Dermatologic Manifestations of End-Stage Renal Disease

Ursula C. Brewster, MD

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are common conditions in the United States. In 2001, more than 6 million people had some form of CKD (as defined by a serum creatinine ≥ 1.5 mg/dL).[1] Currently, more than 300,000 patients are on dialysis in the United States, and this number increases daily.[2] As more patients live longer on dialysis, it is important that physicians be able to recognize the comorbidities that are found in the ESRD population. Although many complications of ESRD are more serious in clinical terms, few have as significant an impact on patients' quality of life as dermatologic disease.

Skin involvement can be extensive, and a number of dermatologic disorders may affect ESRD patients (**Table 1**). Although multiple skin lesions have been described, this article discusses common and newly described disorders, focusing on their clinical presentation and treatment options in patients receiving peritoneal dialysis and standard hemodialysis (3 times/wk). Currently, there is no information available on dermatologic disease in patients receiving daily or nocturnal hemodialysis. Of note, this article does not discuss the dermatologic conditions that are common after transplantation in immunosuppressed patients; this information is available elsewhere.[3]

TAKE HOME POINTS

- The number of end-stage renal disease (ESRD) patients is rising exponentially in the United States.
- Dermatologic disease is very common in ESRD patients and significantly impacts quality of life.
- Uremic pruritus can be treated by maximizing the dialysis prescription and by using a variety of topical and systemic agents.
- Nephrogenic fibrosing dermopathy is a devastating, disfiguring process that occurs in patients with kidney disease, and the etiology is largely unknown.
- Calcific uremic arteriolopathy has a high morbidity and mortality rate and causes intensely painful lesions that frequently get superinfected.

OVERVIEW OF SKIN CHANGES IN ESRD PATIENTS

Skin changes are common in ESRD patients undergoing dialysis therapy. Pico et al[4] found that of 102 ESRD patients, all had at least 1 form of skin alteration. Often, changes in skin coloring are seen, including pallor as a result of chronic anemia and hyperpigmentation. Marked atrophy of sebaceous and sweat glands leads to xerosis (ie, dry skin) with ichthyosiform scaling. Premature skin aging makes these patients appear considerably older than their age. Patients are also prone to increased hair growth on their cheeks and thickening of the eyebrows.[5] Patients with ESRD also develop half-and-half nails (also called Lindsay's nails), in which the proximal two thirds of the nail is white with normal or brown discoloration distally. Half-and-half nails are thought to be the result of edema in the nail bed. Histologic changes also develop in the dermal vessels and include basement membrane thickening, endothelial activation, and chronic inflammatory infiltration.[6]

UREMIC PRURITUS

Pruritus is a common complaint among ESRD patients, affecting patients on hemodialysis more frequently than those on peritoneal dialysis.[7] Studies have shown that pruritus affects 50% to 90% of patients with ESRD; is independent of sex, age, race, or etiology of kidney failure[7]; and can be debilitating.[8] Despite much speculation, the exact mechanism of pruritus remains unclear. Although xerosis is common in dialysis patients, it does not appear to correlate with the severity of pruritus. ESRD patients have excessive numbers of mast cells in the skin, and it has been proposed that histamine (produced by mast cells) plays an important role in the development of pruritus. However, data to

Dr. Brewster is an assistant professor of medicine, Section of Nephrology, Yale University School of Medicine, New Haven, CT.

Table 1. Dermatologic Conditions Associated with End-Stage Renal Disease

Actinic elastosis
Calcific uremic arteriolopathy (calciphylaxis)
Half-and-half nails (Lindsay's nails)
Kyrle's disease
Lichen planus
Nephrogenic fibrosing dermopathy
Porphyria cutanea tarda
Pruritus
Uremic frost
Xerosis cutis

Table 2. Treatment Options for Uremic Pruritus

Increase dialysis efficiency
Topical medications
Moisturizing creams
Capsaicin
Physical treatments
Ultraviolet B light
Parathyroidectomy
Systemic medications
Antihistamines
Cholestyramine
Thalidomide
Nicergoline
Activated charcoal
Alternative strategies
Acupuncture
Homeopathy

support this claim are lacking. Secondary hyperparathyroidism commonly complicates ESRD, and it has been suggested as a cause of pruritus. Case reports support resolution of pruritic symptoms following parathyroidectomy.[9] However, it has been shown that circulating levels of parathyroid hormone do not correlate with degree of itching[7]; additional studies are needed to confirm or disprove this assertion.

Treatment

There are a variety of treatment options for uremic pruritus (**Table 2**). Patients who are not achieving adequate dialysis clearances may benefit from an optimized dialysis prescription. In a study by Hiroshige et al,[10] hemodialysis patients who were aggressively dialyzed had significant reductions in pruritus severity. All ESRD patients who have pruritus should have their dialysis dose evaluated and optimized. Moisturizing creams can be used for patients with extremely dry skin, but response is variable.[8] Also, topical capsaicin cream, which depletes the neuron of substance P, has been used with some success. However, some patients complain of localized burning at the site of capsaicin application, and excessive cost may limit its use. Although there are data to support the use of topical steroid creams or topical tacrolimus, the side effects of these medications can be substantial.

Ultraviolet (UV) B radiation (but not UVA) has been shown to be effective for managing pruritus.[8] Although positive results have been noted with UV therapy, it has limitations. For example, UV therapy represents another procedure in addition to dialysis that the patient must undergo, which can impair quality of life. In addition, the long-term carcinogenic risks to these patients are not clear. In patients expecting transplantation (at which time lifetime immunosuppression therapy brings its own risk of dermatologic malignancies), it remains to be shown if UVB therapy would add to any potential risks.

Systemic therapy for pruritus includes antihistamines, activated charcoal, and thalidomide. Antihistamines are widely prescribed, but they often do not control pruritus and sedation limits their therapeutic ability. Activated charcoal was shown to be effective in a small, double-blind trial for uremic pruritus, but the drop-out rate among patients on charcoal was high because of poor tolerance.[11] Activated charcoal may act by binding pruritogens in the intestinal lumen, preventing their absorption and action. Thalidomide holds promise for uremic pruritus. In a randomized, double-blind trial involving 29 hemodialysis patients with refractory uremic pruritus, 55% of patients given thalidomide demonstrated benefit.[12] Thalidomide is contraindicated in women who menstruate due to the drug's teratogenic effects. Other agents, such as opioid antagonists, cholestyramine, nicergoline, and erythropoietin, have been used with mixed results.

For patients with severe secondary hyperparathyroidism, pruritus may be relieved with parathyroidectomy. However, data on the effects of parathyroidectomy are limited, and this surgical option cannot be recommended to all patients at this time. Finally, alternative medicine may offer relief for some patients. Acupuncture has been reported to be useful, and newer reports of homeopathic techniques show promise for managing pruritus.[8,13]

PERFORATING DISORDERS (KYRLE'S DISEASE)

Kyrle's disease is a perforating skin disorder that occurs in up to 10% of ESRD patients undergoing hemodialysis.[14] In perforating skin disorders, there is transepidermal elimination of altered dermal collagen or elastic fibers, but there is little damage to the surrounding skin. Perforating disorders are frequently found in dialysis patients with diabetes mellitus and in African Americans. Clinically, the lesions of Kyrle's disease appear as 2- to 8-mm domed papules with a keratotic plug, usually located on the trunk and proximal extremities. Papules may coalesce into linear plaques. Intense pruritus often develops at the site of the skin rash.

Treatment

Treatment of perforating disorders is often difficult and unrewarding. Potent topical steroids are useful in some patients. Oral retinoids and vitamin A are other options. Cryotherapy and keratolytics have been successfully employed in a few case reports.[15] Phototherapy with UVB may reduce the pruritus associated with perforating skin disorders.

NEPHROGENIC FIBROSING DERMOPATHY

Nephrogenic fibrosing dermopathy (NFD) was first described in 2000 by Cowper et al[16] in a report of 15 patients with a scleromyxedema-like cutaneous lesion. Patients with NFD develop thickened, hard plaques on their skin with brawny hyperpigmentation, frequently papules or nodules (**Figure 1**). The extremities or trunk are most often affected, but all areas of the body and face can be involved. NFD does not affect internal organs.

Most patients who develop this disorder have undergone either hemodialysis or peritoneal dialysis, and many (> 50%) have received a transplant. More recently, however, NFD has been described in patients with CKD who have not yet required renal replacement therapy.[17] For patients, NFD is a slowly disfiguring, painful, and devastating process. In the early stages, the most common complaints are pruritus and dysesthesia, with more significant symptoms developing as the disease progresses. In more advanced stages, flexion contractures of the joints occur, and mobility becomes severely compromised. Muscle weakness and joint contracture cause patients to become wheelchair-bound over time.

In patients with CKD who present with thickening of the skin, the differential diagnosis includes NFD, scleroderma, or scleromyxedema. A skin biopsy confirms the diagnosis. The skin biopsy of NFD is characterized by an increase in dermal collagen spindle cells, arranged in a haphazard manner.[18] Collagen bundles are thick and are interspersed with CD34-positive dendritic cells. There is an increased number of fibroblast-like cells and increased mucin deposition. Unlike other fibrotic skin disorders, there is a marked absence of inflammatory cells in the skin.

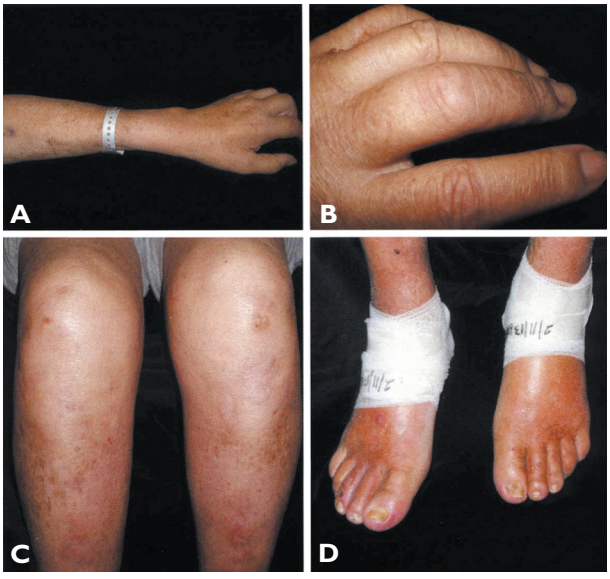

Figure 1. Photographs of a patient with nephrogenic fibrosing dermopathy showing thickening of the skin over (**A**) the wrist and between the thenar and hypothenar prominences, (**B**) the fingers with flexion contractures, (**C**) the legs with shiny appearing skin and brown hyperpigmented areas, and (**D**) the feet with shiny appearance and bilateral heel ulcerations (bandaged). (Adapted with permission from Moschella SL, Kay J, Mackool BT, Liu V. Case 35-2004: a 68-year-old man with end-stage-renal-disease and thickening of the skin. N Eng J Med 2004;351:2221. Copyright © 2004 Massachusetts Medical Society. All rights reserved.)

Treatment

The only successful treatment for NFD is improvement in renal function via transplantation, but even this procedure does not guarantee symptom relief. Given the debilitating nature of this disease, many other therapies have been tried. Empiric trials of topical and systemic corticosteroids, photopheresis, plasmapheresis, and cyclosporine have not been successful.[18,19] More recently, dermatologists have used thalidomide, but this therapy must be used with caution given its teratogenicity, and results are mixed.[20] Patients should be enrolled in physical and occupational therapy to maintain strength and mobility.

CALCIFIC UREMIC ARTERIOLOPATHY

Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is a devastating obliterative vasculopathy that develops in some patients with kidney disease. It

Table 3. Risk Factors for Calcific Uremic Arteriolopathy

Increased body mass index
Poor nutrition
Diabetes
Female sex
Elevated phosphorus level
Elevated parathyroid hormone level
Protein C or S deficiency
Medications (ie, warfarin, steroids, iron, vitamin D)

Figure 2. Skin lesions from patients with calcific uremic arteriolopathy showing skin mottling and eschar formation. (Adapted with permission from Wilmer WA, Magro CM. Calciphylaxis: emerging concepts in prevention, diagnosis and treatment. Semin Dial 2002;15:173. Copyright © 2002, Blackwell Publishing Ltd.)

has been documented in patients with CKD, ESRD, and kidney transplant. The clinical prognosis of patients with this disease is dismal, with many patients dying from systemic infection or visceral organ involvement within months of presentation.

The most common initial presentations of CUA are skin lesions and muscle pains, although multi-organ failure is possible. Skin lesions often evolve rapidly and can be solitary or multiple, extending over many body surfaces. Lesion location is variable, and they will frequently overlie areas of thick adipose tissue, areas where skin surfaces are in contact, and sites of trauma. Lesions appear red and tender early in the course of the disease but can develop quickly into a violaceous pattern with livido reticularis. Subcutaneous nodules are often palpable. Finally, the area becomes overtly necrotic with eschar formation, and lesions may open and become infected (**Figure 2**). Other organ involvement can include myopathy, arthropathy, pulmonary involvement, and pancreatitis.[21] Ocular involvement, such as ischemic optic neuropathy, has also been described.[21] The overwhelming complaint of patients is excruciating pain.

The pathology of CUA is one of severe obliterative vasculopathy with intimal proliferation, calcification, and fibrosis of arteries, arterioles, capillaries, and venules. Medial wall calcification is common in many cases.

The pathogenesis of CUA is not completely understood. Abnormalities of mineral metabolism that occur in the setting of uremia likely play a significant role. Patients at greatest risk are those with a high body mass index (> 40 kg/m^2), a chronically elevated calcium-phosphate product, diabetes mellitus, and severe underlying hyperparathyroidism (**Table 3**). However, none of these risk factors must be present for CUA to develop. Protein C deficiency also has been proposed as a contributing factor.[22] It has been shown that patients with CUA have an increase in some molecular stimulators of calcification, such as osteopontin. Matrix GLA protein dysfunction induced by warfarin also may play a role.

Treatment

Treatment options for patients with CUA are limited and largely unsuccessful. Excellent control of mineral metabolism and serum parathyroid hormone concentration is essential. Often, patients will require more frequent dialysis to decrease their serum calcium and phosphorus concentrations. A low-concentration calcium dialysate is often employed to remove calcium from the body. To control parathyroid hormone, patients frequently must undergo parathyroidectomy by an experienced surgeon. The role of cinacalcet hydrochloride (Amgen, Thousand Oaks, CA), a new calcium mimetic agent used to control hyperparathyroidism in dialysis patients, is not yet known in cases of CUA.

A key to managing patients with CUA is adequate

pain control and wound management. As lesions progress, it is often necessary to consult with pain specialists. Physical and occupational therapy can assist with mobility and strength, and it is important to maintain good nutrition for wound healing. Hyperbaric oxygen has been used with limited success in wound management.[21]

CONCLUSION

As the number of dialysis patients continues to grow, providers in all areas of medicine will be involved in their management. Dermatologic complaints in ESRD patients are common and carry significant morbidity and mortality. Although a number of dermatologic conditions affect these patients, perhaps the most troublesome are pruritus, Kyrle's disease, NFD, and CUA. Therapeutic interventions are available, but their efficacy is limited. Therefore, it is necessary to recognize these conditions early and work closely with a dermatologist in managing these patients. **HP**

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