Nephrocutaneous Disease: Skin Signs of Renal Disease

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Conflict of Interest Disclosure
• I have no conflicts to disclose

Learning Objectives
• Recognize and describe skin manifestations of chronic kidney disease
• Recognize and describe skin manifestations of inflammatory/systemic diseases
• List genetic diseases with skin and renal manifestations
• Describe skin findings more common in renal transplant patients
• Monitor for renal toxicities of dermatologic therapies
• Describe skin manifestations of renal cancer
Which of the following is a common skin finding in patients with renal disease?

A. Alopecia  
B. Hypopigmentation  
C. Hyperhidrosis  
D. Xerosis*  
E. Excessive sebum production

Cutaneous Manifestations of Chronic Renal Disease

• Xerosis – 50-90% ESRD  
• Pruritus 12-90%  
• Pigmentary changes  
• Nail changes (half & half nails/Lindsay nails <40% ESRD)  
• Calciphylaxis  
• Perforating disorders  
• Porphyria cutanea tarda and pseudoporphyria

Xerosis and Ichthyosis

• 50-90% end stage renal disease pts  
• May persists/worsen despite dialysis  
• Often accompanied by pruritus  
• Theories on pathogenesis  
  – Change in skin structure – fragmentation of elastic fibers, atrophy of eccrine glands, abnormal epidermal maturation due to hypervitaminosis A  
  – Diuretics  
• Management: bland emollients, mild keratolytics (salicylic acid, urea, lactic acid)
Pruritus

- Pruritus is reported in 12–90% of patients
- Can have major impact on quality of life
- Theories on pathogenesis:
  - Xerosis
  - Mast cell proliferation and degranulation,
  - Metabolic – hyperparathyroidism, hypercalcemia, hyperphosphatemia increased aluminum level
  - Increase of circulating pruritic cytokines
  - Abnormalities in cutaneous innervation
  - Allergy to components of dialysis membranes

Pruritus

May be localized or generalized

Excoriations  Lichenification  Prurigo nodules

Pruritus

- Treatment is challenging
  1. Optimize metabolic parameters, nutrition, & prevent/treat xerosis
  2. Nonsedating antihistamines, gabapentin/pregabalin, UVB phototherapy, opiate receptor modulators
- Other systemic causes of pruritus:
  - Thyroid disease, hepatic disease, hematologic disorders (polycythemia vera, paraproteinemia, iron deficiency), parasitic infestation, drug reactions, malignancy (esp. lymphomas), HIV/AIDS (CD4 <50 cell/µL)
**Pigmentary Changes**

- **Pallor** – anemia
- **Yellow** – lipochromes & carotenoids, liposoluble pigments, deposited in the dermis and subcutis
- **Hyperpigmentation** – melanin due to increased beta-melanocyte stimulating hormone (esp. in sun exposed skin)

Does not resolve with dialysis

**Nail Changes**

- **Half and half nails / Lindsay nails** – white or normal proximal nail plate with red/brownish distal plate that is > 1/3 the length of the nail
  - Due to increased melanin in nail plate

**Calciphylaxis**

- Most often in patients with renal failure and alterations in calcium, phosphate, PTH levels (uremic calciphylaxis)
  - Less often seen in pts without renal failure and with nrl Ca & Phos (nonuremic calciphylaxis)
- Poor prognosis - 1-yearsurvival rate ~45.8% and 2-year survival rate ~20% (sepsis)
  - Pts on dialysis at dx have reduced median survival
  - Pts with both distal and proximal disease have higher mortality rate
Calciphylaxis

- Sudden onset, rapidly progressive, intensely painful ulcers, which begin as dusky livedo reticularis-like areas and progress to stellate violaceous ulcerating plaques with central necrosis
- Most often on lower extremities and may involve the fatty areas of the trunk or proximal upper extremities

Calciphylaxis Management:
- Biopsy and/or radiographic imaging
- Partner with nephrologist
- Refer to dermatologist with expertise in treating calciphylaxis
- Correct metabolic abnormalities, wound care, pain control, sodium thiosulfate, bisphosphonates, pentoxifylline, stop warfarin

Acquired Perforating Disorders

- Transepidermal elimination of dermal structures
- Pathophysiology unknown
  - Localized irritation from scratching causing inflammatory reaction to uremic substrates in the dermis?
- More common in African American patients
- Strong association with diabetes
- Affects 2-11% dialysis patients
- Pruritic, firm, dome-shaped papules or nodules with central keratotic plug, usually on trunk and extensor surfaces of extremities, koebnerization is coming
- Clinical course: spontaneous resolution of well-developed individual lesions with continued development of new lesions
Acquired Perforating Disorders

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Prophyria and Pseudoporphyria

- Porphyrias - group of diseases caused by abnormalities in the heme biosynthetic pathway
- Enzyme defects cause elevated levels of intermediate metabolites (porphyrins) detectable in blood, urine, stool
- Porphyrins absorb visible light and generate free radicals leading to cell membrane damage and cell death
- Pseudoporphyria is clinically and histologically identical to PCT without serum/urine/stool porphyrin abnormalities

Prophyria and Pseudoporphyria

Photosensitivity, skin fragility, vesicles, erosions and milia, esp. on face and dorsal hands
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Which of the following systemic diseases is characterized by prominent dermatologic and renal manifestations?

A. Sézary syndrome
B. Ehlers Danlos syndrome
C. Systemic lupus erythematosus*
D. Grave’s disease
E. Urticaria pigmentosa

Inflammatory Diseases with Potential Renal Implications

• Vasculitides
  – Small vessel vasculitis (leukocytoclastic)
    • IgA vasculitis
    • Cryoglobulinemia
  – Medium vessel vasculitis
    • Polyarteritis nodosa
    • ANCA vasculitides (granulomatosis with polyangiitis, microscopic polyangiitis)
• Systemic lupus erythematosus
• Systemic sclerosis
• Sarcoidosis
• Nephrogenic systemic fibrosis
### Vasculitis – Small Vessel

- **Palpable purpura, may progress to ulcers**
  - Skin biopsy for H&E and DIF from NEW lesional skin

### Vasculitis – Small Vessel

- **IgA vasculitis/Henoch Schönlein purpura**
  - Glomerulonephritis, joint pain, abdominal pain
  - Urinalysis to look for RBC's, proteinuria AND serum renal function panel at diagnosis
  - Adults with IgA vasculitis are at risk of chronic kidney disease, monthly blood pressure monitoring and renal function + U/A for 6 mo after resolution
- **Cryoglobulinemia**
  - Quantitative cryoglobulins (serum), rheumatoid factor, malignancy work-up, monitor for renal disease

### Vasculitis – Medium Vessel

- **Polyarteritis nodosa**
  - May involve skin, peripheral nerves, GI, kidneys, heart, & CNS
  - Renal disease usually caused by rupture of renal microaneurysms causing tissue infarction or hematoma; hypertension common
- **ANCA + Vasculitides**
  - Granulomatosis with polyangiitis (Wegener’s granulomatosis)
  - Microscopic polyangiitis
    - Typically occur in older adults
    - Often present with fever, malaise, anorexia, weight loss, arthralgias
    - Pulmonary and renal vasculitis (hematuria, subnephrotic range proteinuria)
    - Cutaneous manifestation in about 50%
Vasculitis – Medium Vessel

- Biopsy edge of ulcers for H&E and DIF
- Biopsy center of ulcer for tissue cultures

Systemic Lupus Erythematosus

- Systemic autoimmune disease that can affect virtually any organ system
- Renal involvement occurs in ~50% of SLE pts
  - Glomerulonephritis
  - Abnormal U/A: proteinuria, cellular casts, WBC’s, RBC’s

Systemic Lupus Erythematosus

- Cutaneous findings common
  - Acute cutaneous lupus ("butterfly rash") is a sign of systemic disease
  - Systemic disease seen in ~5-10% of patients with discoid lupus and ~15-20% of patients with subacute cutaneous lupus
  - In those with established cutaneous lupus diagnosis, screen for systemic disease yearly with CBC&dif, CMP, U/A
Systemic Sclerosis

- Autoimmune connective tissue disease
- Thickening of dermal collagen, fibrosis of skin & internal organs
  - Visceral manifestations
    - Pulmonary fibrosis, esophageal dysmotility, pulmonary hypertension, myocardial sclerosis, arthritis
    - Renal involvement uncommon but can be life-threatening - sustained severe hypertension and acute renal failure “scleroderma renal crisis”

Systemic Sclerosis

- Skin
  - Raynaud’s, telangiectases, salt & pepper pigmentary changes, digital ulcers, calcinosis, sclerodactyly, cutaneous sclerosis

Scleroderma is a rheumatologic disease not typically characterized by photosensitivity
**Sarcoidosis**

- Acute or chronic systemic granulomatous disease that can involve all organ systems
  - Renal disease less common than skin, lung, eye
    - Acute interstitial nephritis, nephrocalcinosis, nephrolithiasis

**Skin findings in ~25% of patients**

- Numerous morphologies, usually asymptomatic skin disease
- Erythema nodosum

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**Nephrogenic Systemic Fibrosis**

- Scleroderma-like disorder caused by exposure to gadolinium-based MRI/MRA contrast agents
- Seen almost exclusively in patients with renal insufficiency and a GFR ≤30 ml/min
- Patients with GFR ≤15 ml/min & dialysis patients are at the highest risk
- Incidence is decreasing since discovery of gadolinium as cause
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Genetic Diseases with Potential Skin and Renal Associations

- Neurofibromatosis type-1
- Tuberous sclerosis
- Birt-Hogg-Dube syndrome
- Beckwith-Wiedemann syndrome
- Von Hippel-Lindau syndrome
- Cowden syndrome
- Hereditary leiomyomatosis & renal cell carcinoma syndrome (Reed syndrome)
- Fabry disease
- Nail-patella syndrome
- Turner syndrome

Photos courtesy of Andrea Zaenglein, MD
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Which of these growths is more common in patients who have had a kidney transplant?

A  B*  C  D
Renal transplant associated skin conditions

- Skin cancers
  - Risk increased 3-4X for melanoma, 10-20X for BCC and 65-250X for SCC
  - Risk increases with dose and duration of immunosuppression
  - Risk higher in those with pretransplant hx of BCC/SCC/AK
  - More aggressive
  - Q6-12 month skin exams

- HPV
  - HPV-associated malignancies (mucosal SCCs)
  - Cutaneous warts
  - Molluscum contagiosum (higher risk in heart & lung tx)
  - Drug eruptions—any type more likely in immunocompromised pts

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Dermatologic Therapies with Potential Renal Toxicities

- Cyclosporine – acute renal toxicity is dose dependent and reversible
- Methotrexate – toxicity usually at chemo doses, but check renal function 1-2 times per year
- Trimethoprim sulfamethoxazole (TMP/SMX)
  - Interstitial nephritis
  - Hyperkalemia (esp. in pt with renal disease)
  - Must dose adjust in pts with renal insufficiency
  - Causes reduced serum cyclosporine concentrations which can increase risk of renal transplant rejection
- Tetracyclines – half-life of minocycline is increased in renal failure, but doxy safe choice for patients with renal disease
- Spironolactone –
  - Hyperkalemia in patients with renal insufficiency or in those taking medications that may also increase K+ levels, ACE inhibitors, angiotensin II receptor blockers, other aldosterone inhibitors
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Skin Manifestations of Renal Cancer

• Hereditary cancer syndromes (As discussed)
• Cutaneous metastases (3-7%), may be presenting sign, scalp most common site, purple/vascular dermal nodules
Which of the following is the most likely diagnosis of this painful ulcer on the thigh?  

A. Nephrogenic systemic fibrosis  
B. Leukocytoclastic vasculitis  
C. Metastatic renal cell carcinoma  
D. Calciphylaxis*  
E. Perforating folliculitis

References

• Amiri A, Buryaxis E. Skin manifestations associated with kidney cancer. Seminars in Oncology. 2016;43:408-12  