23 Pruritus and Other Dermatological Problems in Chronic Kidney Disease

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Before You Start: Facts you Need to Know

- Pruritus is one of the most common cutaneous symptoms in patients with chronic kidney disease on dialysis. Treatments offer minimal relief.
- Xerosis cutis, another common finding in chronic kidney disease, can be treated with emollients.
- Disorders in calcium and phosphorus metabolism are common in patients with chronic kidney disease and include calciphylaxis and metastatic calcinosis cutis.

23.1 Pruritus

Pruritus is commonly seen in patients with chronic kidney disease (CKD) on dialysis. In the past, prevalence was reported to be as high as 90% in patients with CKD; however, more recently, rates of 20–56% of patients have been described [1, 2]. It seems to be independent of sex, ethnicity, type of dialysis, and underlying kidney disease. Pruritus itself is not immediately threatening, but it is an independent predictor of mortality [3].

23.1.1 What Causes Pruritus in Chronic Kidney Disease?

The pathophysiologic mechanism of uremic pruritus is poorly understood, but hypotheses implicate immune system dysregulation that results in a proinflammatory state leading to itching [4]. The increase in levels of C-reactive protein and other inflammatory mediators, particularly interleukin-13, contributes to the intensity of itch [5, 6]. Additionally, the derangement in calcium and phosphate metabolism that occurs in CKD can cause accumulation of these substances in the skin, which can further exacerbate pruritus [3]. Some also postulate that changes in neurological perception that occur with chronic itching increase the perception and sensation of itch [3]. The middle molecule theory is based on the idea that non-dialyzable substances accumulate and cause pruritus. This explains why the itching resolves after renal transplantation [7].

23.1.2 What Are the Important Clinical Characteristics?

Pruritus has a negative impact on quality of life. It is frequently disabling and can have a significant

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effect on mental well-being contributing to daytime fatigue, agitation, and depression [3]. Patients may have complaints ranging from intermittent itching to persistent pruritus, usually affecting the back and usually worse at night. The arms, head, and abdomen are also affected [3, 4]. Recurrent itching or rubbing of the skin in the setting of chronic pruritus may lead to lichenification, a focal thickening of the skin that typically presents with exaggerated skin lines. Patients with CKD presenting with itching and white scale formation may be exhibiting uremic frost, a cutaneous finding that generally occurs at blood urea nitrogen levels of approximately 200 mg/dl and is indicative of profound renal failure [8]. Because uremic frost tends to occur in hair-covered areas in men, it may be confused with seborrheic dermatitis.

23.1.3 How Is Pruritus in CKD Treated?

Treatment for pruritus associated with CKD is limited. The evidence for the treatments described in the literature is mostly anecdotal or based on case series [9]. When approaching a patient with pruritus, a stepwise approach may be helpful. Treatment of xerosis with emollients is essential because pruritus can be worsened by dry skin (xerosis). A trial of emollients containing menthol or pramoxine can be beneficial [3]. Topical capsaicin is also cited as being beneficial for localized pruritus but has not been effective in our clinical practice. Studies have demonstrated a dramatic reduction in pruritus with the use of topical tacrolimus [3], but this treatment may not be as effective and is not practical in patients with more diffuse pruritus.

Systemic treatments like gabapentin have been shown to be effective in some case studies [4]. However, other studies have also failed to demonstrate any improvement with gabapentin [4]. In cases where it is effective, gabapentin was shown to decrease the mean pruritus score with a dosage of 300 mg three times a day. There is an increased risk of gabapentin toxicity in patients on dialysis; therefore, it is recommended to start with a low dose and gradually increase until the maximum dose is reached [4]. Other treatment options that have recently gained attention include difelikefalin [10], sodium thiosulfate [11], cannabinoid formulations [12], and dupilumab [13].

Fig. 23.1 Lichenification in a CKD patient with pruritus

Broadband ultraviolet B (UVB) phototherapy is another treatment option for pruritus in CKD and is regarded by many clinicians as the treatment of choice. UVB light decreases the level of proinflammatory cytokines, which, as mentioned previously, may play a role in the pathogenesis of itch. Case series and pilot studies have shown UVB to be effective [4, 9]. It is important to consider the risk of skin cancer associated with UVB exposure because CKD patients are immunosuppressed and thus are predisposed to malignancy. This is especially important to consider if they have light skin types and are candidates for renal transplantation (Fig. 23.1).

23.2 Xerosis

Xerosis is a common cutaneous manifestation of CKD and was shown in at least three different studies to be the most prevalent of skin changes observed [14–16].

It is characterized by dryness of the skin, ichthyosis, roughness, and poor skin turgor [17]. The effects of this condition can lead to compromised functional integrity of the skin barrier resulting in increased susceptibility to contact irritants and infection. Some studies have reported a difference in prevalence of xerosis between patients receiv-

ing dialysis and those that are not receiving dialysis, but others have not observed any difference between these two groups [18].

23.2.1 What Causes Xerosis in CKD?

The cause of xerosis is unknown; however, many theories exist to explain its occurrence. The skin is a primary site of water homeostasis and with dialysis treatment and the associated high-dose diuretic therapies, water balance can be disturbed leading to skin dryness [17]. Other theories cite the reduction in size of sebaceous glands and eccrine sweat glands as the cause for xerosis [19].

23.2.2 What Are the Important Clinical Characteristics?

Xerosis can be generalized or localized and is most often located on the extremities. Patients complain of dry "cracked" skin that can be superimposed on uremic pruritus [19]. An important diagnosis to exclude is ichthyosis vulgaris as the clinical characteristics of this entity can closely resemble those of xerosis.

23.2.3 How Is Xerosis in CKD Treated?

It is important to ensure the skin is adequately lubricated. Daily use of gentle skin care and emollients can be helpful in treating xerosis and its associated symptoms [3]. In xerosis, there is a known decrease in glycerol content in the stratum corneum leading researchers to test the efficacy of emollients containing glycerol and paraffin. Glycerol has a hydrating effect, while paraffin protects the skin from irritants therapy addressing two of the major components of xerosis [20]. A recent study found that application of a heparinoid-containing product for an 8 week period is effective in treating xerosis in patients undergoing dialysis [21]. Traditional soaps should be avoided in the setting of xerosis, primarily since these products alkalinize the skin and damage the skin's moisture barrier. Instead, synthetic detergents such as syndet cleansers are preferred since their lower pH resembles the acidic pH of the skin and do not disturb its barrier function [22]. Other recommendations include bathing with lukewarm water, the use of humidifiers, and refraining from excessive skin washing (Fig. 23.2).

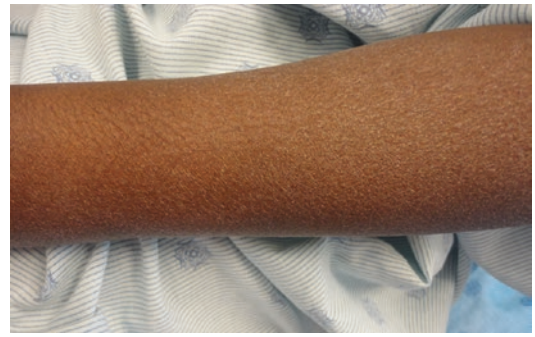

Fig. 23.2 Xerosis in a patient with CKD

23.3 Lindsay's (Half-and-Half) Nails

Lindsay's nails or half-and-half nails are a characteristic finding in patients with CKD. They are seen in patients with any degree of azotemia and present as a proximal white portion and distal reddish pink to brown portion of the nail. This specific nail finding is present in approximately one-third of patients with CKD [23]. Usually, this nail finding develops before patients need chronic dialysis, but it also is a frequent finding in patients on chronic dialysis [24]. A recent case series has reported the appearance of Lindsay's nails in patients with severe COVID-19 infection and without a history of known kidney disease [25].

23.3.1 What Causes Lindsay's Nails in CKD?

Although this condition is poorly understood, it is hypothesized that the distal brown band is the result of increased tissue concentration of beta-melanocyte-stimulating hormone due to its poor

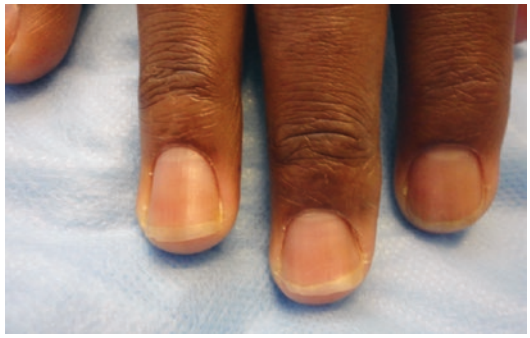

Fig. 23.3 Lindsay's (half-and-half) nails in a CKD patient. Note proximal white portion and distal reddish brown portion

dialyzability [19]. The white band, however, may result from long-standing anemia [26].

23.3.2 How Do you Treat Lindsay's Nails?

There are no treatments of Lindsay's nails, but the condition sometimes resolves with renal transplantation [19]. It has not been known to resolve with initiation of dialysis (Fig. 23.3) [27].

23.4 Acquired Perforating Dermatosis

This is an acquired pruritic disorder seen most commonly in patients with CKD with overlapping clinical and histologic features of primary perforating disorders including perforating folliculitis, Kyrle's disease, elastosis perforans serpiginosa, and reactive perforating collagenosis [28]. This disorder is characterized by hyperkeratotic follicular papules. It has also been described in the setting of diabetes mellitus (DM), copper deficiency, and PD-1 inhibitor therapy [29–31].

23.4.1 What Causes Acquired Perforating Dermatosis?

The pathogenesis of this disorder is not well understood, but a common finding is the transepidermal elimination of altered dermal substances [28]. The theory suggests that acquired perforating dermatosis may be caused by the accumulation of dermal microdeposits containing substances like calcium salts that cause a foreign body reaction [32]. Another hypothesis cites local trauma induced by excoriation and microvasculopathy causing extrusion of substances through the dermis as another cause for acquired perforating dermatosis [19].

23.4.2 What Are Important Clinical Considerations of Acquired Perforating Dermatosis?

It is important to remember that acquired perforating dermatosis is a spectrum of clinical disorders, and thus the specific underlying disease may vary with a similar presentation. Furthermore, the patient may also have pruritus associated with acquired perforating dermatosis or due to uremic pruritus. Koebnerization, or the development of new lesions induced by trauma, can occur with acquired perforating dermatosis; thus, adequate treatment of pruritus as well as counseling to decrease scratching is appropriate. Skin biopsy is required to make a diagnosis of acquired perforating dermatosis. While the histology of this condition varies, the main diagnostic feature is a central keratotic core overlying a focus of epidermal perforation [33].

23.4.3 How Do you Treat Acquired Perforating Dermatosis?

Topical and systemic retinoids, ultraviolet B phototherapy, psoralen and ultraviolet A (UVA), cryosurgery and photodynamic therapy, topical corticosteroids, and keratolytics should all be considered in the treatment of acquired perforating dermatosis [19]. Recent case reports have suggested that allopurinol may treat this condition [34]. Renal transplantation has also been known to clear acquired perforating dermatosis [32] (Fig. 23.4).

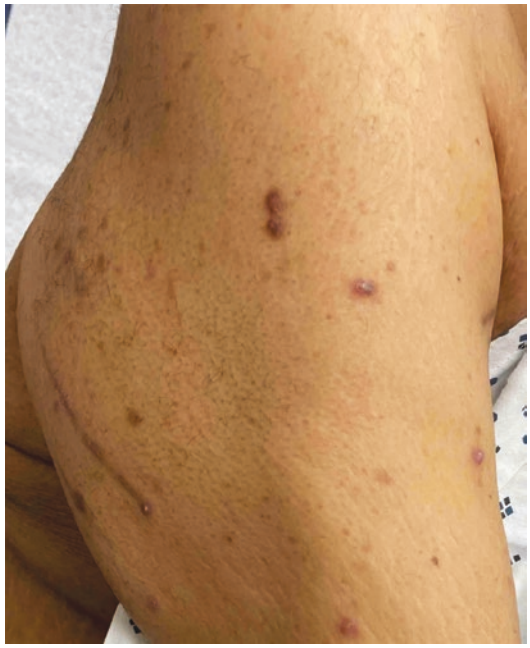

Fig. 23.4 Acquired perforating dermatosis with Koebnerization in a patient with CKD (Image courtesy of Deep Joshipura, MD)

23.5 Calciphylaxis

Calciphylaxis is also known as calcific uremic arteriolopathy and is a rare vasculopathy that typically presents in the setting of end-stage kidney disease (ESKD) associated with secondary hyperparathyroidism. It results from arteriolar deposition of calcium leading to evolving lesions of livedo reticularis (net-like erythema), livedo racemosa (a broken net-like pattern), and retiform purpura (purpuric patches with stellate borders) signifying necrosis of the deep dermis and subcutaneous tissues. It is particularly seen in patients on hemodialysis, but even in this population, it is only present in 1–4% [35]. Calciphylaxis is also seen in patients without uremia, specifically those with primary hyperparathyroidism. Additionally, calciphylaxis may occur in patients with both normal kidney and parathyroid function, these nontraditional patients may demonstrate a variety of comorbidities including: malignancy, connective tissue disease, osteomalacia, Crohn's disease, previous corticosteroid use, alcoholic liver disease, and protein C or S deficiency [35, 36]. Non-uremic calciphylaxis shows a predilection for obese postmenopausal people who are usually lupus anticoagulant positive [37].

23.5.1 What Causes Calciphylaxis?

The precise pathogenesis of calciphylaxis remains unknown, but small vessel endovascular fibrosis, fibrin thrombi, intimal proliferation, obliterative vasculopathy, tissue ischemia, calcification, panniculitis, and subcutaneous fat necrosis are all seen on histopathological examination [35]. CKD also leads to decreased clearance of phosphorus resulting in extraosseous calcification [19]. This calcification decreases lumen diameter and can predispose to sudden vascular occlusion, which leads to livedo reticularis and subsequent necrosis.

23.5.2 What Are Important Clinical Considerations of Calciphylaxis?

Patients may report exquisite tenderness overlying stellate or retiform purpura. These purpuric patches are typically symmetric and progress to deep stellate ulcers. The ulcers may become gangrenous and are most commonly located on the proximal thigh and lower abdomen or distally on shins, digits, or glans penis [19, 38]. In patients with ESKD, calciphylaxis should be suspected if they present with painful livedoid plaques and/or retiform purpura [39]. Skin biopsy may aid in diagnosis, yet excisional biopsy may be needed to obtain appropriate tissue depth. A negative skin biopsy does not preclude this diagnosis, and high clinical suspicion for calciphylaxis may guide empiric management. Imaging may aid in diagnosis, as these characteristic changes may be detected by ultrasound and plain radiograph [40, 41]. A high morbidity and mortality are associated with calciphylaxis, with death most commonly occurring secondary to sepsis. The medial survival rate after the appearance of lesions is

1 year [39]. Pain and palliative care consultations may be an underutilized resource for this patient population [42].

23.5.3 What Are the Treatments of Calciphylaxis?

Treatment for calciphylaxis includes both medical and surgical modalities. Sodium thiosulfate, ordinarily used to treat cyanide toxicity, can be given intravenously. There are no standard dosages but case reports citing efficacy of sodium thiosulfate administered dosages ranging from 5 to 25 g IV three times a week, usually after hemodialysis [35]. This treatment is thought to work because it acts as an antioxidant, vasodilator, and calcium chelator.

It is also important to normalize serum phosphate and calcium. Studies using bisphosphonates to treat calcium and phosphate disturbances seen in calciphylaxis have found that they reduce pain and promote ulcer healing [35]. They are thought to have an anti-inflammatory effect by suppressing cytokine release and inhibiting macrophages. There have also been numerous recent clinical trials investigating the utility of treating calciphylaxis with oral vitamin K supplementation, lanthanum carbonate, and SNF472 (hexasodium phytate) [39].

The role of surgical debridement in calciphylaxis is an issue that is debated. Some advocated for aggressive surgical debridement. Studies do show an association between surgical debridement and significant improvement in survival rates [35]. Still, others advocate for the use of hydrocolloid dressing and atraumatic debridement methods as any skin trauma can lead to new lesions. Other treatment methods including fish skin graft and cryopreserved human amniotic membranes have been reported [43, 44].

Parathyroidectomy is a potential surgical treatment for calciphylaxis in patients with hyperthyroidism, but there are variable outcomes and the evidence behind this treatment is not based on studies of large patient populations. Therefore, when considering this option, it is important to carefully consider the risk of post-surgical effects of parathyroidectomy [35].

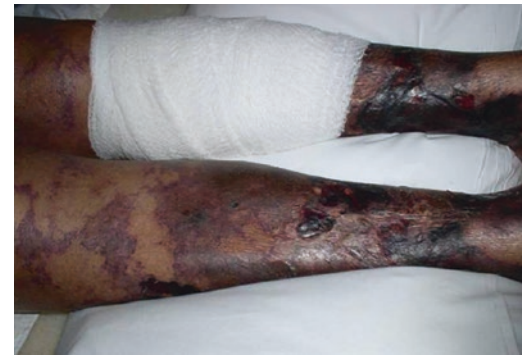

Fig. 23.5 Calciphylaxis in a patient with CKD (Image courtesy of Nathaniel Jellinek, MD)

Hyperbaric oxygen therapy has also been studied as a treatment for calciphylaxis. Its purported benefits include stimulation of fibroblast proliferation, conversion to myofibroblasts, stimulation of angiogenesis, and toxicity to various organisms that have the potential to cause serious infection and impair wound healing [35] (Fig. 23.5).

23.6 Metastatic Calcinosis Cutis

Metastatic calcinosis cutis (MCC), also referred to as benign nodular calcification, is a condition presenting with firm nodules and plaques in the skin and subcutaneous tissue. They are usually painless but occasionally periarterial depositions or depositions near joints can be painful [45].

23.6.1 What Causes Metastatic Calcinosis Cutis?

Increased serum calcium or phosphate levels or both cause MCC. When the levels of these substances are increased in blood, they precipitate into the skin and subcutaneous tissue causing palpable nodules and plaques [46]. Elevated calcium and phosphate are seen in kidney failure due to poor renal excretion of phosphate and secondary hyperparathyroidism that develops as a

result of poor intestinal absorption of calcium. Iatrogenic calcinosis cutis resulting from microtrauma and extravasation of intravenous calcium-containing fluids have also been reported [47].

23.6.2 What Are the Important Clinical Considerations?

Patients may present with skin-colored or pink, firm, tender papules, nodules, or plaques with well-defined borders [45]. These lesions can undergo secondary change resulting in ulceration. They may also become fluctuant and extrude contents, which are chalky in nature. Calcium and phosphate deposition can extend beyond the skin and may occur in other organs.

23.6.3 What Is the Treatment for Calcinosis Cutis?

MCC lesions usually resolve after serum normalization of calcium and phosphate [19]. The surgical treatments of MCC lesions are similar to the treatment of calciphylaxis lesions including parathyroidectomy for hyperparathyroidism.

23.7 Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis (NSF) is a generalized fibrotic disorder that can occur in patients with CKD who have been exposed to gadolinium (see Chap. 3). Acute or chronic kidney dysfunction in combination with inflammation contributes to the development of NSF [19]. Liver disease, erythropoietin, and acidosis are suspected contributors.

23.7.1 What Causes NSF?

Gadolinium exposure as a contrast agent in magnetic resonance angiography (MRA) or magnetic resonance imaging (MRI) was identified as a potential trigger for NSF [19]. Precipitates of gadolinium are produced and serve as activating substances for macrophages and fibroblasts. These precipitates may be endocytosed by fibrocytes resulting in a fibrotic expression in fibroblasts subsequently leading to an activation of kappa B pathway and transforming growth factor beta, thus promoting fibrosis that is seen in this condition [19]. Mice models have suggested that dysregulations in neutrophil elastase activity may facilitate the onset of NSF [48].

23.7.2 What Are the Important Clinical Considerations in NSF?

Consider the diagnosis of NSF if the patient reports a recent history of undergoing a procedure requiring MRI or MRA with contrast. This condition can present with indurated plaques or diffuse areas of skin induration but can also involve joints causing contractures [19].

23.7.3 What Is the Treatment of NSF?

No treatments have proven effective in curing NSF, so it is important to counsel patients to avoid the known trigger of this disorder. There is anecdotal evidence that improvement of this condition can be observed with topical or systemic steroids, cyclophosphamide, thalidomide, plasmapheresis, immunoglobulin infusion, imatinib mesylate, and rapamycin [19] (Fig. 23.6).

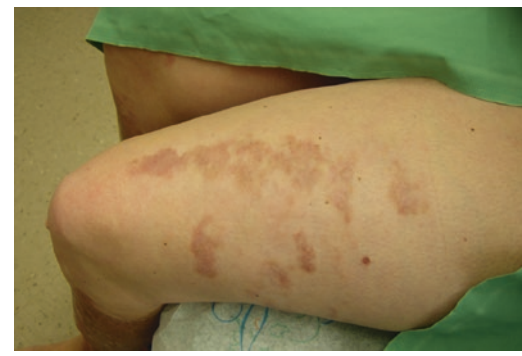

Fig. 23.6 Nephrogenic systemic fibrosis in a patient with CKD (Image courtesy of Seth Feder, MD)

23.8 Pseudoporphyria

Pseudoporphyria is a photodermatosis that is also known as bullous dermatosis of end-stage kidney disease. It is seen in patients with CKD or in patients undergoing long-term dialysis [19]. It has also been rarely reported in the setting of certain medications including voriconazole, furosemide, and olanzapine [49–51].

23.8.1 What Causes Pseudoporphyria?

The exact pathophysiology of pseudoporphyria is unknown, but ultraviolet (UV) light is thought to play a role in this entity given its association with UVA light exposure and medications that sensitize the skin to damage in UV light. Furthermore, in patients with CKD, risk of injury due to free radicals is higher due to low levels of glutathione in the blood and red blood cells [19].

23.8.2 What Are the Important Clinical Considerations in Pseudoporphyria?

This condition usually affects sun-exposed areas, usually the dorsal aspect of the forearms and hands. The patient may describe having fragile skin and blisters.

23.8.3 What Is the Treatment for Pseudoporphyria?

Photoprotection and sun avoidance are important aspects of pseudoporphyria treatment. N-acetylcysteine can also be used as it is thought to increase the production of plasma glutathione, thus reducing the risk of damage due to free-radical injury. These symptoms are slow to resolve and may recur with discontinuation of treatment.

23.9 Porphyria Cutanea Tarda

Porphyria cutanea tarda (PCT) is a disorder caused by a deficiency in uroporphyrinogen decarboxylase, a cytoplasmic enzyme involved in heme synthesis. This results in accumulation of heme substances in the blood causing skin changes on exposure to UV light. Scarring, fragility, hyperpigmentation, hypertrichosis, and milia are common changes seen in PCT [52]. PCT can occur in many disease states and has an estimated prevalence of 1.2–18% in CKD [52].

23.9.1 What Causes PCT?

As mentioned above, an accumulation of heme products in the blood leads to skin changes upon sun exposure. The cause of PCT in patients with CKD is not well understood but is likely multifactorial. Hypotheses implicate the distance of iron balance that can be seen in patients in dialysis.

23.9.2 What Are some Clinical Considerations?

There are two types of PCT: Type I (sporadic) and type II (familial). Patients presenting in their twenties likely have familial PCT, while those presenting in middle age are more likely to have sporadic PCT [19]. In addition to the skin changes mentioned above, patients may also have complaints of dark urine ("port wine urine") from porphyrin pigments and pruritus without abdominal pain unlike acute intermittent porphyria.

23.9.3 How Do you Treat PCT?

Photoprotection and avoidance of sun exposure are key components in the management of PCT. Patients are also advised to avoid triggering factors including alcohol, smoking, estrogen oral contraceptives, and supplemental iron.

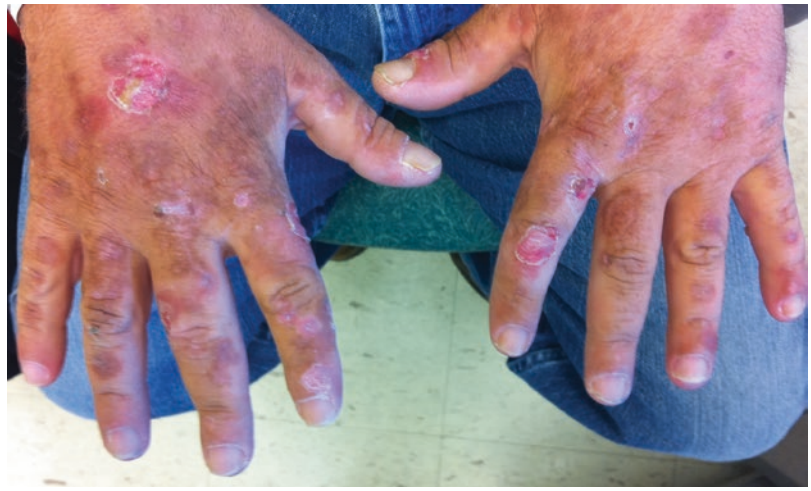

Fig. 23.7 Porphyria cutanea tarda in a patient with CKD (Image courtesy of Sandy Chai, MD)

Phlebotomy is an effective treatment of PCT and can be a treatment consideration in patients with CKD. However, some patients with CKD cannot tolerate the removal of 250–500 mL of blood twice a week. For these patients, small-volume phlebotomy is an option [53]. Research has also shown efficacy of deferoxamine treatment administered concurrently with dialysis. There is also a reported synergistic effect when deferoxamine is given with erythropoietin treatment [52] (Fig. 23.7).

Before You Finish: Practice Pearls for the Clinician

- There is no treatment for Lindsay's nails but sometimes it resolves with renal transplantation.
- Normalization of serum calcium and phosphate levels is the cornerstone of treatment in calciphylaxis and MCC.
- There are no effective treatments for NSF and therefore it is best to avoid gadolinium, a known trigger of the condition.
- Photoprotection is an important component of PCT and pseudoporphyria treatment. Deferoxamine and small-volume phlebotomy have also been effective in past studies.

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