptions

*Phenytoin*

Up to 1 in 5 patients who receive phenytoin have some type of cutaneous eruptions

Cutaneous Drug Eruptions

*Phenytoin*

Eruption may be papules and pustules

Cutaneous Drug Eruptions

*Phenytoin*

Pleomorphic: Morbilliform rash, erythroderma, toxic epidermal necrolysis (TEN)
Drug Eruptions

Trimethoprim-SMX

• Has a bad name!!
• Statistically, not more likely to produce rash than other antibiotics

Drug Eruptions

Trimethoprim-SMX

• Erythema multiforme
• Stevens-Johnson syndrome

Erythema Multiforme

• Usually caused by infection (herpes simplex virus or Mycoplasma pneumoniae); sometimes meds

*Cutaneous Hypersensitivity Reaction*
**SJS and TEN**

*Toxic epidermal necrolysis*

- Severe, idiosyncratic reactions
- Fever, mucocutaneous lesions

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**TEN vs. SJS**

*Distinguished by severity*

- TEN more severe than SJS (involves > 30% of body surface area)

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**TEN vs. SJS**

*Most common factor is medication*

- SJS: 30-50% from meds
- TEN: 80% from meds
WHAT meds?

- **Antibiotics** (Sulfa >>> PCN > Cephs)
- **Anti-gout** (especially allopurinol)
- **NSAIDs** (especially piroxicam)

Most Common?

**Allopurinol**

Drug Eruptions

*Anticoagulant-induced skin necrosis*

*Warfarin*: usually occurs within the first several days of therapy

More likely with large loading doses
Drug Eruptions

*Phenytoin*

Up to 1 in 5 patients who receive phenytoin have some type of cutaneous eruptions

Serum Sickness

- Cardinal symptoms: rash, fever, *polyarthralgias* or *polyarthritis*
- Begins 1-2 weeks after first exposure
- Resolves within a few weeks of d/c

Serum Sickness

- Gell and Coomb’s type III or immune complex mediated hypersensitivity disease
Types of Allergic Reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Immediate-type hypersensitivity</th>
<th>Anaphylaxis, angioedema, hives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II</td>
<td>Antibody dependent cytotoxicity</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Type III</td>
<td>Immune complex disease</td>
<td>Serum sickness</td>
</tr>
<tr>
<td>Type IV</td>
<td>Cell mediated or delayed hypersensitivity</td>
<td>Contact dermatitis</td>
</tr>
</tbody>
</table>

Serum Sickness

- **Type III**: Immune complex disease
- Damage is caused by formation or deposition of Ag-AB complexes in vessels or tissue
- **Example**: Serum Sickness

Clinical Manifestations

- **PRURITIC RASH!!!**
- **Mucous membranes are NOT involved**
  (this can help distinguish it from others)
Serum Sickness

- Urticarial lesions (last longer than typical hives)
- Macular rash starts in ant. lower trunk, groin, axillary regions and spreads to involve back, upper trunk, extremitys

Clinical Manifestations

- Other skin manifestations: palpable purpura, morbilliform rashes, papules
- Rash lasts a few days to 2 weeks

Serum Sickness

- Fever in almost 100% of patients
- Characterized by high spikes that return to normal in the same day
Serum Sickness

- Joint Aches:
  - Fingers, knees, wrists, ankles, shoulders
  - Occurs after the rash has started
  - Resolves before rash resolves

Laboratory Findings

- Neutropenia
- Reactive lymphs
- Mild thrombocytopenia
- CRP elevated
- UA demonstrates mild proteinuria

Treatment

- Stop the offending substance!
- Antihistamines (for pruritis and mild rash)
- Steroids (for low-grade fever and arthralgias)
- Avoid drug in the future!!!
Clinical Pearl

An *uncommon* presentation of a common disease is WAY more *common* than a *common* presentation of an *uncommon* disease.

Wrap Up

Thank you!

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