Inside Out
Cutaneous Manifestations of Internal Disease

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Updated Disclosures
- Consultant to Allergan
  - Botox
  - Juvederm
  - Skin Medica Products

Goals
- Identify cutaneous manifestations of some internal diseases
- Discuss clinical and laboratory findings associated with those diseases

Alopecia Areata
- Well demarcated round to oval patches of alopecia
- Scalp, beard, eyebrows, eyelashes commonly affected
- May see “exclamation point” hairs and white hairs
- Skin often has salmon pink erythema
Alopecia Areata Associations

- Atopic dermatitis, Down syndrome, lichen planus
- Autoimmune diseases
  - Lupus, thyroiditis, diabetes, myasthenia gravis, vitiligo
  - Only screen if ROS suggests other disease states

Acanthosis Nigricans (Type III)

- Velvety hyperpigmented plaques on neck, axillae, knuckles, elbows, knees
- Associated with insulin resistant states and syndromes
  - Obesity, diabetes, PCOS, Cushing's, pseudoacromegaly, hyperandrogenic states
  - Hypogonadal syndromes, and numerous other insulin resistant states

Malignant Acanthosis Nigricans (Type I)

- Affects the lips, tongue and palms (tripe palms)
- Associated with internal malignancy
  - Adenocarcinoma of the GI tract, lung, and breast most common
  - May be associated with other adenocarcinomas
  - Tripe palm alone—lung CA more common
  - Tripe palm + AN—gastric CA more common
Metastatic Adenocarcinoma to the Skin

- Erythematous papule or nodule
- Has a very vascular appearance
- Usually from a known malignancy

Amyloidosis

- Cutaneous manifestations include macroglossia, translucent papules around the eyes, nose, mouth, and mucocutaneous junctions
- Purpura of the eyelids, limbs, mouth after trauma (pinch purpura)
- Primary (AL amyloidosis) deposition of the AL portion of immunoglobulin light chain
- Secondary (AA amyloidosis) deposition of serum amyloid A
- Affects the kidneys, heart, liver, GI tract, peripheral nerves, and skin

Aphthous Ulcer

- Well demarcated ulcer with surrounding erythema and a fibrinous base
- Painful, on mucosal surfaces including mouth, vagina, anus, conjunctiva
- May be primary or associated with many disease states
  - Folic acid or B12 deficiency
  - Gluten sensitive enteropathy, UC, Crohn’s, Behcet’s, HIV, malabsorption, anemia
Carney Complex (NAME, LAMB)

- Lentigenes, blue nevi, cutaneous myxomas, mammary myxoid fibromas
- Cushing syndrome, testicular tumors
- Atrial myxoma (7%)  
- Pituitary growth hormone secreting tumors
- NAME (nevi, atrial myxoma, myxoid neurofibroma, ephelides)
- LAMB (lentigenes, atrial myxoma, mucocutaneous myxoma, blue nevi)

Churg-Strauss Syndrome

- Palpable purpura and sub-q nodules of the extensor surfaces and scalp
- Phase 1: Allergic rhinitis, asthma, nasal polyps. Onset in the 30’s
- Phase 2: Fever, peripheral eosinophilia, pneumonia, and gastroenteritis
- Phase 3: Diffuse angiitis affecting the lungs, heart, kidneys, liver, spleen, intestines and pancreas
- Mortality due to myocarditis
- p-ANCA (MPO) 55-60%, c-ANCA (PR3) 10-15%

Wegener Granulomatosis

- Palpable purpura, cutaneous nodules on the extensor surfaces (may ulcerate)
- “Strawberry gingiva”, saddle nose deformity, conjunctivitis, episcleritis, proptosis
- Lung, renal, GI, cardiac involvement is possible
- High mortality without treatment
Dermatitis Herpetiformis
- Extremely pruritic autoimmune blistering disorder
- Affects extensor surfaces including elbows, knees, neck, scalp, and low back
- Vesicles often absent due to scratching
- 70-100% have abnormalities of the jejunal mucosa but most are asymptomatic. Associated with celiac disease
- Anti-endomysial antibodies (70%), TTG2, TTG3, gliadin
- Gluten free diet and dapsone are treatments of choice

Dermatomyositis
- Clinically characterized by violaceous erythema of the cheeks, eyelids (heliotrope), knuckles, nail folds, upper back (shawl sign), upper chest
- Nail fold telangiectasia, Gottron's papules
- May or may not have muscle weakness, elevated CK and aldolase
- Associated with internal malignancy in adults (10-50% reported)
- Ovarian, colon, breast, lung, gastric, pancreatic, lymphoma, genital carcinoma
- Consider CT chest abdomen and pelvis

Ehlers Danlos Syndrome
- Hyper mobile joints, hyperextensible skin, skin fragility, easy scarring
- 10 types
- Defect in collagen synthesis
- Aortic aneurysm or dissection
- Cardiothoracic imaging is recommended
Erythema Nodosum

- Tender, erythematous, subcutaneous nodules. Pretibia and other extensor surfaces. May be associated with constitutional symptoms.
- Infections - Strep, TB, GI infections, deep fungal infections
- Drugs - Sulfas drugs, BCP and HRT, bromides, iodides
- Inflammatory diseases - Crohn's, Ulcerative Colitis, Sarcoidosis, Behcet's, Sweet's, Pyoderma Gangrenosum
- Treatment - NSAIDs, SSKI, corticosteroids, rest, elevation

Eruptive Xanthoma

- Yellow/orange papules with surrounding erythema on extensor surfaces, especially buttocks, thighs, arms, axillae
- Pruritus is variable
- Associated with elevated triglycerides
- Associated with diabetes, renal failure, hypothyroidism, estrogens, corticosteroid and oral retinoid therapy.

Erythema Gyratum Repens

- Rapidly expanding concentric annular plaques with trailing scale.
- “Wood grain” appearance
- Rare; 80% have underlying malignancy (lung). May be associated with medication or TB. Rash precedes tumor dx by 9 months.
Extramammary Paget's Disease

- Well demarcated erythematous plaques, usually located in the groin.
- Considered an intraepithelial adenocarcinoma
- Vulva: 10-20% have malignancy of breast, cervix, vagina, bladder, ovary, colon, rectum, liver, gall bladder or skin.
- Perianal: 10-40% malignancy of rectum, stomach, breast, uterus.
- Penoscrotal: 10-35% malignancy of prostate, bladder, ureter, kidney, testicles

Generalized Granuloma Annulare

- Annular non-scarly plaques on trunk and extremities. Flesh colored or erythematous. Usually asymptomatic
- Sometimes associated with diabetes
- Phototherapy or antimalarials may be helpful

Nevoid Basal Cell Carcinoma Syndrome (Gorlin's Syndrome)

- Major Criteria: >5 bcc's before age 30, odontogenic jaw cysts, palmar/plantar pits, lamellar calcification of the falx before age 20, 1st degree relative with disease
- Minor criteria: Childhood medulloblastoma, pleural cysts, macrocephaly, cleft lip or palate, vertebral or rib abnormalities, syn or polydactyly, ovarian/cardiac fibromas, ocular abnormalities
- Autosomal dominant inheritance defect in PTCH gene
Guttate Psoriasis

- Acute eruption of 2-5mm erythematous scaly papules on the trunk and extremities.
- Usually associated with strep infection.
- Responds well to 1 month of anti-strep therapy and UV light.

Acquired Ichthyosis

- Generalized xerosis with “fish scale appearance”
- Commonly associated with beta blockers, diuretics and statins
- May be associated with hypothyroidism, lymphoreticular malignancies

Keratoderma

- Hyperkeratotic waxy plaques on the palms and the soles
- May be associated with carcinoma of the esophagus, larynx, stomach, lung, breast, and bladder
**Leukocytoclastic Vasculitis (LCV)**

- Palpable purpura especially on the lower extremities. May be bullous or ulcerative.
- Usually post infectious or drug induced.
- Most drug classes have been implicated. Time frame hours-years after initiation of drug.
- Most common infections include group A strep, Mycoplasma, viral, TB.
- Remove offending agent. Corticosteroids.
- Recurrent LCV is suggestive of underlying malignancy.

**LEOPARD Syndrome**

- Lentigenes, Ecg abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retardation of growth, Deafness.
- May have learning disability as well.
- Lentigenes are dark and irregular.

**Lichen Planus**

- Pruritic, purple, polygonal papules on extensor surfaces.
- May have lacey white plaques in the mouth or vaginal mucosa.
- Severe cases may be associated with hepatitis C, hepatitis B immunization, and Primary Biliary Cirrhosis.
Necrolytic Migratory Erythema

- Erythematous erosive plaques in the inguinal region
- Associated with glucagonemia (glucagonoma, somatostatin use)
- Similar clinical features to zinc and niacin deficiency

Paget’s Disease of the Breast

- Erythematous plaque of the nipple or areola. May be erosive or resemble eczema. Not steroid responsive
- Intraepidermal adenocarcinoma
- 35-65% have underlying ductal carcinoma
- Take home point: if “nipple eczema” doesn’t respond to topical steroids, it needs a biopsy!

Porphyria Cutanea Tarda (PCT)

- Erythematous erosions and bullae with milia on the dorsal hands
- Temporal hypertrichosis. Photosensitivity and skin fragility
- Typically associated with liver disease, cirrhosis, Hep C, iron overload, increased estrogens, medications
- Urine porphyrins are extremely high
- Therapeutic phlebotomy works well. 1 unit every 1-2 weeks until Hgb is below 10. Hydroxychloroquine may be useful as well
Pemphigus

- Characterized by erosions in the mouth, flaccid bullae and erosions on the extremities and intertrigenous areas. Resemble Steven's-Johnson syndrome
- Usually autoimmune disease with antibodies vs desmosomal proteins
- May be paraneoplastic: Lymphoma, Leukemia, Castleman tumor, Sarcoma, Thymoma
- Drug induced: Penicillamine, captopril, enalapril
- Treat underlying tumor balancing treatment with immunosuppression

Pyoderma Gangrenosum

- Ulcers with violaceous undermined border. Exhibits pustulosis (don't debride!)
- Look like infections. Diagnosis of exclusion
- Associated with Crohn's, UC, lymphoreticular malignancies, myelodysplasia, HIV, Hep C, monoclonal gammopathy (IgA)
- Corticosteroids, Infliximab, or cyclosporine

Pretibial Myxedema

- Pearly translucent papules and plaques in the pretibial region. May affect hands and forearms as well
- Orange peel appearance due to deposition of mucin
- Associated with Grave's disease, thyroiditis, primary hypothyroidism
- Difficult to treat. Compression, potent topical steroids under occlusion, intralesional steroids have been used with some success
Progressive Systemic Sclerosis (Scleroderma)

- Raynaud's phenomenon often precedes sclerosis. Sclerodactyly, pitting scars of the fingertips or loss of fingertip substance, bilateral basilar pulmonary fibrosis
- Other skin changes include tightness, proximal sclerosis, salt and pepper pigmentation, telangiectasia, narrowing of the mouth aperture, “pinched face”, contractures
- Visceral manifestations include esophageal dysphagia and dysmotility, colonic strictures, sclerosis of bone, polyarthritis, pericarditis

Peutz-Jeghers Syndrome

- Clinically characterized by hyperpigmented macules on the lips and oral mucosa. May also appear in other mucosal sites and on the hands
- Associated with GI tract polyposis with a preference for the small intestine
- 15x lifetime risk of malignancy, especially of the colon, stomach, and small intestine. Malignancies usually appear by age 30.
- Also may see malignancy of the breast, thyroid, pancreas, and ovary

Systemic Lupus Erythematosus (SLE)

- Photodistributed erythema, especially “butterfly” distribution on the face
- May have discoid lesions
- ACR criteria: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, proximal muscle weakness, Raynaud phenomenon, new onset seizures, pericarditis, proteinuria, hemolytic anemia, leukopenia, thrombocytopenia, immunologic disorders (ds-DNA, Sm, antiphospholipid ab, etc.), + ANA
Sweet’s Syndrome

- Sharply marginated rapidly expanding tender plaques. Often violaceous and edematous. May become vesicular, pustular, or necrotic.
- Found on trunk, face and extremities. Pathergy may occur. Fevers, arthralgias, myalgias common
- Most associated with URI. Yersinia, toxoplasmosis, histoplasmosis, salmonella, TB, vulvovaginal infections
- Rarely associated with hematologic malignancy (10%) or pregnancy

Tendinous Xanthoma

- Flesh colored or yellow papules/plaques 5-25mm in diameter on the extensor tendons
- Associated with increased LDL, obstructive liver disease, diabetes, myxedema, cerebrotendinous xanthomatosis, phytosterolemia
- Check serum lipids

Tuberous Sclerosis

- Classic triad of adenoma sebaceum (angiofibroma), mental deficiency, and epilepsy.
- Also associated with ash leaf macules, shagreen patches, café-au-lait macules, periungual fibromas, oral papillomas, gingival hyperplasia
- May see retinal phakomas, angiod streaks, renal hamartomas, renal cysts, cardiac rhabdomyomas, renal angiomyolipomas may cause renal failure
- Women of child bearing age may have pulmonary lymphangioleiomyomatosis leading to respiratory failure and pneumothorax
Vitiligo

- Depigmented macules, usually symmetric
- Face, extremities, trunk, genitals
- Associated with other autoimmune diseases such as Grave's, thyroiditis, Addison's disease, type 1 diabetes, and alopecia areata
- UV light, topical steroids, and topical tacrolimus have been helpful

Xanthelasma

- Yellow plaques on the upper and lower eyelids
- The younger the patient the more likely to be associated with hypercholesterolemia
- May be excised

References

McKee, Calonje, Grant (2005). Pathology of the Skin, with Clinical Correlations 3rd ed.
Ackerman, A. Bernard (1978). Histologic Diagnosis of Inflammatory Skin Disease.

Thank you for your attention