SKIN MANIFESTATIONS OF INTERNAL DISEASES

Nelly Rubeiz, MD

CUTANEOUS ASPECTS OF RENAL DISEASE

1. A variety of inherited and acquired disorders with specific/characteristic renal and cutaneous manifestations exist. This includes diseases in which the same basic process leads to clinical manifestations in both kidney and skin. Here examples include systemic lupus erythematosus with deposition of immunoglobulins; amyloidosis with deposition of amyloid. Or the renal and skin involvement are unrelated histologically but still represent different expressions of the same multisystem disease, such as tuberous sclerosis, nail patella syndrome and others, scleroderma and others.

2. Nonspecific skin changes that accompany chronic renal disease (namely uremia):

- Hyperpigmentation: Accentuated on sun-exposed areas (↑ β - MSH, retained carotene, anemia).

- Pruritus: Nature poorly understood - it is hypothesized that the accumulation of metabolites normally cleared by the kidneys as well as dryness contribute to the itching.

- Xerosis: excessive dryness.
- Acquired perforating disorder.
- Uremic frost: terminal finding among patients with severe renal failure- numerous white - tan granules, most prominent on the nose, beard area and neck - represent crystallization of urea in sweat.

- Subepidermal bullous dermatosis
- Cutaneous calcification: uncommon - may be seen in patients with overt hyperparathyroidisim- may appear as papules/ nodules - may ulcerate and discharge a chalky material.

- Half and half nail: Proximal white band and distal red-brown band.
- Xerostomia and stomatitis.

SKIN & GI TRACT:

GI Hemorrhage and the skin:

- **Vascular abnormalities:**

- Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu Disease): autosomal dominant involves the skin, mucous membranes and numerous internal organs.

  Multiple small ectatic , vascular lesions are present on face, lips, tongue, nose, hands, chest, feet (to be differentiated from CREST). Expistaxis is the most common form of bleeding. In the GI tract AV malformations, aneurysms may be present as well.

- Blue Rubber Bleb Nevus Syndrome:

  Skin and GI hemangiomas. Aut. dominant or sporadic. Skin lesions few mm to l0 cm vascular papules/nodules and tumors.

- **Inherited defects of connective tissue**:

- Pseudo Xanthoma Elasticum:

  Genetic disorder characterized by alteration of elastic tissue throughout the body. Characterized by skin lesions, retinal changes, vascular calcifications and GI bleeding. Skin lesions consist of confluent yellowish papules, that form plaques, usually on the neck and axillary areas.

- Ehlers - Danlos syndrome:

  l0 different types. (AD, AR or x-linked recessive). Defective connective tissue production. Characteristic findings: hyperextensible and fragile skin, hyperextensible joints, poor wound healing, scarring, easy bruisability.

- **GI Polyposis:**

- Gardner's syndrome: (AD). Colonic adenomatous polyps that may undergo malignant degeneration (risk). Patients have multiple epidermal cysts on the skin, also osteomas of skin and mandible and desmoid (fibrous) tumors.

- Peutz - Jeghers syndrome: (AD) hamartomatous polyps throughout GI tract (mainly small intestine). Also risk of GI malignancy, pancreatic and breast carcinomas. Skin: peri-orificial lentiginosis (pigmented lesions).

- Cowdens syndrome: Hamartomas of skin and mucous membranes. 40% have GI polyps. Have trichilemmomas on skin. risk of thyroid and breast tumors (usually benign).

- **Vasculitis:**

  As part of multisystem involvement; at the level of skin palpable purpuric lesions (usually on lower extremities).

  e.g.: Henoch-shonlein purpura: leukocytoclastic vasculitis with IgA immune complexes. Affects skin, GI and joints.

- **Tumors:**

- Kaposi's sarcoma:

- **Inflammatory Bowel Disease:** e.g. ulcerative colitis and Crohn's disease.
  Abdominal pain, diarrhea, often associated with blood, pus or mucous. Skin lesions include aphthosis, pyoderma gangrenosum, erythema nodosum and granulomatous skin lesions.

- **Skin and Malabsorption:**

- Ichthyosis -like changes develop (mainly on legs). Brittle hair and nails. Generalized hyperpigmentation due to melanin (~ to Addison's disease). May develop stomatitis /glossitis, and dermatitic, psoriasiform lesions - due to deficiency in zinc (acrodermatitis enteropathica), essential fatty acids, vitamins A,B,C, and K, folic acid, iron and protein deficiency.

HEPATIC DISEASE AND THE SKIN:

- Alteration in skin color: This is the best recognized cutaneous manifestation of hepatic disease. The two main factors that produce this (may act alone or in combination) are bilirubin and melanin.

  Jaundice: Deposition of bilirubin (or its metabolites) in tissue (skin, sclera and others) . Here, serum bilirubin is usually greater than 2.5 mg/dl - (NL < l.5 mg/dl).

  Hyperpigmentation: Most often associated with hemochromatosis and cirrhosis. Hemochromatosis is characterized by a triad of liver cirrhosis, diabetes mellitus and hyperpigmentation. Hemochromatosis can be familial, or acquired. This leads to increased iron deposition in various organs, resulting in dysfunction. It is melanin that causes the hyperpigmentation rather than the iron itself.

- Pruritus: Especially with obstructive disease of the biliary tree. Deposition of bile salts in the skin, is suspected to be the cause.

- Cutaneous vascular changes: Spider nevi, "liver palms" or palmar erythema. These are believed to be secondary to estrogen levels.

- Nail changes: Leukonychia (white nails), white bands, koilonychia (spoon nails).

CUTANEOUS MANIFESTATIONS OF DIABETES MELLITUS:

- Cutaneous infections: (↑ incidence in poorly controlled diabetes)
  -Candidiasis (oral thrush, angular stomatitis, paronychia, web spaces, vulvovaginal)
  - Bacterial: Erythrasma, impetigo, folliculitis, furunculosis, ecthyma, cellulitis, erysipelas.
  Malignant external otitis (Pseudomonas aeroginosa).

  - Mucormycosis
  - Dermatophytosis: Toe webs important portal of entry for bacteria that will invade and cause cellulitis.

- Diabetic dermopathy: Brown atrophic macules over the shins - ? post - trauma
- Diabetic thick skin:
  - Scleroderma - like waxy skin and stiff joints of the fingers and dorsum of hand
  - Skin thickening of back of hands (finger pebbles)
  - Scleredema: Marked skin thickening of the neck and back.

- Diabetic bullae: Spontaneous, hands and feet, heal with or without scarring (cleavage plane: intraepidermal, subepidermal)

- Necrobiosis lipoidica diabeticorum: erythematous plaques with atrophic yellowish telangiectatic center - shins.
- Acanthosis nigricans: Velvety brown - black thickening in flexural areas - syndromes of insulin resistance.
- Eruptive xanthomas: Sudden onset of crops of yellowish papules - hyperlipidemia, glycosuria, hyperglycemia.
- Yellow skin, yellow nails.
- Macroangiopathy: Skin atrophy, hair loss, nail dystrophy, rubor ....
- Microangiopathy.
- Neuropathy: Distal motor and sensory
  Autonomic (sweating disturbances, peripheral hyperemia)
- Diabetic foot: Result of the neuropathy and microangiopathy.

SKIN AND THYROID:

- Pretibial myxedema: Most commonly associated with hyperthyroidism caused by Graves disease. Appear as shiny waxy indurated plaques - with prominence of the follicular orifices --- peau d' orange appearance. Sometimes such lesions appear in other areas as well . It is a cutaneous mucinosis.

- Generalized myxedema: Most characteristic of hypothyroidism. The entire skin is pale, dry, waxy with a boggy non-pitting edema.

- Epidermal changes: Dry skin, with scaling in hypothyroidism decreased sebum and eccrine sweat.
  Moist warm skin in hyperthyroidism (metabolism). Normal sebum secretion, and eccrine sweat production.

- Hair: Hypothyroidism: Decreased hair density on scalp and lateral eyebrows.

- Vitiligo and alopecia areata: May be associated with autoimmune thyroid states.

HEART AND SKIN:

- Familial hyperlipidemia:
  Increased risk of coronary heart disease. Xanthomatosis may be present in these disorders.

- Cholesterol emboli:

  In patients with advanced atherosclerosis of the abdominal aorta, cholesterol crystals may microembolize to the lower extremities. Pulse may remain normal, patients may develop livedo reticularis (reticulated erythematous/vascular pattern) on lower legs, abdomen, with focal cyanosis, crusting and gangrenous changes.

- Subacute bacterial endocarditis (SBE): Vasculitic lesions (Oslers nodes and Janeway's lesions) appearing as purpuric palpable lesions on finger tips, palms and soles. Also splinter hemorrhages (not specific). Petechiae and larger purpuric lesions may be more widespread. Pathogenesis may be immunologic or septic vasculitis.

SKIN SIGNS OF INTERNAL MALIGNANCY:

I. Syndromes (some genetically determined with a cutaneous component and an inherent predisposition to internal malignancy):

- Gardner's syndrome
- Peutz - Jegher's syndrome
- Muir-Torre syndrome
- Cowden's syndrome
- Neurofibromatosis
- Mucosal neuroma syndrome
- Palmar and plantar keratoderma

II. Cutaneous markers of exposure to a carcinogen capable of inducing internal malignancy.

- Arsenic
- Nicotine staining
- X-ray damage (radiodermatitis)

III. Proliferative, inflammatory, deposition and other skin changes associated with internal malignancy:

- Pruritus
- Erythema gyratum repens
- Sweet's syndrome
- Hypertrichosis lanuginosa
- Necrolytic migratory erythema
- Clubbing
- Eruptive seborrheic keratoses
- Dermatomyositis (adult)
- Acanthosis nigricans
- Acquired ichthyosis
- Flushing
- Thrombophlebitis
- Telangiectasia, palmar erythema.
- Deposition (jaundice, melanosis, hemochromatosis, xanthomas, systemic amyloidosis)
- Vascular hypersensitivity reaction (e.g. vasculitis, erythema multiforme)

IV. Skin Metastasis

SKIN CHANGES IN PREGNANCY

Common Alterations of the Skin During pregnancy:

- Pigmentation: Hyperpigmentation occurs in 90% of pregnant women, more commonly it is localized, involving areas of increased melanocytic density. These areas include areolae, umbilicus, linea alba, genitalia, perineum, axillae, inner thighs. Melanocytic nevi and other pigmented lesions may get darker. Melasma/chloasma (mask of pregnancy) may develop. Cause: estrogen; progesterone and MSH role questionable.

- Vascular changes: The vascular changes result from increased vascular volume and mechanical impairment of blood return leading to venous distension (varicosities arise in 40% of women, lower extremities, rectum, and vulvar areas) - these usually regress after delivery.

  Spider angiomas may appear. Also pyogenic granulomas (epulis), frequently on the gingiva, appearing as red papules/nodules that bleed easily.

- Hair: Hair loss during first few months following delivery: Telogen effluvium.

- Striae: Common over lower abdomen and breast.

Dermatoses Usually Associated with Pregnancy:

- Herpes gestationis: Pruritic blistering disease of pregnancy, usually resolves after delivery. Similar to bullous pemphigoid. May affect pregnancy course, and may recur in future pregnancies.

- Pruritic urticarial papules and plaques of pregnancy - PUPPP - a common gestational dermatosis. Usually starts on abdominal skin (striae). Generally a benign self-limited eruption not affecting fetus.

- Cholestasis of pregnancy (Prurigo Gravidarum):

  Usually generalized pruritus, may be accompanied by jaundice - onset usually in third trimester. Abnormal liver function tests. Liver biopsy shows dilated bile canaliculi. May be associated with premature labor, low birth weigh and post partum hemorrhage.

- Impetigo herpetiformis (pustular psoriasis of pregnancy) - the most serious among the dermatoses of pregnancy.