A Picture is Worth 1000 Words:

Skin Manifestations of Systemic Disease

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Objectives

• Compare diseases of the skin with reactions of the skin to diseases (20 minutes)
• Review some cutaneous manifestations of internal malignancies, and cardiovascular and pulmonary disease (20 minutes)
• Evaluate some cutaneous reactions to medications (20 minutes)

Speaker has no relationship to disclose.
A Picture is Worth 1000 Words:

Dermatologic Manifestations of Systemic Disease

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Outline

• Common skin disorders
• Cutaneous malignancies
• Cardiovascular disease
• Pulmonary Disease
• Rheumatic disease
• Hematologic
• Wrap up

There are 2 Ways to Think About Your Skin...
Common Skin Disorders

DISEASE of the skin? or REACTION by the Skin?

One of the most common adverse reactions to medications is on the skin!
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
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

....so what is it?
Clue: “3 color zones”
*are hallmark for identification*
Erythema Multiforme

• Usually caused by infection (90% of time) (herpes simplex virus or Mycoplasma pneumoniae); sometimes meds (<10%)

Cutaneous Hypersensitivity Reaction

Erythema Multiforme

Meds (<10%)

• NSAIDs
• Sulfonamides
• Antibiotics
• Antiepileptics

Cutaneous Hypersensitivity Reaction

Erythema Multiforme

• Erythema multiforme-like lesions may occur in lupus

Cutaneous Hypersensitivity Reaction
Erythema Multiforme

What other clues?
• Usually on extremities ("acral distribution")
• Self-limited; resolves in 2-4 weeks

Common is a targetoid or iris appearance
Also papules, macules, plaques, vesicles

Erythema Multiforme

Differential Diagnosis
• Infection (most common)
• Meds
• Lupus??
• Others

Next Patient

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.
**Erythema Nodosum**

- **Panniculitis:**
  inflammation of the subcutaneous adipose tissue
- Occurs most commonly in females 20-40 y/o

**Erythema Nodosum**

- Delayed type hypersensitivity reaction
- Triggers: infection, drugs, pregnancy, malignancy, inflammatory conditions, idiopathic

**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
Erythema Nodosum

- *Streptococcus* infection is most common cause

Infection

- *Hhhmmmmm Etiology of cutaneous manifestations (erythema multiforme, erythema nodosum)*
- *HOWEVER.....*

Erythema Nodosum

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

- Triggers: infection, drugs, pregnancy, malignancy, inflammatory conditions, idiopathic

**Erythema Nodosum**

* Differential Diagnosis
  - Infection (most common)
  - GI infection
  - IBD
  - Others

**Evaluation of Erythema Nodosum**

- CBC with differential
- LFTs and BUN/Cr
- ASO titer (now and in 2-4 weeks)
- Chest x-ray (evidence of sarcoidosis, TB, or fungal infection)
- TB skin test
- HIV?
- 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 Internal Malignancies

- The skin reflects many internal malignancies
Cutaneous Manifestations of Internal Malignancy: 2 Considerations

1. Non-malignant skin disorders that occur in association with internal malignancy (paraneoplastic dermatoses). When you recognize these, can lead to early diagnosis

2. Infiltration of skin by malignant cells due to metastasis or spread of malignancy

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 in Women

- 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 of Internal Malignancy

- May be the site of primary malignant disease (Kaposi’s sarcoma)
- Purple, dark blue in color; can ulcerate, bleed
Cutaneous Manifestations of Internal Malignancy

- “Skin lesions related to underlying malignancy” (paraneoplastic dermatologic syndromes)

- …so look for nodules (flesh colored or violaceous in color)
- Changes in skin color
- …..AND

Acanthosis Nigricans (AN)

- Disorder of keratinization
- Reactive skin pattern
- Velvety hyperpigmented plaques in intertriginous areas
- Majority of cases are benign and associated with obesity, insulin resistance
Acanthosis Nigricans
• Gastric cancers (55%) are most common causes of malignant AN
• Usually GI malignancies (gastric and hepatocellular)
• Also associated with lung, ovary, endometrium, kidneys, pancreas, bladder, breast malignancies
• Precede or follow diagnosis of cancer

Clinical Clues to AN as Malignancy
• Patient is older

Clinical Clues to AN as Malignancy
• NOT obese
• Recent unintentional weight loss
Clinical Clues to AN as Malignancy

- Lesions develop in unusual locations or in combination with multiple skin tags (face, palms, and trunk)
- Sudden appearance of multiple skin tags

Clinical Clues to AN as Malignancy

- Sudden onset; extensive distribution
- Rapid progression of AN

How do you evaluate a patient with AN?

- Age of onset
- S/S of hyperinsulinemia
- New medications (glucocorticoids, niacin, OCs)
- Fasting glucose; consider A1C
- If normal....
Acanthosis Nigricans
- Screening tests for GI cancers

Clue to Malignant Acanthosis Nigricans
- Unexplained anemia

Acanthosis Nigricans
- When malignancy is treated, skin manifestations resolve!
The MOST miserable patients I take care of…….

A patient presents with generalized pruritus.

What's the most important thing to assess in the patient?

Generalized Pruritus

Is there jaundice?
If Jaundice…
- Medications
- Drugs/Herbs
- Alcohol
- Hepatitis
- Liver diseases; hemolytic diseases
- Travel history
- Exposure to toxic substances

Pruritus without Jaundice

*Search for Systemic Disease*
- Iron deficiency anemia
- Thyroid disease
- Hepatic and renal disease
- Malignancy
- Others

Evaluation of Pruritus
- History and physical exam
- CBC
- CMP (LFTs)
- TSH
Malignancies associated with Pruritus
1. Lymphoma (Hodgkin lymphoma)
2. Leukemia
3. Carcinoids of the stomach

Hodgkin Lymphoma
- Asymptomatic, enlarged lymph node (most common presentation)
- Mass on chest x-ray (2nd most common presentation)
- Refractory pruritus
2. “Carcinoid”: neuroendocrine tumor usually in GI tract (lung 2nd most common)
   “Carcinoid Syndrome”: symptoms from carcinoid tumors

Why Pruritus?

• Primary gastric carcinoids produce histamine
• Responsible for atypical flushing and pruritus

GI Malignancies

• Malignancies of the small intestine produce cutaneous flushing
GI Malignancies
- Malignancies of the upper GI tract produce a "histamine" flush that is pruritic

Carcinoid Syndrome
- Episodic flushing is the clinical hallmark of carcinoid syndrome
- Diarrhea

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

- 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
Flushing Differential

Drugs
• Alcohol (Asians)
• Diltiazem
• Niacin
• Amyl nitrate

Malignancies associated with Pruritus
1. Lymphoma (Hodgkin lymphoma)
2. Leukemia
3. Carcinoids of the stomach

Cardiovascular Disease
Xanthelasma

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

Xanthelasma

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

NOT

Cardiovascular Disease
Xanthomas

• Yellowish-reddish macules in the head and neck area, but can occur anywhere
• Not common

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
Xanthomas

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

Xanthomas

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

Pulmonary Disease
Sarcoidosis

• Multisystem, granulomatous disease of the lungs, bones, CNS, lymph nodes, eyes, and skin
• “Extrapulmonary”

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

Erythema Nodosum

Remember the Differential Diagnosis?

• Infection (most common)
• GI infection
• IBD
• Others (Add Sarcoidosis!)

Rheumatic Disease
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*

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

Cutaneous Drug Reactions: Reaction by the skin!

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

Phenytoin

Pleomorphic:
Morphilliform 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

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**Erythema Multiforme**

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

*Cutaneous Hypersensitivity Reaction*

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**SJS and TEN**

*Toxic epidermal necrolysis*

- Severe, idiosyncratic reactions
- Fever, mucocutaneous lesions
TEN vs. SJS

*Distinction by severity*

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

TEN vs. SJS

*Most common factor is medication*

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

WHAT meds?

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

Skin Necrosis
Clinical Pearl

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

Thank you!
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References

References


