Cutaneous Manifestations of ESRD

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Summary
A broad range of skin diseases occurs in patients with ESRD: from the benign and asymptomatic to the physically disabling and life-threatening. Many of them negatively impact on quality of life. Their early recognition and treatment are essential in reducing morbidity and mortality. The cutaneous manifestations can be divided into two main categories: nonspecific and specific. The nonspecific manifestations are commonly seen and include skin color changes, xerosis, half-and-half nails, and pruritus. The specific disorders include acquired perforating dermatosis, bullous dermatoses, metastatic calcification, and nephrogenic systemic fibrosis. This review article describes these conditions and considers the underlying pathophysiology, clinical presentations, diagnosis, and treatment options.


Introduction
In 2010 in the United States, 593,086 patients received treatment for ESRD (1). A broad range of skin diseases occurs in these patients: from the benign and asymptomatic to the physically disabling and life-threatening. Many of them negatively impact on quality of life. The prevalence of ESRD is increasing, and it is, therefore, likely that the incidence and prevalence of associated skin diseases will also increase. Their early recognition and treatment to reduce morbidity and mortality are essential.

Many factors are involved in the pathogenesis of the cutaneous manifestations of ESRD, including electrolyte imbalance, buildup of uremic substances, and comorbid disease (2). Some conditions are easily diagnosed but can be difficult to manage. Others are less straightforward to diagnose, largely because of clinical similarities with more common diseases, and they are notoriously difficult to manage.

In this review, we focus on two main categories of the cutaneous manifestations of ESRD: nonspecific and specific. Nonspecific manifestations include pruritus, which will be discussed in detail, as well as skin color changes, xerosis, and half-and-half nails, which are briefly described. Specific manifestations include acquired perforating dermatosis, bullous dermatoses, metastatic calcification, and nephrogenic systemic fibrosis, all of which will be considered in depth. Underlying pathophysiology, clinical presentations, diagnosis, and treatment options are considered.

Nonspecific Manifestations
Skin color changes, such as pallor and hyperpigmentation, are seen in approximately 40% and 20% of patients, respectively (3,4). Half-and-half nails (or Lindsay’s nails) are seen in approximately 20% of patients, and xerosis (dry and scaly skin) is seen in 50%–85% of patients with ESRD (3,4). The clinical manifestations, pathogenesis, treatment options, and dermatological sequelae of these nonspecific manifestations are set out in Table 1 (3–10).

Pruritus is one of the most common symptoms associated with ESRD. The exact pathophysiology of uremic pruritus is unknown, but it is likely multifactorial. Possible etiological factors are presented in Table 2 (11–15). There is conflicting evidence regarding the relationship between the onset and severity of pruritus and the duration of ESRD and dialysis therapy (11,12,16). No clear association between pruritus and underlying renal disease has been established (12). The proportion of ESRD patients with uremic pruritus has decreased significantly with modern dialysis from approximately 85% in the 1970s to the present day rate of 40%–50% (11,17,18).

Uremic pruritus may be localized or generalized. The frequency, severity, and clinical characteristics vary widely, ranging from mildly irritating, to severely debilitating (19). Patients frequently present with excoriations, lichen simplex chronicus, or prurigo nodularis from continuous scratching (Figure 1B) (11).

Before making the diagnosis of uremic pruritus, other causes of pruritus must be ruled out. Uremic pruritus is difficult to treat. A summary of effective treatments that decrease the severity of pruritus is presented in Table 3. No single agent has been shown to be universally effective. Topical therapy, aimed principally at alleviating the xerosis that many ESRD patients have, has been of moderate benefit. Only a few oral medications have shown any significant efficacy, and ultraviolet B phototherapy has been used with some reported success. Optimal treatment is individualized and usually requires combination therapy (43).

Specific Manifestations
Acquired Perforating Dermatosis
Perforating disorders are a heterogeneous group of dermatoses characterized by transepidermal elimination of dermal structures. The perforating disorders seen in ESRD, known as acquired perforating...
dermatosis (APD), are both clinically and histologically similar to the primary perforating dermatoses. The majority of affected patients are African American, and there is a strong association with CKD and diabetes mellitus (44–46). APD usually develops after dialysis treatment has started (44–47). The prevalence in dialysis patients is between 2% and 11% (45,48).

The exact pathophysiology is unknown. Localized skin irritation, typically from scratching, may cause an inflammatory cutaneous reaction to uremic substrates in the dermis, leading to lesion formation (45,46). Patients present with moderate to severe pruritus in the affected skin areas and characteristically have pruritic, firm, dome-shaped papules or nodules with a central keratotic plug distributed on the extensor surfaces of the extremities and trunk (Figure 2). Koebnerization (formation of lesions in areas of skin trauma, most notably from scratching) is common. Spontaneous resolution can occur (44–46).

Histologically, these disorders are characterized by transepidermal elimination of dermal substrates, such as collagen, keratin, and elastic fibers (Figure 2) (44,47). The diagnosis of APD is made clinically and confirmed with a lesional skin biopsy. Individual case reports and small case series have provided evidence of effective treatment with topical, systemic, and other therapies, such as phototherapy and cryotherapy. This information is presented in Table 4. To date, there has not been a randomized controlled trial to evaluate the efficacy of a single treatment.

| Table 1. Nonspecific cutaneous manifestations seen in ESRD patients (Figure 1) |
|---|---|---|---|
| Disorder (Refs.) | Clinical Manifestations | Pathogenesis | Treatment |
| Skin color changes (3–6) | Pallor | Attributed to anemia of chronic disease | May improve with erythropoietin |
| | Yellowing of the skin | Secondary to excessive deposition of urochrome and carotenoids | No skin treatment available |
| | Hyperpigmentation | Secondary to increased levels of melanocyte-stimulating hormone | Daily sunscreen and sun protection |
| | Ecchymoses | Associated with platelet dysfunction from elevated urea and creatinine | Routine dialysis can reduce ecchymosis |
| Xerosis (dry skin) (7–9) | Patients present with dry, scaly skin on the trunk and extensor surfaces of the extremities | Exact mechanism is not clear; it is believed that the xerosis is caused by dehydration of the stratum corneum and reduced sebum and sweat production secondary to sebaceous and sweat gland atrophy, respectively | Apply emollients daily |
| | Pruritus is common and can range from mild to severe | | Avoid known skin irritants |
| | | | Wear nonirritating fabrics |
| Half-and-half nails (also known as Lindsay’s nails) (4,10) | Seen in ~20% of uremic patients; distal half of the nail appears normal or brown, and the proximal half appears white | Exact mechanism is unknown; one hypothesis is that there is an increased tissue concentration of melanocyte-stimulating hormone | No nail treatment available |

| Table 2. Etiologic factors involved in uremic pruritus (11–15) |
|---|---|---|---|
| Electrolyte Abnormalities | Endocrine Disorders | Neurocutaneous | Other |
| Hypervitaminosis A | Secondary hyperparathyroidism | Abnormal signaling within cutaneous C nerve fibers | Xerosis (dry skin) |
| Hypercalcemia | Peripheral neuropathy | Elevated levels of inflammatory cytokines IL-2 and -6 |
| Hyperphosphatemia | Increased serum β-endorphin, a μ-receptor agonist, in hemodialysis patients | Iron deficiency anemia |
| Hypermagnesemia | Substance P | ↑ Amounts of dermal mast cells and histamine |
| | | ↑ Serum C-reactive protein |
| | | ↑ γ-Aminobutyric acid |
Bullous Diseases

Bullous diseases manifest with vesicular/bullous eruptions on the skin and/or mucous membranes. In ESRD, porphyria cutanea tarda and pseudoporphyria may be seen (4,62). Both are caused by the accumulation of photosensitive molecules in the skin that, on ultraviolet light exposure, leads to skin fragility and vesiculation on sun-exposed areas (4).

Porphyrnia cutanea tarda (PCT) is characterized by uroporphyrinogen-decarboxylase (URO-D) deficiency or dysfunction. Alcohol abuse, hepatitis C virus, HIV infection, and iron supplementation contribute to decreased URO-D activity (63). Porphyrins may form complexes with high-molecular weight proteins, which are poorly dialyzed by conventional methods. In hemodialysis (HD) patients, PCT occurs secondary to decreased URO-D activity and poor clearance of the plasma porphyrins (63,64). PCT is uncommon with peritoneal dialysis (PD), most probably because PD achieves more effective clearance of larger molecules (63).

Pseudoporphyria is clinically and histologically identical to PCT without the serum and urine porphyrin abnormalities. The pathophysiology in ESRD patients is unknown. Patients with PCT and pseudoporphyria have skin

Figure 1. | The nonspecific cutaneous manifestations seen in ESRD. (A) Patches of xerotic eczema on the lateral thigh. (B) Lichenified plaque with few excoriations on the antecubital fossa from repeated scratching. (C) Half-and-half nails with the characteristic proximal white half of the nail and the distal red half of the nail. (Courtesy of Timothy G. Berger.)
### Table 3. Effective treatments to decrease the severity of uremic pruritus in dialysis patients

<table>
<thead>
<tr>
<th>Drug or Therapy</th>
<th>Dose Range</th>
<th>Ref.</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Outcome: Percent Decrease in Mean Pruritus Score (Based on VAS)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gabapentin</strong></td>
<td>100–300 mg PO three times per week after each dialysis session</td>
<td>20</td>
<td>2004</td>
<td>25</td>
<td>86% decrease in the treatment group versus 9.5% in controls</td>
<td>Used 300 mg PO three times per week for 1 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21</td>
<td>2007</td>
<td>34</td>
<td>92.8% decrease in the treatment group versus 21% in controls</td>
<td>Used 400 mg PO two times per week after each dialysis session for 1 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>2009</td>
<td>34</td>
<td>93.5% decrease in the treatment group versus 18% in controls</td>
<td>Used 100 mg PO three times per week for 1 mo</td>
</tr>
<tr>
<td><strong>Pregabalin</strong></td>
<td>25–75 mg PO daily</td>
<td>23</td>
<td>2010</td>
<td>16</td>
<td>77.2% decrease</td>
<td>Prospective trial without control group; used 25 mg PO daily for 1 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
<td>2012</td>
<td>50</td>
<td>79.2% decrease in pregabalin group versus 77.9% decrease in gabapentin group (equivalent efficacy)</td>
<td>All participants had established peripheral neuropathy and/or neuropathic pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>2012</td>
<td>12</td>
<td>69% decrease</td>
<td>Prospective trial without control group; used 25 mg PO three times per week (if ineffective, dose ↑ to 25–50 mg PO daily for 24 wks)</td>
</tr>
<tr>
<td><strong>Nalfurafine</strong></td>
<td>5 µg iv three times per week directly after each HD session</td>
<td>26</td>
<td>2005</td>
<td>144</td>
<td>40% decrease in treatment group versus 19% in control group</td>
<td>Study I: Parallel group design, 1-mo duration, 5 µg iv three times per week directly after each HD session</td>
</tr>
<tr>
<td></td>
<td>2.5–5 µg PO nightly</td>
<td>27</td>
<td>2010</td>
<td>337</td>
<td>35.4% decrease in treatment group versus 20% in control group</td>
<td>Study II: Crossover design, 2-wk treatment period, 3-wk washout period, 1-wk run-in period, and 2-wk treatment period; results of both studies similar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28</td>
<td>2012</td>
<td>211</td>
<td>58.9% decrease</td>
<td>Used 2.5 or 5 µg PO nightly for 2 wks; results between different dosing groups were the same</td>
</tr>
<tr>
<td><strong>Cromolyn</strong></td>
<td>135 mg PO TID</td>
<td>29</td>
<td>2010</td>
<td>62</td>
<td>89.6% decrease in treatment group versus 34.2% in control group</td>
<td>Open-label, single-arm, prospective trial; used 5 µg PO nightly for 52 wks</td>
</tr>
<tr>
<td><strong>Topical cromolyn sodium 4% cream daily</strong></td>
<td></td>
<td>30</td>
<td>2012</td>
<td>60</td>
<td>88% decrease in treatment group versus 51.6% in control group</td>
<td>4-wk trial</td>
</tr>
</tbody>
</table>
Table 3. (Continued)

<table>
<thead>
<tr>
<th>Drug or Therapy</th>
<th>Dose Range</th>
<th>Ref.</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Outcome: Percent Decrease in Mean Pruritus Score (Based on VAS)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sericin cream</td>
<td>Sericin 8% cream BID</td>
<td>31</td>
<td>2012</td>
<td>50</td>
<td>68.4% decrease in treatment group</td>
<td>Intersubject control using a split-body biometrological assessment. 6-wk trial</td>
</tr>
<tr>
<td>High-permeability HD</td>
<td>High-permeability dialyzers</td>
<td>32</td>
<td>2009</td>
<td>116</td>
<td>69.3% decrease in treatment group versus 11.5% in control group</td>
<td>HD was performed three times per week for 12 wks; high-permeability dialyzers (F60; Fresenius) were used, with polysulphone membranes of 1.3 m² and an ultrafiltrate coefficient of 40 ml/h per mmHg</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>Capsaicin 0.03% ointment</td>
<td>33</td>
<td>2010</td>
<td>34</td>
<td>Not based on VAS; 84.3% decrease in treatment group versus 52% in control group</td>
<td>Crossover design with 4 wks of treatment, a 2-wk washout period, and 4 wks of treatment; because of the burning sensation with the initial use of capsaicin, it is highly likely that those patients knew their group assignment. Did not use VAS; scored pruritus based on severity, distribution, and sleep disorder 4-wk trial</td>
</tr>
<tr>
<td>Pramoxine</td>
<td>Pramoxine 1% lotion BID</td>
<td>34</td>
<td>2009</td>
<td>28</td>
<td>61% decrease in treatment group versus 12% in control group</td>
<td>6-wk trial; open pilot trial, with only 10 patients completing the trial</td>
</tr>
<tr>
<td>Narrow-band UVB therapy</td>
<td>Narrow-band UVB to whole-body surface</td>
<td>35</td>
<td>2005</td>
<td>20</td>
<td>70.8% decrease in treatment group</td>
<td>Open-label trial with two groups: Group 1 had 17 patients with uremic pruritus, and group 2 had 29 patients with idiopathic pruritus 6-wk treatment period</td>
</tr>
<tr>
<td></td>
<td>Three times per week</td>
<td>36</td>
<td>2007</td>
<td>46</td>
<td>54.2% decrease in group 1 after a mean of 22 treatments; 67.9% decrease in group 2 after a mean of 22 treatments</td>
<td>Single-blind, randomized, controlled trial; 6-wk treatment period</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37</td>
<td>2011</td>
<td>21</td>
<td>54.9% decrease in treatment group Versus 59.3% in control group³</td>
<td>Control group received matched UVA treatments</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50 mg PO daily</td>
<td>38</td>
<td>2012</td>
<td>19</td>
<td>Not based on VAS; 57.8% of patients had improved pruritus severity from severe or moderate to weak</td>
<td>Open-label, single-arm, prospective trial for 4 mos of active treatment; severity graded by a researcher-developed 30-item inventory (content validity for this form was 0.82)</td>
</tr>
<tr>
<td>γ-Linolenic acid</td>
<td>Topical γ-linolenic acid 2.2% cream to entire body daily and TID to pruritic areas</td>
<td>39</td>
<td>2006</td>
<td>17</td>
<td>51.2% decrease in treatment group (group A) versus 15% in control group (group B) After crossover, 45.51% decrease in treatment group (group B) versus 11.2% in control group (group A)</td>
<td>Crossover design with two groups randomized into treatment versus urea cream control; 2-wk treatment periods with a 2-wk washout period</td>
</tr>
<tr>
<td>Drug or Therapy</td>
<td>Dose Range</td>
<td>Ref.</td>
<td>Year</td>
<td>Number of Patients</td>
<td>Outcome: Percent Decrease in Mean Pruritus Score (Based on VAS)</td>
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<tr>
<td>Thalidomide</td>
<td>100 mg PO</td>
<td>40</td>
<td>1994</td>
<td>29</td>
<td>Not based on VAS</td>
<td>Crossover design; 1-wk treatment periods with a 1-wk washout period (pruritus intensity was scored TID from zero to three); Response in control group could be caused by placebo effect versus carryover effect</td>
</tr>
<tr>
<td></td>
<td>QHS</td>
<td></td>
<td></td>
<td></td>
<td>78% decrease in treatment group versus no change in control group</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>After crossover, 81% decrease in treatment group versus 54% in control group</td>
<td></td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>Activated powdered charcoal 6 g PO daily</td>
<td>41</td>
<td>1995</td>
<td>23</td>
<td>Not based on VAS</td>
<td>Nonrandomized, single-blind, controlled trial for 6 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70.4% decrease</td>
<td></td>
</tr>
<tr>
<td>Glycerin and paraffin emulsion</td>
<td>Glycerin 15% and paraffin</td>
<td>42</td>
<td>2011</td>
<td>100</td>
<td>Did not compare change in VAS in period I</td>
<td>Pruritus intensity scored from one to six; 10 patients initially given a placebo for 1 wk before all patients received treatment (data from 10 patients only)</td>
</tr>
<tr>
<td></td>
<td>10% in an oil and water emulsion BID</td>
<td></td>
<td></td>
<td></td>
<td>75% overall decrease at the end of open-label period (period II)</td>
<td></td>
</tr>
</tbody>
</table>

All therapies listed showed a statistically significant reduction in the mean pruritus score. All are randomized, double-blind, and controlled trials unless otherwise noted in the comments. VAS, visual analog scale; PO, per os; HD, hemodialysis; iv, intravenous; TID, three times daily; BID, two times daily; UVB, ultraviolet B; UVA, ultraviolet A; QHS, nightly.

*Lack of statistical significance could be attributed to small sample size, effect of UVA on pruritus, or placebo effect.*
photosensitivity and fragility, and they present with tense vesicles/bullae, erosions, and crusts distributed on the face, extensor surface of the forearms, and dorsal hands (Figure 3). Lesions typically heal with atrophic scarring and milial cysts (Figure 3C). Sclerodermatous plaques, hypertrichosis, and hyperpigmentation in sun-exposed areas are also seen in patients with PCT but not patients with pseudoporphyria.

Increased serum levels of iron and ferritin, increased urinary uroporphyrin excretion, and increased levels of plasma uroporphyrin in anuric patients are typical in PCT (63,64). Treatment of PCT includes avoiding triggers, like alcohol, hepatotoxic medications, and sun exposure, and using sunscreen. Decreasing iron overload is effective for symptom management. The combination of erythropoiesis-stimulating agents with small volume phlebotomy (50–100 ml once or twice weekly) to decrease hepatic iron stores can induce remission within several months. Alternatively, deferoxamine can be used intravenously with each dialysis session in those patients unable to tolerate phlebotomy (63,64). High-flux membrane HD, which is more effective at removing plasma porphyrins, is an effective adjunct (63).

Treatment of pseudoporphyria involves stopping/avoiding any of the medications known to induce the disease (for example, diuretics, antibiotics, and antifungals) as well as

Figure 2. | Acquired perforating dermatosis. (A and B) Multiple clustered, hyperpigmented, dome-shaped nodules and coalescing plaques with a central keratotic plug. (C) Hyperpigmented macules and patches from lesions that have resolved. (D) There is a cup-shaped epidermal depression filled with parakeratosis and neutrophilic debris. At the base of the depression, the epidermis is thinned, and degenerated collagen fibers are noted protruding through this attenuated epidermis. (Courtesy of Timothy G. Berger, Anna K. Haemel, and Thaddeus W. Mully.)
The exact pathogenesis of CUA is unclear but multifactorial. Metabolic factors, systemic inflammation, oxidative stress, and endothelial injury along with certain triggers have been implicated. Risk/triggering factors include local trauma, women (73,74), Caucasian ethnicity (75), hypoalbuminemia (72,74,75), therapy with calcium salts, vitamin D supplements, erythropoiesis-stimulating agents (69,70,76), warfarin (72–74,77), and iron supplements (78). Other independent risk factors include obesity (body mass index >30 kg/m²) (69,73,74), liver disease (69,79), and systemic corticosteroids (65,69,73,74).

CKD/ESRD, dialysis therapy, and commonly occurring comorbid conditions, like hypertension, hypercholesterolemia, obesity, and diabetes mellitus, increase oxidative stress (69,74,76,80). Vascular calcification is promoted in the presence of increased oxidative stress by reactive oxygen species that also leads to a state of systemic inflammation, which is evidenced by increased levels of TNF-α, IL-1, and IL-6 (76). The body’s natural antioxidants, such as glutathione, are depleted when these disorders are chronic. Vascular calcification causes endothelial injury and luminal narrowing. The low-flow rate within cutaneous vessels, combined with luminal narrowing, leads to decreased blood flow and can cause blood stasis (73). It creates a procoagulant state in the narrowed vessels, which increases the risk of thrombus formation and can lead to localized tissue ischemia and necrosis (73,76). The relationship between the implicated etiologic factors in CUA and its pathogenesis is schematically represented in Figure 5.

Clinically, patients initially experience pain or localized tenderness associated with erythema, violaceous mottling, or reticulate discoloration of the skin that resembles livedo reticularis. Lesions progress over days to weeks to become severely painful plaques or nodules surrounded by a reticular purple discoloration (Figure 6). They tend to be distributed bilaterally and symmetrically, and they are most commonly located on the lower extremities, which may relate to poor circulation, as well as the abdomen and buttocks, both of which have large amounts of subcutaneous fat (69–72). Patients can present with hemorrhagic vesicles/bullae that precede the progression to necrosis and commonly develop painful, irregularly shaped, nonhealing ulcers. Lesion distribution, specifically proximal...
lesions (lesions on the trunk, thighs, and upper arms) versus distal lesions (lesions on the calves and forearms), does not seem to be a clear prognostic indicator as previously thought (69,74,80). Systemic symptoms secondary to vascular and extravascular calcification of internal organs and soft tissues may also occur. Patients may develop cardiac valve or electrical conduction dysfunction, myocardial, pulmonary, or cerebrovascular infarction (80,81), myositis, muscle weakness, and bowel infarction (70,80).

Histologically, calcification of small- and medium-sized blood vessels is seen in the dermis and subcutaneous tissue, although this finding can be quite subtle and may be missed. Typically, there is little or no inflammatory infiltrate, but panniculitis (inflammation of adipose tissue) is often seen (65,70). Fibrin thrombi within vessels, epidermal ulceration, and ischemic necrosis of the epidermis, dermis, and/or subcutaneous tissue may occur (65,70). Close examination, multiple tissue sections, and Von Kossa staining, highlighting the calcium deposits, may be required for an accurate diagnosis.

Patients may present with hypercalcemia, hyperphosphatemia, elevated calcium-phosphate product, and elevated parathyroid hormone (PTH) levels. However, more recent data suggest that calcium, phosphate, and PTH levels are often normal at presentation (69,72,74,80). Patients may also have raised inflammatory markers,
**Figure 4.** Calcinosi cutis. (A) Firm nodules on the palmar aspect of the fingers with central white calcium globules. (B) A calcified nodule around the knee. (C) A large, white, indurated calcified plaque on the right posterior shoulder and arm. (D) A linear, white calcified plaque in the axilla. (E) A plain radiograph of the lower extremity showing radio-opaque soft tissue calcium deposits. (F) There is a nodular deposit of basophilic refractile calcium in the dermis (black arrows). Minimal inflammation is present. (Courtesy of Timothy G. Berger and Thaddeus W. Mully.)
Nuclear factor \( \kappa B \) (NF\( \kappa B \)), a transcription factor involved in the production of cytokines and inflammatory mediators, the receptor activator of NF\( \kappa B \) (RANK), and its ligand are vital for bone mineral resorption and development (68,73,76). They can be activated by chronic inflammatory states, parathyroid hormone (PTH), aluminum, corticosteroids, free radicals, and infectious agents (73,76). Increased NF\( \kappa B \) activity leads to bone mineral loss and vascular calcification. Osteoprotegerin (OPG) is an antagonist of RANKL. RANK/RANKL and OPG are expressed on endothelial cells, osteoblasts/osteoclasts, and vascular smooth muscle cells (VSMCs) (73,76). Transformation of VSMCs into osteoblast-like cells is initiated by metabolic disturbances (particularly hyperphosphatemia), reactive oxygen species (ROS), and decrease of local vascular calcification inhibitors, such as matrix \( \gamma \)-carboxy-glutamate protein (MGP), a vitamin K-dependent protein (68,76). Fetuin-A, a hepatically synthesized protein that functions systemically to inhibit vascular calcification, is reduced in inflammatory states, renal failure, and calcific uremic arteriolopathy (68,76). Progressive subintimal fibrosis and medial-arteriolar calcification lead to endothelial injury and luminal narrowing. The low-flow rate within the cutaneous vessels combined with luminal narrowing leads to decreased blood flow and may lead to blood stasis (73). Systemic inflammation also causes endothelial dysfunction. It creates a procoagulant state in the narrowed vessels and increases the risk of thrombus formation, which can lead to localized tissue ischemia and necrosis (73,76,78).
Figure 6. **Calcific uremic arteriolopathy.** (A) Violaceous, indurated plaque with surrounding reticular purple discoloration. (B) Violaceous reticulation resembling livedo reticularis. (C) Necrotic ulcerations on the right buttock and thigh. (D) Close view of a necrotic ulcer with a violaceous border. (E and F) Low- and high-power magnification views showing basophilic calcium deposits (at the tips of the black arrows) in the deep dermal blood vessels. Minimal associated inflammation is noted. More superficially, congested blood vessels are identified. Focal epidermal necrosis is present. (Courtesy of Timothy G. Berger, Anna K. Haemel, and Thaddeus W. Mully.)
hyperglycemia, and hypercholesterolemia (68,69,72–74). The typical serum biochemistry profile of a patient with ESRD presenting with CUA is set out in Table 5. In isolation, these metabolic abnormalities lack the sensitivity for predicting disease, but their presence should be noted, because they increase the patient’s risk for vascular calcification. Radiographic imaging may be helpful in making the diagnosis. Small vascular calcifications and a net-like pattern of soft tissue calcification have been described on plain radiography, although this finding has not been validated. Computed tomography can also identify calcified arterioles in the soft tissues as well as calcification of the viscera. These findings and other radiographic findings seen in CUA are summarized in Table 5 (81–83).

Early recognition, diagnosis, and treatment of CUA are paramount to halt disease progression. However, there is a paucity of controlled, prospective clinical trial data to guide treatment, which is often difficult and supportive. Pain relief takes weeks, and lesion resolution can take several months.

Management includes correcting serum calcium and phosphate levels. Serum electrolyte levels should be, where possible, maintained at target per National Kidney Foundation guidelines (84). Lowering the calcium concentration in the dialysate to 1.0–1.5 mEq/L as tolerated and intensifying dialysis to four to six times per week have been used (76,77). Bisphosphonates, both intravenous and oral preparations, have been used successfully, resulting in pain relief within days and lesion resolution within weeks (75,85,86). Although bisphosphonate use is controversial in those patients with a GFR <30 ml/min because of the potential risk of adynamic bone disease and direct nephrotoxicity (87), the benefit of decreasing morbidity and/or mortality in the case of CUA outweighs the risks. The use of parathyroidectomy in patients with normal or mildly elevated iPTH (<200 ng/L) is controversial and may even increase morbidity and/or mortality. Medical management for patients with normal or mildly elevated iPTH is the gold standard and should be used in preference to parathyroidectomy, which should only be considered in this setting if medical management fails. However, parathyroidectomy may be required for those patients with significant iPTH elevations (>300 ng/L). Survival benefit has not been consistently shown in small case series or larger retrospective studies (74,75,88,89).

Sodium thiosulfate is a dialyzable calcium chelator that increases the solubility of calcium deposits. Sodium thiosulfate also enhances antioxidant glutathione production, has vasodilatory properties by increasing endothelial nitric oxide production, and can reduce inflammation (75,80,90). It has been shown to relieve pain within days and lead to wound healing in approximately 8 weeks (75).

Several recent case reports suggest that Cinacalcet, a calcimimetic agent that increases parathyroid cell calcium sensitivity, can be used successfully in patients with normal and elevated PTH levels to normalize electrolyte levels and may serve as a medical alternative to parathyroidectomy (75,76,91,92). Optimizing the nutritional status and if needed, albumin replacement in select patients may be beneficial (75). Wound care, with gentle surgical debridement, has been shown to improve survival in retrospective studies. However, its use is controversial because of an

### Table 5. Common serum biochemistry laboratory tests and radiographic findings in calcific uremic arteriolopathy

<table>
<thead>
<tr>
<th>Laboratory Tests and Values</th>
<th>Findings (Ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory Tests</strong></td>
<td><strong>Findings</strong></td>
</tr>
<tr>
<td><strong>Value</strong></td>
<td><strong>Ref.</strong></td>
</tr>
<tr>
<td>Phosphate</td>
<td>Elevated</td>
</tr>
<tr>
<td>Calcium</td>
<td>Elevated</td>
</tr>
<tr>
<td>Calcium-phosphate product</td>
<td>Elevated</td>
</tr>
<tr>
<td>iPTH</td>
<td>Elevated</td>
</tr>
<tr>
<td>Calcium-phosphate product</td>
<td>Elevated</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Normal</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Normal</td>
</tr>
<tr>
<td>ESR</td>
<td>Normal</td>
</tr>
<tr>
<td>CRP</td>
<td>Normal</td>
</tr>
<tr>
<td>Aluminum</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Radiographic Findings</strong></td>
<td><strong>Ref.</strong></td>
</tr>
<tr>
<td>Plain x-ray</td>
<td>Small vascular calcifications (81,82)</td>
</tr>
<tr>
<td>CT scan</td>
<td>Net-like pattern of soft tissue calcifications (82)</td>
</tr>
<tr>
<td>Mammography</td>
<td>Soft tissue arteriolar calcifications (82)</td>
</tr>
<tr>
<td>Bone scan</td>
<td>Increased tracer uptake in affected areas of subcutaneous tissues (82)</td>
</tr>
</tbody>
</table>

*pHtH, intact parathyroid hormone; CT, computed tomography; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.*

**Note:** Plain imaging can miss small-vessel calcifications (81). Limited by affected tissue thickness (82).
increased risk of infection and the potential to induce new lesions or cause additional progression of lesions if the disease process is still active (69,70,74,75). Antibiotics, skin grafting, and biologic dressings can be used to prevent infection (70,89). A recent analysis of tissue plasminogen activator as an adjunctive therapy did not show a survival benefit. It did show variable degrees of wound healing but with some significant risks (93). More data are needed to assess the use of tissue plasminogen activator. Hyperbaric oxygen therapy (HBO) promotes wound healing by improving tissue oxygenation. HBO has been used successfully to reverse CUA progression (70,75,76,89). Reported side effects are minimal, but access and cost of HBO limit its use (75).

The clinical management of CUA is challenging. Interventions focused on treating the different causes of vascular calcification and hypercoagulability have been shown to be effective in one case series that used a standardized treatment approach (77). Controlling and minimizing the triggering factors are also important adjuncts (70,76,89). Additional investigation to evaluate the use of a multi-intervention standardized protocol for calciphylaxis is required.

Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis (NSF) is a scleroderma-like disorder caused by exposure to gadolinium-based contrast agents (GBCAs) used in diagnostic imaging. NSF is seen almost exclusively in patients with renal insufficiency with a GFR <30 ml/min; however, NSF in normouremic patients has been reported. Patients with a GFR <15 ml/min and severe AKI on dialysis and patients with ESRD on dialysis, especially PD, are at the highest risk of developing NSF (94,95). It can also occur in renal transplant patients with abnormal graft function. The international NSF registry contains over 335 confirmed cases (96); however, this number is likely an underestimate of the total number of cases, because misdiagnosis was common before NSF was well described and widely known. Increased awareness and routine screening of patients undergoing GBCA-enhanced magnetic resonance imaging/angiography have led to a reduction in the incidence of NSF over the last few years (94). NSF affects men and women equally. It has no known association with ethnicity or etiology of the patient’s primary renal disease. Most cases are seen in middle-aged adults, with an average age at onset of 51 years (94).

The pathogenesis of NSF is related to gadolinium (Gd) exposure, GFR, type and frequency of dialysis, and presence of a concomitant triggering event. Gd is renally eliminated. In patients with normal renal function, Gd has a half-life of 1–2 hours but is markedly increased (up to 60 hours) in patients with renal insufficiency or on dialysis (94,97). A prolonged half-life allows Gd to disassociate into its toxic ionic form, which can form precipitates with anions, such as phosphates, and lead to tissue deposition. After deposited in the tissues, dissociated Gd is phagocytized by macrophages, which may lead to the recruitment and/or activation of circulating fibrocytes (CFs) into the area (98–100).

CFs, are fibroblast-like collagen-producing spindle cells that circulate within the peripheral blood and enter areas of inflammation and tissue injury (98–100). They are involved in wound repair, fibrosis, and cytokine/chemokine production, including TGF-β1 and PDGF, both of which are involved in tissue fibrosis (98,99,101). CFs have been implicated in causing pathologic fibrosis, such as in keloid formation and scleroderma (98,99). The rapid development and
symmetry of NSF lesions and the proliferation of dermal spindle cells typically seen on biopsy specimens support the pathogenic role of CFs in NSF (98,99,101).

Patients with ESRD on PD, which is less effective at removing Gd than HD, and patients with an elevated serum phosphate level are at an increased risk of developing NSF (94,95). ESRD patients who receive a high dose (>0.2 mmol/kg) or multiple cumulative doses of GBCA (with an overall GBCA volume>0.2 mmol/kg) versus a single standard dose of GBCA (0.1 mmol/kg) and the use of linear or nonionic chelating agents pose the highest risk of NSF (94,101,102). Although no GBCA is risk-free, most cases have been associated with gadodiamide (Omniscan), a linear nonionic agent, which has less in vivo stability than the ionic and macrocyclic GBCAs (94,95,101).

Concomitant triggering factors include vascular injury (such as thrombosis and acute ischemia), infection, and high-dose erythropoietin therapy. These triggering factors are proinflammatory and stimulate the production of bone marrow-derived CFs, which increases CF migration (94,97,103).

Patients initially present with a severely painful, symmetrical erythema and edema that evolve into sclerodermatous and erythematous induration of the skin with firm papules/plaques and nodules (Figure 7). Lesions are commonly symmetrical, distributed on the lower extremities, and less often on the arms and trunk. Patients can have hyper- or hypopigmentation of the skin, skin thickening, and swelling, especially of the hands. Progression of skin fibrosis can lead to flexion contractures, causing limited joint mobility (94,100,101). Although rare, patients can have rapidly progressive fibrosis and fulminant disease, sometimes within weeks of disease onset (97). Patients may also complain of pain, burning, and pruritus at sites of fibrosis. Fibrosis can affect the lungs, heart, liver, kidneys, intestines, and skeletal muscle (94,97).

The prominent histologic feature of NSF on deep skin biopsy is dermal fibrosis with thickened collagen bundles. Proliferation of dermal spindle cells, increased stromal mucin, and minimal inflammatory infiltrate are common. The epidermis is usually unaffected (98,99), and patients may have abnormal calcification in the dermis and subcutaneous tissue (99,104). The entire dermis may be involved, with the fibrocytes extending through the subcutaneous tissue. Fibrosis can extend through the fascia and into the skeletal muscle, which can lead to atrophy (98).

Diagnosis is made after medical history and examination and confirmed by the histologic features. Diagnosis can be difficult, because the initial clinical presentation is often subtle and can mimic scleroderma. Clinicians must have a high index of suspicion in ESRD patients recently exposed to Gd. Avoiding linear and ionic GBCAs in patients with a GFR<30 ml/min or AKI, avoiding high-dose GBCA, and dialyzing patients as soon as is reasonably possible after GBCA exposure is recommended to prevent NSF (94).

Spontaneous improvement of NSF has been reported in a few cases of AKI that resolved quickly (94,97,100). Improving renal function seems to slow NSF progression and may improve the signs and symptoms of disease (96,105). Renal transplant for patients with NSF does not guarantee disease improvement, but the majority of cases has had successful outcomes, with skin softening and increased joint mobility (94,97,105,106). Treatments with limited benefit include oral corticosteroids, ultraviolet A phototherapy, plasmapheresis, sirolimus, high-dose intravenous Ig, methotrexate, and pentoxifylline (97,100,104,107). Several case reports of extracorporeal photopheresis have shown moderate clinical improvement (100,108,109). Physical therapy can also be used to decrease the extent of joint contractures and improve joint mobility (96,97).

Imatinib mesylate (Gleevec) blocks Abelson murine leukemia viral oncogene homolog 1 and PDGF receptor signal transduction involved in mediating fibrosis. Skin softening, improvement in lesion size, decreased pain, and increased mobility were reported in three cases with imatinib treatment (110,111). An open-label, nonrandomized, uncontrolled clinical trial of imatinib in four patients showed improvement in disease progression and symptom severity (112). Alefacept, which acts to inhibit the activation of CD4+/CD8+ T lymphocytes and also induces the apoptosis of memory effector T lymphocytes, has been shown to be effective in treating graft-versus-host disease, which has scleroderma features. Alefacept improved the cutaneous manifestations of three patients in a single case series (113). Sodium thiosulfate was shown to increase joint mobility, lead to skin softening, and decrease pain in one case series and one case report (114,115). These therapies are promising, but additional investigation is needed.

Conclusion

There is a broad range of cutaneous manifestations of ESRD. They can usefully be divided into nonspecific and specific categories. Although often benign, they may decrease patients’ quality of life and can be life-threatening. Increasing clinical awareness and implementing preventive strategies combined with early detection and treatment are all required to decrease the morbidity and mortality of dermatological disorders in ESRD patients.

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