A Picture is Worth
1000 Words:

Skin Manifestations of Systemic Disease

Amelie Hollier, DNP, FNP-BC, FAANP
Lafayette, LA
President, APEA

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

Amelie Hollier, DNP, FNP-BC, FAANP
Lafayette, LA
President, APEA

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

Cutaneous Manifestations of Internal Malignancy

- 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)*

Cutaneous Manifestations of Internal Malignancy

- …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

Malignancies associated with Pruritus

1. Hodgkin lymphoma

Hodgkin Lymphoma

- Asymptomatic, enlarged lymph node (most common presentation)
- Mass on chest x-ray (2nd most common presentation)
- Refractory pruritus

GI Malignancies

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 pruritis

GI Malignancies

- Malignancies of the small intestine produce cutaneous flushing

GI Malignancies

- Malignancies of the upper GI tract produces "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

Flushing Differential

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

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

TEN vs. SJS

Distinguished 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 > Cephs)
- 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!

For questions or to contact me:
amelie@apea.com
Amelie Hollier
Lafayette, LA 70508

Advanced Practice Education Associates

References

- Flamm, S., Kaplan, A., Poupon, R., Chopra, S. (2020). Hypercholesterolemia in primary biliary cholangitis. *UpToDate*. Retrieved July 11, 2020 from https:/www.uptodate.com/contents/hypercholesterolemia-in-primar-biliary-cholangitis.
- Fukuchi K, Tatsuno K, Matsushita K, et al. Familial acanthosis nigricans with p.K650T FGFR3 mutation. J Dermatol 2018; 45:207.
- Heinze A, Tollefson M, Holland KE, Chiu YE. Characteristics of pediatric recurrent erythema multiforme. Pediatr Dermatol 2018; 35:97.
- Owens, C. (2019). Cutaneous manifestations of internal malignancy. *UpToDate*. Retrieved July 10, 2020 from https://www.uptodate.com/contents/cutaneous-manifestations-of-internal-malignancy.
- Räßler F, Goetze S, Elsner P. Acrokeratosis paraneoplastica (Bazex syndrome) - a systematic review on risk factors, diagnosis, prognosis and management. J Eur Acad Dermatol Venereol 2017; 31:1119.
- Shah KR, Boland CR, Patel M, et al. Cutaneous manifestations of gastrointestinal disease: part I. J Am Acad Dermatol 2013; 68:189.e1.

References

- Stevens, D.L. and Bryant, A. (2020). Group A Streptococcus: Virulence factors and pathogenic mechanisms. *UpToDate*. Retrieved July 10, 2020 from https://www.uptodate.com/content/group-a-streptococcus-virulence-factors-and-pathogenic-mechanisms.
- Strosberg, J.R. (2019). Clinical features of carcinoid syndrome. *UpToDate*. Retrieved July 10, 2020 from https://www.uptodate.com/contents/clinical-features-of-carcinoid-syndrome.
- Wang L, Long H, Wen H, et al. Image Gallery: Generalized mucosal and cutaneous papillomatosis, a unique sign of malignant acanthosis nigricans. Br J Dermatol 2017; 176:e99.
- Werner, J.P. (2017). Drug allergy pathogenesis. *UpToDate*. Retrieved July 10, 2020 from https://www.uptodate.com/content/drug-allergy-pathogenesis.
- Werner, J.P. (2019). Drug hypersensitivity: Classification and clinical features. *UpToDate*. Retrieved July 10, 2020 from https://www.uptodate.com/contents/drug-hypersensitivity-classification-and-clinical-features.
- Wetter, D.A. (2019). Erythema multiforme: Pathogenesis, clinical features, and diagnosis. In *UpToDate*. Retrieved July 10, 2020 from https://www.uptodate.com/contents/erythema-multiforme-pathogenesis-clinical-features-and-diagnosis.