CORE CURRICULUM IN NEPHROLOGY

Dermatological Disease in Patients With CKD

Ursula C. Brewster, MD

BACKGROUND

I. Studies show that nearly 100% of patients with end-stage renal disease (ESRD) are affected by at least 1 dermatological disorder
II. Also common in patients with chronic kidney disease (CKD)
III. Skin disorders have significant effects on quality of life and general appearance
IV. Some disorders are associated with excessive morbidity and must be treated aggressively

GENERAL CHANGES IN SKIN

I. Changes in skin color range from pallor (from anemia) to hyperpigmentation
II. Xerosis, or dry skin, results from significant atrophy of sebaceous and sweat glands
III. Premature skin aging is common
IV. Lindsay nails (so-called half-and-half nails) occur when the proximal two thirds of the nail is white with normal or dark discoloration distally
V. Dermal vessels show basement membrane thickening, endothelial activation, and chronic inflammation

UREMIC PRURITUS

I. Occurs in 50% to 90% of patients with ESRD
II. Often disabling due to work and sleep disturbances
III. More common in patients on hemodialysis (HD) therapy than those on peritoneal dialysis (PD) therapy
IV. Difficult to predict who will be affected with severe disease
V. Severe disease more common in patients of male sex and with high blood urea nitrogen (BUN) levels

Pathogenesis

I. Can be related to kidney disease specifically
   A. Xerosis
   B. Secondary hyperparathyroidism
   C. Anemia
   D. Increased levels of substance P, magnesium, or aluminum
II. May be related to comorbid illnesses associated with ESRD
   A. Diabetes mellitus
   B. Hepatitis or other chronic infections
   C. Hypothyroidism
   D. Drug hypersensitivity
   E. Malignancy
III. Dermal mast cell number is higher in patients with ESRD, although there is little correlation between mast cell number and degree of pruritus
   A. These cells release histamine in response to a variety of stimuli
   B. Histamine stimulates C-terminal nerve endings
   C. These in turn stimulate the central nervous system (CNS), leading to itch
IV. Substance P stimulates μ-opioid receptors in the peripheral nervous system and CNS, leading to the itch
   A. κ-Opioid agonist, nalfurafine, may reduce pruritus

Diagnosis

I. History and physical examination show broad excoriations of the skin
II. Skin biopsy: usually unnecessary and often unhelpful
III. Diagnostic criteria
   A. Pruritus generally appears around the time of dialysis, but may occur anytime
   B. Must have 3 or more episodes of itch that trouble the patient over less than 14 days, lasting a few minutes

From the Section of Nephrology, Yale University School of Medicine, New Haven, CT.

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Address correspondence to Ursula C. Brewster, MD, Section of Nephrology, Yale University School of Medicine, FMP 107, 330 Cedar St, PO Box 208029, New Haven, CT 06520-8029. E-mail: ursula.brewster@yale.edu

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C. Any itch that appears in a regular pattern not meeting the frequency criteria noted

Treatment

I. Increase dialysis efficiency and optimize Kt/V
II. Renal transplantation remains the only definitive cure
III. Topical therapies
  A. Cleanse the skin with mild soaps
  B. Moisturize the skin with emollients containing 80% water
  C. Capsaicin depletes peripheral neurons of substance P and was moderately successful
IV. Physical treatments
  A. Ultraviolet B (UVB) light: effective, but mechanism unclear
    1. May be difficult to schedule regular light treatments for patients on chronic maintenance HD therapy (busy schedule)
    2. Long-term carcinogenic risk unknown
    3. Consider carefully in patients eligible for kidney transplantation (long-term immunosuppressive therapy) because they are at increased risk of dermatological malignancies
  B. Acupuncture: data anecdotal, but may have some benefit
V. Parathyroidectomy (PTX)
  A. Surgery may relieve symptoms with secondary hyperparathyroidism
  B. Indicated in patients with tertiary parathyroidism uncontrolled by medications
  C. Data are limited
  D. No clear data for cinacalcet era
VI. Systemic medications
  A. Antihistamines: limited effect, sedation limits therapeutic ability
  B. Activated charcoal:
    1. Theoretically binds intestinal puritogens, reducing symptoms
    2. Requires high doses and is poorly tolerated
  C. Nalfurafine: a κ-opioid agonist. Data suggest patients improve more on drug therapy than placebo (35% versus 14%), but results are variable
  D. Nicergoline: data to support its use are variable
  E. Thalidomide: randomized trial showed benefit in 55% of patients
    1. Known teratogen, so prescribe cautiously to women
    2. Increases risk of thrombosis
  F. Primrose oil: rich in γ-linolenic acids that reduce lymphocyte proliferation and lymphokine production
    1. Data suggest good benefit when administered orally
  G. Cholestyramine: mixed results
  H. Naltrexone: beneficial in small studies, but double-blind crossover study showed no benefit
    1. Significant side-effect profile

ADDITIONAL READING

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ACQUIRED PERFORATING DERMATOSIS (APD)

I. Shares features with Kyrle disease (idiopathic perforating dermatosis), but acquired related to kidney failure or other systemic diseases
II. Prevalence: approximately 10% of patients on maintenance dialysis therapy
III. Occurs most commonly in patients with ESRD, but also described in patients with advanced CKD and kidney transplant recipients
IV. Risk greatest in African Americans and patients with diabetes mellitus

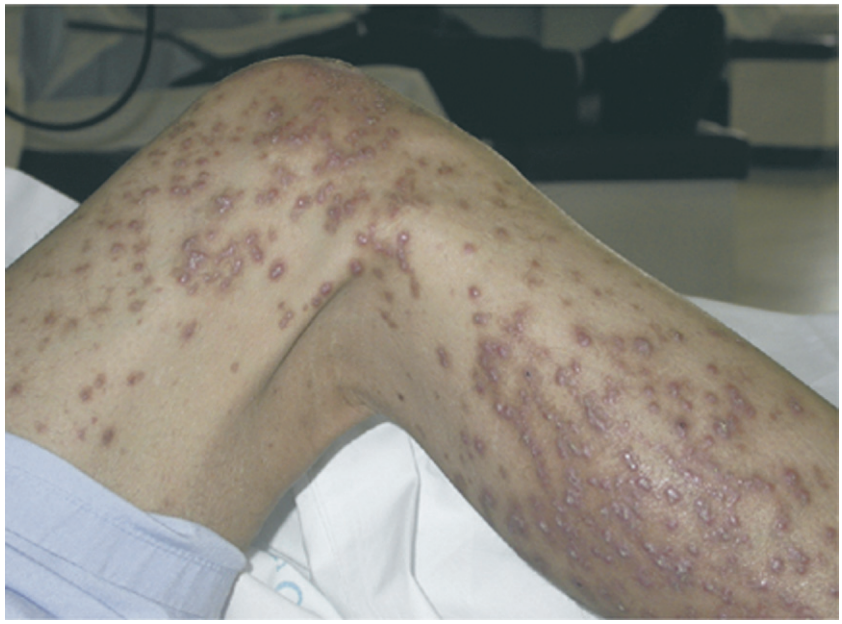

Figure 1. Acquired perforating dermatosis seen on the leg of a dialysis patient. (Printed with permission from Martins J, Rivera M, Carillo-Gijon R, Teruel JL, Ortuno J: Acquired perforating dermatosis in a peritoneal dialysis patient. Kidney Int 71:832, 2007.)

Pathogenesis

I. Not definitively known
II. Results from transepidermal elimination of dermal constituents
III. Theories include:
   A. Abnormalities in epidermal proliferation or dermal connective tissue
   B. Scratching may cause dermal necrosis and inflammation
   C. A "foreign-body" reaction to altered dermal constituents
   D. Crystalline dermal deposits of uric acid causing an inflammatory reaction

Clinical Features (Fig 1)

I. The 2- to 8-mm domed papules with centralized keratotic plug may coalesce in a linear pattern
II. Commonly found on trunk and proximal limbs or in hair-bearing areas, including face and scalp
III. May develop along scratch marks (Koebner phenomenon)
IV. Lesions pink on white skin or hyperpigmented on darker skin
V. Lesions often umbilicated
VI. Intensely pruritic

Histological Characteristics (Fig 2)

I. Biopsy shows epidermal invagination with a keratotic plug containing basophilic cellular debris
II. May find hair follicles or fragments within lesions
III. May find uric acid and calcium hydroxyapatite deposits within lesions
IV. Over time, lesions develop chronic inflammation and granulomas with necrotic debris

Treatment

I. Challenging, with lesions resistant to therapy
II. Therapies include:
   A. Lubricants
   B. Topical steroids
   C. Keratolytics
   D. Topical retinoids or oral isotretinoin
   E. Oral vitamin A

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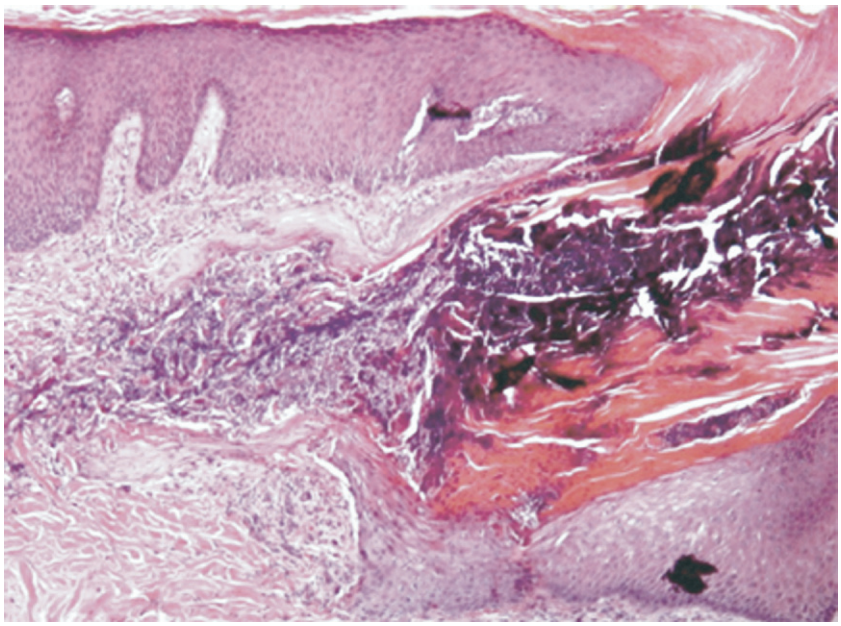

Figure 2. Skin biopsy specimen of acquired perforating dermatosis shows a dilated follicle with keratinous and necrotic debris. The follicular epithelium is disrupted with dermal collagen entering the perforation. (Printed with permission from Martins J, Rivera M, Carrillo-Gijon R, Teruel JL, Ortuno J. Acquired perforating dermatosis in a peritoneal dialysis patient. Kidney Int 71: 832, 2007.)

BULLOUS LESIONS

Porphyria Cutanea Tarda (PCT)

I. Dialysis patients at increased risk
II. Occurs in 1% to 9% of patients on HD therapy; less common, but occurs with PD therapy
III. Can be acquired and "sporadic" (type 1), autosomal dominant (type 2), or inherited with features of type 1 (type 3); most patients with ESRD have type 1
   A. Associated with a defect in heme biosynthesis with a uroporphyrinogen decarboxylase deficiency
   B. Patients with ESRD have poor clearance of uroporphyrins and they accumulate
   C. Other triggers of PCT include alcohol, iron, estrogens, and chronic infections with hepatitis B/C or human immunodeficiency virus (HIV)
IV. Uroporphyrins are not removed by conventional HD, and plasma porphyrin levels are often increased (>200 μg/dL)
V. Clearance is improved with the use of high-flux membranes

Clinical Presentation

I. Bullae on dorsal surfaces of hands and feet or occasionally on face
II. Facial hypertrichosis and hyperpigmentation in sun-exposed areas
III. Healing associated with scarring
IV. Superinfection is common

Diagnosis

I. Clinical findings are diagnostic
II. Increased serum uroporphyrin levels

Pathological Characteristics

I. Subepidermal vesicles with minimal inflammation
II. Periodic acid–Schiff (PAS)-positive material stains around dermal blood vessels
III. Linear staining of immunoglobulin G (IgG), C3, and fibrin at the dermoepidermal junction

Treatment

I. Sun protection (physical barriers and lotions [zinc oxide])
II. Lower serum levels of uroporphyrin
   A. Phlebotomy with accelerated recombinant erythropoietin therapy to avoid anemia
III. Maintain serum ferritin levels at the lower limit of normal
   A. Iron overload is a trigger for disease

IV. Deferoxamine has been used as a chelator, but without renal elimination, is unlikely to be successful

Pseudoporphyria

I. Includes patients with the clinical features described, but normal porphyrin levels
II. Appears to develop in association with certain medications
    A. Furosemide
    B. Naproxen
    C. Amiodarone
    D. Nalidixic acid
    E. Tetracycline
    F. Isotretinoin
    G. Chronic UV radiation
III. Clinical features very similar to PCT, although most patients do not develop hypertrichosis or sclerodermoid plaques

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Calcific Uremic Arteriolopathy (CUA): Previously Calciphylaxis

I. Devastating obliterative vasculopathy
II. Occurs in patients with ESRD, CKD, and kidney transplant
III. Remains rare, but is increasing in prevalence
IV. Often, but not exclusively, occurs in patients with severe secondary hyperparathyroidism and high calcium-phosphate product
V. Risk highest in females, the obese, and patients with diabetes mellitus
VI. Mortality rates can be as high as 80%
    A. Wound infection
    B. Severe pain with these lesions can promote withdrawal from dialysis treatment

Risk Factors

I. Lesions frequently occur in patients with:
    A. Thick adipose tissue
        1. Thick adipose tissue has decreased blood flow
            a) may predispose to thrombosis and hypoxia in small blood vessels and the development of CUA
        2. Not the only trigger because:
            a) lesions develop in the distal extremities without adipose tissue
            b) majority of cases occur in the nonobese
    B. Increased serum phosphate concentration
        1. A case-control study showed serum phosphate as an independent risk factor for CUA
    C. Hyperparathyroidism
        1. Appears to be a "sensitizer" for tissues, priming them for calcification
            a) CUA was shown in patients with primary hyperparathyroidism, but normal calcium-phosphate metabolism
        2. Data to support high parathyroid hormone (PTH) level as an independent risk factor have mixed results
    D. Malnutrition
        1. Low serum albumin level seems to predispose to CUA
            a) cause of this is unclear and may be a marker of overall morbidity
        2. Low albumin level predisposes to poor wound healing and infection complicating lesions
    E. Female sex
        1. Cause of sex influence is unclear
        2. May be related to distribution or percentage of adipose tissue
        3. Increased subcutaneous tissue creates stress on septae that connect skin and deep fascia and subsequently on arterioles, which leads to hypoperfusion and ischemic necrosis
    F. Warfarin anticoagulation
        1. Warfarin downregulates matrix GLA protein (MGP), normally a local vascular inhibitor of calcification, which may predispose patients to CUA
        2. However, MGP knockout mice show extensive vascular calcification, but not CUA, so the association is not clear

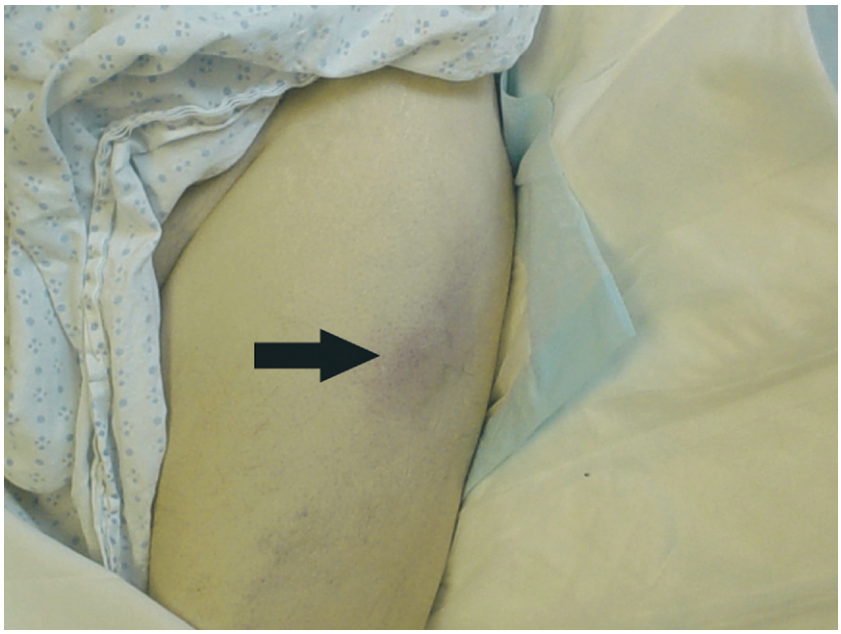

Figure 3. Early lesion of calcific uremic arteriolopathy shows violaceous area (arrow) with no skin breakdown.

3. May also be related to decreased protein C and S levels in the setting of warfarin therapy and a predisposition to thrombosis

Clinical Presentation (Figs 3, 4, and 5)

I. Lesions frequently overlie thick adipose tissue, areas of skin contact, or sites of trauma
   A. Insulin or heparin injection sites common
II. Common presentation is dysesthesia, followed by a violaceous livido reticularis, and finally an exquisitely painful eschar
III. Pain often the first symptom (before lesions erupt)
IV. Subcutaneous calcified nodules and plaques may be palpable
V. Surrounding areas may be pruritic

Diagnosis

I. Clinical diagnosis frequently requires histological confirmation by skin biopsy
   A. Biopsy must be done with caution because it may produce a nonhealing ulceration that accelerates the lesions
II. Radiographs may show small-vessel calcification in a lacy network
   A. Digital subtraction mammography techniques showed high sensitivity in detecting small-vessel calcification (not performed routinely)

Pathological Characteristics of Lesions

I. Marked by a severe obliterative vasculopathy with intimal proliferation
II. Medial wall calcification
III. Endovascular fibrosis
IV. Fibrin thrombi in subcutaneous and superficial dermal vessels appear, helping to explain necrosis
V. Panniculitis with fat necrosis and inflammatory infiltrate consisting of neutrophils, lymphocytes, and histiocytes

Pathogenesis

I. Until recently, vascular calcification in patients with ESRD was assumed to be a passive process caused by high calcium-phosphate product, but now known to be carefully regulated
II. Increased serum phosphate concentration likely is a key trigger in the development of CUA
III. Therapeutic doses of vitamin D may increase the risk of vascular calcification by inducing hypercalcemia, inhibiting PTH-related peptide (an inhibitor of calcification), and enhancing osteopontin expression (discussed next)

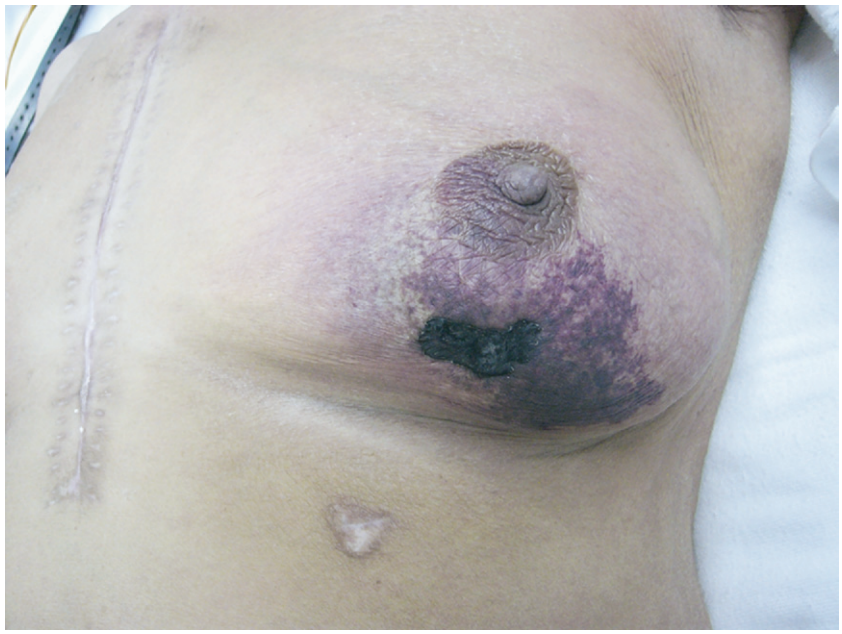

Figure 4. Calcific uremic arteriolopathy of the breast. Adapted with permission from Li G, Polokoff EG, Panait L, Roer D. Semin Dial 20:91-92, 2007.

IV. Molecular mechanisms explain the increased risk of calcification with advanced CKD:
  A. Increased expression of osteogenic markers that induce calcification
    1. Osteopontin, expressed by vascular smooth muscle cells, is increased in patients with CUA lesions
    2. Bone morphogenic protein 4 (BNP-4), normally involved in bone development, was found in atherosclerotic lesions and is upregulated in periarterial dermal cells with CUA
  B. Decreased inhibitors of calcification
    1. MGP: γ-carboxylation binds calcium and inhibits vessel calcification
      a) warfarin inhibits vitamin K–dependent carboxylation
    2. Fetuin A concentration (α2-Heremann Schmitt glycoprotein) was decreased in HD patients and is a known inhibitor of vascular calcification
      a) inflammation reduces fetuin A synthesis
      b) fetuin A helps induce phagocytosis of apoptotic cells, which can act as a nidus for medial arterial calcification
      c) the fetuin-mineral complex inhibits mineral precipitation in vitro
    3. Pyrophosphate levels are decreased in HD patients
      a) appears to be related to dialytic clearance in combination with reduced synthesis and increased extrarenal clearance

Treatment

I. Wound care
  A. Requires an experienced surgical and nursing team
  B. Frequent debridement of necrotic tissue
  C. Systemic antibiotics often indicated
  D. Vacuum dressings may aid in wound healing
  E. Adequate analgesia: usually requires opioids
II. Control calcium-phosphorus product
  A. Use non–calcium-based binders to avoid hypercalcemia, although data for the use of newer non–calcium- non–aluminum-based phosphate binders are limited to a few case reports
  B. Increasing the frequency of dialysis sessions and using low-calcium baths may have merit
III. PTX
  A. Surgical PTX

1. Shown to convey survival benefit in patients with CUA and secondary hyperparathyroidism
2. Requires an experienced surgeon and should be done quickly when the diagnosis of CUA is confirmed in a patient with increased intact PTH level
3. May improve calcium-phosphate control in these patients

B. Medical PTX
1. Treatment with oral cinacalcet (Amgen, Thousand Oaks, CA) shown to aid in treatment in several case reports
2. May have a role in patients who cannot undergo surgical PTX (use in CUA should be limited to those patients)

IV. Sodium thiosulfate
A. Mechanism
1. Thiosulfate binds calcium and is much more soluble (250- to 100,000-fold greater solubility in aqueous solution) than other calcium salts
2. Believed to chelate calcium from soft-tissue deposits
   a) reduces urinary calcium stone volume in patients with nephrolithiasis
   b) reduces metastatic calcification in patients with ESRD
3. Acts as an antioxidant and may induce endothelial nitric oxide synthesis
   a) improves tissue blood flow and oxygenation
4. Side effects:
   a) anion gap metabolic acidosis expected from the unmeasured anion, thiosulfuric acid
   b) nausea
5. Drug normally 98% excreted in urine (2% biliary), but in anuric patients, drug found to have increased biliary excretion
6. Dosage: case reports describe 5.0 to 25 g intravenously (IV) over 10 minutes at the end of each HD treatment
7. Successful therapy was described in both HD and PD patients

V. Bisphosphanates
A. Mechanism unclear and may relate to
1. Modification of calcium-phosphate crystal deposition in ectopic calcification
2. Inhibition of local macrophage activity and suppression of proinflammatory cytokines
3. Action similar to pyrophophate, a normal inhibitor of calcification

B. Both pamidronate (IV) and etidronate (oral) shown to be effective
C. Case reports showed dramatic improvements in pain shortly after initiation of therapy and decreases in C-reactive protein level
D. Risk is low

VI. Hyperbaric oxygen (HBO)
A. Mechanism involves an increase in amount of dissolved oxygen in the blood, which improves oxygen delivery to damaged tissues and promotes wound healing
B. Patient breathes 100% oxygen and is placed in a pressurized chamber with pressures of 2 to 2.4 atmospheres absolute (ATA)
C. Successful use in patients with CUA is case-report based, but seems substantial
D. Wound healing is enhanced
1. Enhanced oxygen gradient from external tissue to wound center increases neoangiogenesis
2. Improved neutrophil activity as respiratory burst and production of reactive oxygen species (hydrogen peroxide, superoxide, hydroxyl radicals) is enhanced by the presence of HBO, improving bacterial killing
3. Stimulation of fibroblasts in formation of collagen matrix
4. Higher oxygen tension is toxic to anaerobic microorganisms that frequently infect these wounds

E. Risks
1. Barotrauma risk is low at 2 ATA, but patients may report ear pain
2. Pulmonary barotrauma negligible at this low pressure
3. Seizure risk from high oxygen ranges from 1:5,000 to 1:10,000

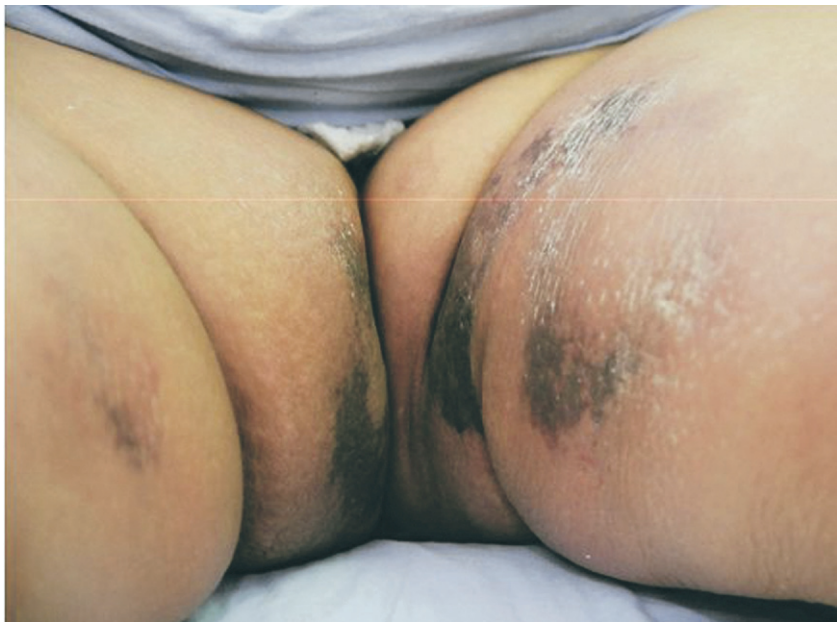

Figure 5. Inner thighs of a young woman who reported increasing pain for 2 days before the development of lesions consistent with calcific uremic arteriolopathy.

a) cessation of oxygen therapy resolves seizures and patients usually have no sequelae

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NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

I. Scleroderma-like fibrosing disorder initially coined "scleroderma-like disorder in renal patients"
II. Subsequently called nephrogenic fibrosing dermopathy (NFD), followed by NSF when systemic involvement noted
III. First case series published in 2000, and numbers have grown steadily, with an international registry tracking all reported cases (available at http://www.icnfdr.org)
IV. Debilitating and painful illness characterized by fibrosing of the skin and can involve systemic organs (lungs, heart, esophagus, diaphragm, and so on)
V. Occurs in patients with abnormal kidney function, most of whom are dialysis dependent (HD and PD), but occurs in those with failing renal transplants and acute kidney injury (AKI)
VI. Occurs in males and females equally and across all racial lines
VII. New data suggest that gadolinium exposure (magnetic resonance imaging [MRI]-based intravenous contrast agents) may be an important trigger for the development of this disorder

Clinical Presentation (Figs 6 and 7)

I. Progressive fibrosing skin disorder
II. Typically starts with patients reporting swelling and a "tight" feeling in extremities
III. Skin changes may be red or dark patches, papules, plaques, or nodules
IV. Progressing over days to weeks to inhibit flexion and contraction of joints and contractures
V. Skin becomes "woody" with peu d'orange consistency

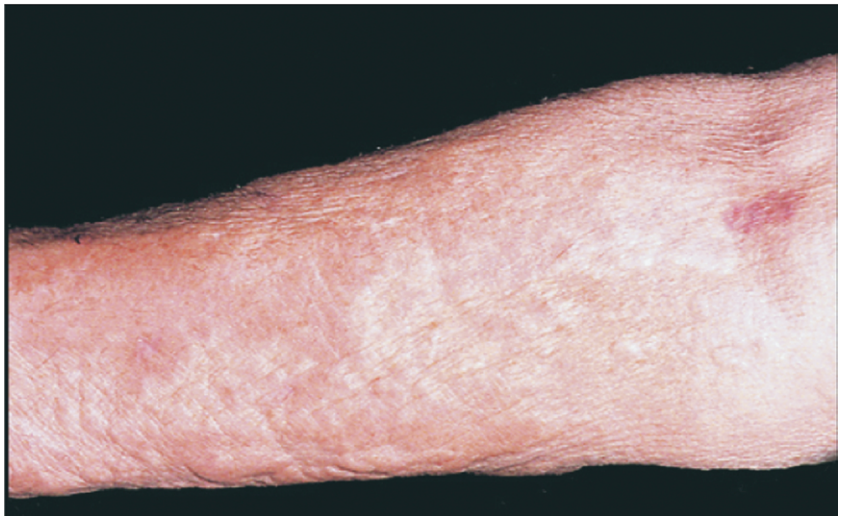

Figure 6. Forearm of a patient with nephrogenic systemic fibrosis shows thickening of the skin with peau d'orange appearance. (Reprinted with permission from Cowper SE. Nephrogenic fibrosing dermopathy [NFD/NSF Website]. 2001-2007. Available at: http://www.icnfdr.org. Accessed June 7, 2007.)

VI. Lesions commonly are symmetrical, often involving lower extremities first, then upper extremities
VII. Rest of skin surface follows as disease progresses and patients become immobilized
VIII. The face is spared
IX. Five percent have rapidly progressive course (2 weeks)
X. Systemic involvement may be silent or evident by organ failure

Diagnosis

I. Made by history and physical examination, but biopsy is essential to confirm the diagnosis
II. If a case is confirmed, it should be communicated to the NSF registry noted
III. Pathological characteristics of skin biopsy (Figs 8 and 9)
   A. Thickened dermis
   B. An increase in collagen bundles with clefts
   C. Increased interstitial mucin deposition
   D. Proliferation of dermal spindle cells (which stained positive for CD34/procollagen I)
   E. Lack of inflammatory cells
   F. Circulating fibrocytes (CFs) with a dual positive CD34/procollagen I immunologic profile are blood-borne cells responsible for the fibrosis seen with this disorder

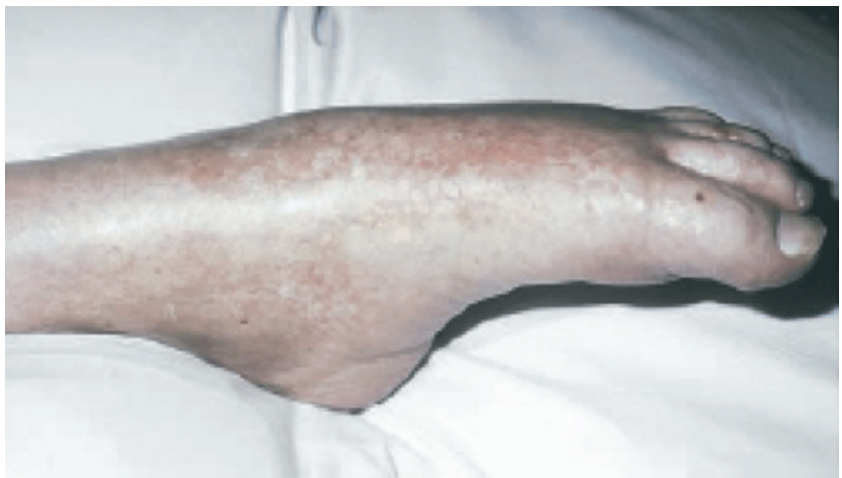

Figure 7. Foot image from a patient with nephrogenic systemic fibrosis shows thickening of the skin with peau d'orange appearance. (Reprinted with permission from Cowper SE. Nephrogenic fibrosing dermopathy [NFD/NSF Website]. 2001-2007. Available at: http://www.icnfdr.org. Accessed June 7, 2007.)

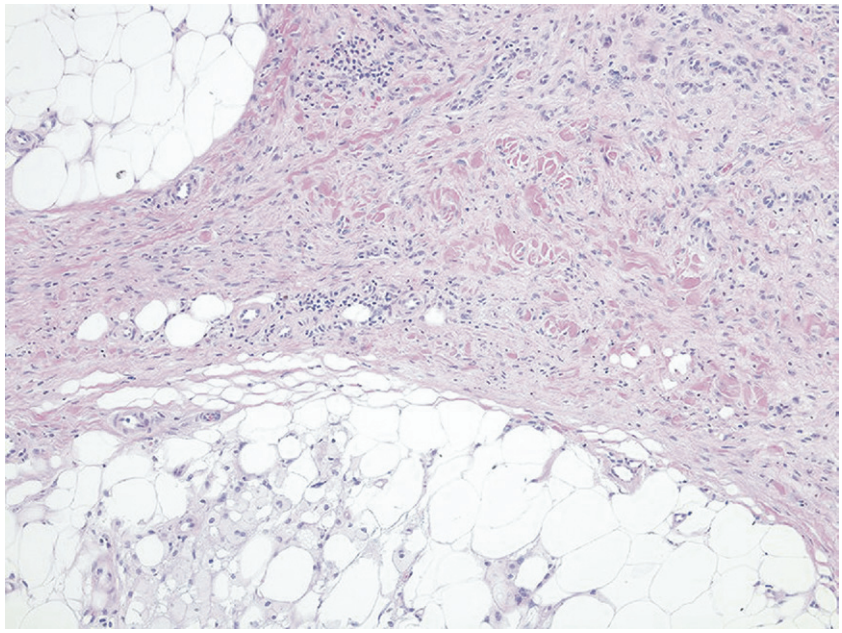

Figure 8. Skin biopsy from a patient with nephrogenic systemic fibrosis shows thickened dermis and increased collagen bundles with interstitial mucin deposition at low power. (Reprinted with permission from Cowper SE. Nephrogenic fibrosing dermopathy [NFD/NSF Website]. 2001-2007. Available at: http://www.icnfdr.org. Accessed June 7, 2007.)

1. These cells normally respond to tissue or endothelial injury and enter tissue to repair and build scar tissue
2. In patients with NSF, CF cells circulate in the blood and by an unknown mechanism enter the uninjured dermis and differentiate into cells that resemble dermal fibroblasts that cause fibrosis

Pathophysiology

I. Initially, the dialysis procedure or equipment was believed to predispose patients to NSF, but with approximately 10% of cases occur-

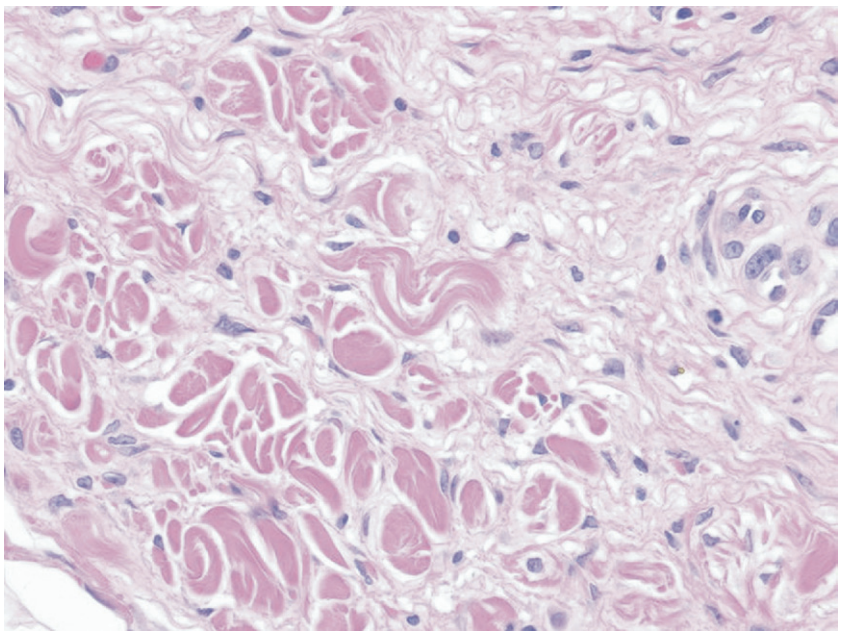

Figure 9. Skin biopsy from a patient with nephrogenic systemic fibrosis shows thickened dermis and increased collagen bundles with interstitial mucin deposition at high power. (Reprinted with permission from Cowper SE. Nephrogenic fibrosing dermopathy [NFD/NSF Website]. 2001-2007. Available at: http://www.icnfdr.org. Accessed June 7, 2007.)

ring in patients who have not been on dialysis therapy, this theory is untenable

II. Endothelial dysfunction and injury, commonly found in patients with CKD and ESRD, may predispose to NSF

III. Other cofactors explored without definitive proof of their role include:
   1. Coagulation abnormalities (hypercoagulable states)
   2. Administration of high-dose recombinant erythropoietin
   3. Angiotensin-converting enzyme inhibitors
   4. "Vascular trauma" (in the form of central catheter placement, deep venous thrombosis, thrombosed arteriovenous access, or vascular surgery)
   5. Proinflammatory states

IV. Mechanism associated with gadolinium as noted next

Role of Gadolinium (Gd^{3+})

I. The Food and Drug Administration released a public health advisory in June 2006 reporting the increased incidence of NSF after gadolinium contrast exposure for MRI

II. Since then, the NSF registry maintained at Yale University confirmed that 95% of the 239 cases collected in the registry had confirmed exposure to gadolinium before the onset of the disease

III. Guidelines for the use of gadolinium contrast agents in patients with CKD and AKI need to be developed

IV. What is gadolinium contrast?
   A. Gadolinium is atomic number 64 on the periodic table in the Lanthanide series
   B. Gadolinium has paramagnetic properties that make it ideal as a contrast agent for MRI
   C. Gadolinium is extremely toxic to tissues; thus, in contrast preparations, it is stabilized by "chelate," large organic molecules the bind gadolinium and do not readily associate, causing the gadolinium to be inert
   D. Chelate preparations vary among manufacturers, with differences in configurations (macrocyclic versus linear) or charge (ionic versus nonionic) that lend some chelates to more readily dissociate from gadolinium
      1. Linear and nonionic preparations more likely to dissociate
   E. Normally, contrast is excreted by kidney through glomerular filtration
      1. In the setting of reduced glomerular filtration rate (GFR), the half life (t½) of these agents is increased, thereby increasing the risk of dissociation of gadolinium from its chelators and potentially increasing the risk of toxicity
         a) CKD stage 3 (GFR, 30 to 60 mL/min): t½ approximately 5 hours
         b) CKD stage 4 (GFR, 15 to 30 mL/min): t½ approximately 9.6 hours
         c) CKD stage 5 (GFR, 0 to 15 mL/min): t½ approximately 34 hours
   F. Gadolinium contrast agents currently available in the United States
      1. Gadodiamide (Omniscan; GE Healthcare, Waukesha, WI)
      2. Gadopentetate (Magnevist; Hospira, Lake Forrest, IL)
      3. Gadoversetamide (OptiMARK; Mallinckrodt/Tyco Healthcare, Hazelwood, MO)
      4. Gadobenate (MultiHance; Bracco Diagnostics, Princeton, NJ)
      5. Gadoteridol (Prohance; Bracco Diagnostics, Princeton, NJ)
   G. Gadolinium contrast is cleared effectively by HD, with studies showing elimination of 73.8% after 1 dialysis treatment, 92.4% after 2 treatments, and 98.9% after 3 treatments
      1. PD clearance appears to be poor

II. Possible mechanism of toxicity with NSF
   A. Although data are not clear, the longer t½ of gadolinium contrast in patients with reduced GFR likely leads to an increase in dissociation of gadolinium from its chelate
   B. This increases tissue exposure to gadolinium and, in the setting of chronic inflammatory states, vascular injury, and endothelial dysfunction, gadolinium may enter dermal and solid organ tissues
      1. Scanning electron microscopy and energy-dispersive x-ray spectroscopy

Table 1. Medical Therapies Possibly Offered for Nephrogenic Systemic Fibrosis

Drug	Administration	Comments
Oral prednisone	1 mg/kg/d orally	Some mild efficacy in some patients Patients should be warned of side effects of steroid therapy
Topical Calcipotriene	Apply daily under occlusion	Anecdotal evidence only
Thalidomide	Oral	No formal data available
Cyclophosphamide	Oral	No data to show success
Ultraviolet therapy	Psoralen ultraviolet irradiation (PUVA)	Anecdotal data suggest it may have a role, but is limited to just a few cases
Pentoxifylline	1,200 mg/d orally	Disease stabilized in 2 patients (case reports) Possible mechanism is anti–tumor necrosis factor α activity
Immunoglobulin	Intravenous	Data poor to support this
Plasmapheresis	Intravenous	Data from case reports mixed, but it is unlikely to have a significant effect
Extracorporeal photopheresis	Intravenous	Data mixed, but may have a role in patients with a recent diagnosis. Data for patients who had the disease longer are poor

showed gadolinium in tissues of patients with NSF
2. Subsequently, another group of investigators showed gadolinium levels in tissues 35- to 150-fold higher than in healthy patients exposed to gadolinium contrast

C. Gadolinium that has entered tissues may be phagocytosed by macrophages, which release profibrotic cytokines and signals that attract CFs to tissues
D. CF cells appear to be the causative agents for the fibrosing process

III. Risk of developing NSF with gadolinium exposure
A. Absolutely requires reduced GFR (AKI, CKD, or ESRD)
B. Increases with higher doses of gadolinium contrast administered
C. Increases in the setting of a proinflammatory state
D. A small case-control study showed an absolute risk of 3.4% in a patient exposed to gadolinium contrast
E. A case-control study from the Centers for Disease Control and Prevention showed the risk to be greater in patients on PD than HD therapy, likely related to reduced gadolinium clearance
F. Although the development of NSF after gadolinium contrast exposure likely is a class effect, approximately 85% of cases reported were with gadodiamide and 15% with gadopentetate
1. Linear non-ionic chelate more likely to dissociate

IV. Prevention of NSF with gadolinium exposure
A. Limit exposure to gadolinium contrast unless absolutely necessary in patients with CKD
1. Computed tomographic (CT) scan with low or iso-osmolar IV contrast may be acceptable risk to take if appropriate prophylaxis for contrast nephropathy (IV fluids, *N*-acetylcysteine) is given
2. This decision should be weighed on a patient-specific basis

B. If gadolinium must be administered to patients with:
1. CKD stage 5 on HD or PD therapy:
a) practitioners should consider following exposure with two 4-hour HD treatments to remove gadolinium contrast
b) there is no role for intensive PD because removal by this modality is poor
2. CKD stage 3 and 4: there are no convincing data to date to initiate these patients on dialysis therapy for preventive purposes

V. Treatment of patients with NSF:

A. There is no reliably effective treatment for patients with NSF
B. Improving kidney function by resolution of AKI or transplantation anecdotally appears to slow or stop the progression of NSF, and in some patients, symptoms may improve over time
C. Given the rarity of this disease, there are no large randomized controlled trials of therapy
D. Physical therapy has an important role to increase and maintain mobility
   1. Swimming may help prevent contractures
   2. Deep-tissue massage was reported to be helpful
E. Multiple medical therapies have been attempted with minimal success (Table 1)

ADDITIONAL READING

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3. DeHoratius DM, Cowper SE: Nephrogenic systemic fibrosis: An emerging threat among renal patients. Semin Dial 19:191-194, 2006
4. Perazella MA, Rodby RA: Gadolinium use in patients with kidney disease: A cause for concern. Semin Dial 20:179-184, 2007
5. High WA, Ayers RA, Cowper SE: Gadolinium is quantifiable within the tissue of patients with nephrogenic systemic fibrosis. J Am Acad Dermatol 56:710-712, 2007
6. Perazella MA: Nephrogenic systemic fibrosis, kidney disease and gadolinium: Is there a link? Clin J Am Soc Nephrol 2:200-202, 2007

DERMATOLOGIC MANIFESTATIONS ASSOCIATED WITH COMMON KIDNEY DISEASES

Henoch-Schönlein Purpura

I. Early phases show erythematous wheels that may be macular or urticarial
II. Over time, these coalesce to petechiae and palpable purpura
III. Typically symmetrical
IV. Occur in dependent or pressure areas

Cryoglobulinemia

I. Dermatological manifestations early in disease course
II. Erythematous macules over lower extremities
III. Also possible
   A. Raynaud phenonomenon
   B. Livido reticularis
   C. Acrocyanosis
IV. Capillarioscopy shows tortuous nail bed vessels

Systemic Lupus Erythematosus

I. Malar rash
   A. Histological examination may show immunoglobulin and complement at the dermal-epidermal junction
II. Discoid lupus: erythematous plaques with adherent scale
   A. Usually on face, neck, scalp, or upper torso
   B. Histological examination shows hyperkeratosis, follicular plugging, and thickened basement membrane
III. Bullous skin lesions: subepidermal bullous lesion from toxic necrolysis of the skin on sun-exposed areas
IV. Oral ulcers
V. Alopecia
VI. Nail changes: pitting, ridging
VII. Photosensitivity
VIII. Livido reticularis: erythematous, blanching, reticulated rash
   A. Often associated with antiphospholipid antibodies
IX. Telangectasias
X. Raynaud phenomenon
XI. Lupus tunidus: violaceous papules or nonscarring plaques
   A. Intense $CD3^+/CD4^+$ lymphocytic infiltration

Atheroembolic disease

I. Livido reticularis
II. Cyanosis
III. Gangrene
IV. Ulcerations
V. Petechiae or purpura

ADDITIONAL READING

1. Petri M: Dermatologic lupus: Hopkins Lupus Cohort. Semin Cutan Med Surg 17:219-227, 1998
2. Berk DR, Mallory SB, Keeffe EB, Ahmed A: Dermatologic disorders associated with chronic hepatitis C: Effect of interferon therapy. Clin Gastronterol Hepatol 5:142-151, 2007