**Background:** The primary hyperoxalurias are a group of rare autosomal recessive metabolic disorders associated with abnormal overproduction of serum oxalate and subsequent deposition in tissue. Most patients present at an early age with recurrent urolithiasis and renal failure. Vascular deposition of oxalate-producing skin manifestations, such as livedo reticularis, acrocyanosis, peripheral gangrene, and ulcerations, is typical of the primary hyperoxalurias.

**Observations:** We present the case of a 38-year-old woman with end-stage renal disease receiving hemodialysis with progressive skin changes, including livedo reticularis, superficial eschars, and brawny, woody fibrosis of her extremities, who was clinically suspected to have calciphylaxis or nephrogenic systemic fibrosis. Cutaneous biopsy specimens revealed rectangular, birefringent, yellowish-brown, polarizable crystalline material suggestive of oxalate within the dermis, subcutis, and medium-size vessels along with areas of focal epidermal and superficial dermal necrosis. Her subsequent medical history was obtained and was suggestive of a diagnosis of primary hyperoxaluria.

**Conclusions:** This case highlights the variability of clinical presentations in primary hyperoxaluria and that the disease can be diagnosed in adulthood. In addition, this case demonstrates that hyperoxaluria should be included in the differential diagnosis of calciphylaxis and nephrogenic systemic fibrosis.

**Oxalosis Involving the Skin**

**Case Report and Literature Review**

Joseph A. Blackmon, MD; Brooke Grant Jeffy, MD; Janine C. Malone, MD; Alfred L. Knable Jr, MD

Oxalosis is defined as the systemic accumulation of calcium oxalate, the insoluble salt of oxalic acid, outside of the urinary system. The pathologic disease processes responsible for systemic oxalosis include primary and secondary hyperoxalurias. Major sites of oxalate deposition include the kidneys, bone, myocardium, blood vessels, and skin leading to subsequent disease.

The cutaneous findings associated with primary hyperoxaluria tend to result from vascular deposition and include livedo reticularis, acrocyanosis, ulceration, and peripheral gangrene. Conversely, skin manifestations in patients who develop a secondary oxalosis attributable to renal insufficiency are rare, and when they do occur are the result of deposition extravascularly, producing calcified nodules and miliary papules. We present this extraordinary case to highlight the cutaneous manifestations associated with hyperoxaluria and to provide a framework for review of the types of hyperoxaluria and the differential diagnosis.

A 38-year-old white woman with end-stage renal disease (ESRD) requiring hemodialysis for the past 5 years was referred by her nephrologist for evaluation of persistent acral sores and livedo of her extremities with a presumed diagnosis of calciphylaxis. Her comorbidities included cardiomegaly with heart failure, bilateral pleural effusions, blurred vision, and self-reported arthritis. She had no history of diabetes mellitus.

The patient recalls being healthy until her early 20s when she experienced 2 episodes of nephrolithiasis. Subsequently she was asymptomatic until her early 30s when, 2 months after an uncomplicated pregnancy and delivery, she was hospitalized with pancreatitis and acute renal failure requiring hemodialysis. Approximately a year and a half later, she began to notice the development of a woody-type fibrosis and tautness in both her upper and lower extremities leading to difficulty with ambulation.

The patient had previously received a right renal transplant, but the procedure...
was complicated by hyperacute rejection. Workup for her transplant rejection included a bone marrow biopsy in which findings showed diffuse granulomata and birefringent crystals with polarized light. Prior to presenting to dermatology, workup for her lower extremity ulcerations included a normal ankle-brachial index.

Dermatological examination was significant for a woman of normal weight with brawny, woody fibrosis of the distal upper and lower extremities within a diffuse background of livedo reticularis (Figure 1). She had superficial eschars involving the acral surface of the left dorsal hand and around both lower extremity malleoli but no evidence of frank ulceration (Figure 2). These areas were minimally tender to deep palpation. The patient reported a recent history of imaging with gadolinium that postdated the onset of her skin complaints; however, based on her initial history and physical examination, the differential diagnosis was nephrogenic systemic fibrosis vs calciphylaxis.

Two 5-mm punch biopsy specimens were taken from the left upper extremity just distal to her hemodialysis shunt and from the right anterior thigh. Both specimens demonstrated fibrosis of the dermis and subcutaneous septa with deposition of yellowish-brown crystalline material in the dermis and subcutis and focally within the lumen of a medium-size vessel with a muscular wall near the dermal-panniculus interface, likely an arteriole or large vein. The vessel appears completely occluded by this material without evidence of thrombus or fibrin (Figure 3). The crystalline material was polarizable and exhibited variable needle-shaped and rectangular platelike configurations (Figure 4). Focal epidermal and superficial dermal necrosis was also seen. There was no evidence of intravascular or extravascular calcium deposition in multiple sections examined from each specimen, each containing an adequate amount of fat, making calciphylaxis unlikely. Examination of multiple sections also failed to reveal
Hyperoxaluria is classified as either primary or secondary. There are 2 subtypes of primary hyperoxaluria (PH), PH-1 and PH-2, which are autosomal recessive disorders distinguished based on a specific enzyme deficiency within hepatocytes. Secondary hyperoxaluria occurs with excessive intake of oxalate or oxalate precursors and can be seen with ethylene glycol poisoning, methoxyflurane anesthesia, excessive intake of ascorbic acid, pyridoxine deficiency, various intestinal diseases, repeated oral antibiotic use leading to elimination of oxalate-degrading Oxalobacter formigenes in the intestines, ileal resection, and chronic hemodialysis. Because oxalate is only excreted renally, renal failure of any cause resulting in hemodialysis may result in accumulation of oxalate in body tissues though to a much lesser degree than results from primary hyperoxaluria. Regardless of underlying etiology, excessive oxalate in the body precipitates as calcium oxalate initially in the kidneys and ultimately in other tissues, causing damage and subsequent disease. Skin manifestations of hyperoxalosis are not common. Cutaneous disease associated with primary hyperoxaluria often manifests with vascular complications such as livedo, acrocyanosis, and peripheral gangrene, whereas secondary hyperoxalosis more commonly results in mild cutaneous disease owing to extravascular deposition resulting in acral or facial papules or nodules.

PH-1, the most common type of primary hyperoxaluria, is caused by deficiency of alanine: glyoxylate aminotransferase leading to accumulation of glyoxylate and its oxidation product, oxalate. PH-1 is further divided into 3 forms: infantile, juvenile, and adult. In the infantile form there is no history of nephrolithiasis, and renal failure is rapidly progressive. The juvenile form is the most prevalent and is characterized by recurrent calcium oxalate nephrolithiasis prior to the development of renal failure. In the rare adult form, patients present with renal failure prior to development of complications related to oxalate deposition in other tissues. PH-2 is caused by a deficiency of D-glyoxylate dehydrogenase/glyoxylate reductase subsequently leading to hyperoxaluria and excretion of L-glycero. These patients generally present with urolithiasis; nephrolithiasis leading to renal failure can rarely occur, but again is more commonly seen in PH-1.

The diagnosis of hyperoxaluria often presents a challenge to the clinician. The presence of renal failure in our patient, along with cutaneous findings of livedo reticularis, fibrosis, and eschar formation, suggested a clinical differential diagnosis of calciphylaxis and nephrogenic systemic fibrosis, prompting biopsy.

Both calciphylaxis and nephrogenic systemic fibrosis generally occur in patients with renal failure undergoing hemodialysis. Calciphylaxis manifests clinically as violaceous, reticulate areas of cutaneous necrosis and eschar primarily of the extremities. Elevation of the calcium phosphorus product and parathyroid hormone levels as well as radiographic and histopathologic evidence of basophilic vessel and soft-tissue calcification further support this diagnosis. Nephrogenic systemic fibrosis presents with tender, brawny indurated plaques generally of the trunk and lower extremities that occur in patients undergoing hemodialysis exposed to the radiocontrast agent gadolinium. Histopathologic evaluation of skin biopsy specimens characteristic of nephrogenic systemic fibrosis discloses fibrosis of the dermis and subcutis in association with increased numbers of bland spindle cells and variable mucin deposition.

If oxalosis is suspected clinically, elevated urine levels of oxalate, L-glycerate, or the oxalate-creatinine ratio support the diagnosis; however, these studies are generally not helpful once renal failure leads to impaired urine output. In addition, most renal calculi are composed of calcium oxalate; thus, these types of stones are not specific for hyperoxaluria. In suspected cases, plasma oxalate levels should be measured. If elevated, and secondary hyperoxaluria is ruled out, genetic testing and possibly liver biopsy should be pursued to determine the disease subtype, which has treatment and prognostic implications. Our patient's dermatologic findings most closely resembled those of primary hyperoxaluria, with predominantly vascular complications including livedo reticularis, eschar formation, and acrocyanosis, and subsequently her nephrologist confirmed primary hyperoxaluria as the etiology of her renal failure. She died 4 months after presentation to the dermatology department. Genetic testing was ultimately performed in her 2 children, with negative test results.

Treatment depends on the etiology of hyperoxaluria. In patients with PH-1 who have not yet developed renal failure, oral pyridoxine can be effective if there is some residual alanine: glyoxylate aminotransferase activity in which it acts as a cofactor. Once renal failure occurs, the only effective treatment is combined liver-kidney transplant. The liver must be simultaneously replaced because it is the organ responsible for the enzyme deficiency otherwise the transplanted renal graft will ultimately fail. Hemodialysis cannot remove enough oxalate from the body to prevent disease progression. The treatment of PH-2 is supportive with high fluid intake. The primary treatment for secondary hyperoxaluria is removal of the inciting agent.

In summary, primary hyperoxaluria is a rare autosomal recessive disorder that can present many decades into
life. Dermatologists must consider it in the differential diagnosis when patients present with livedo reticularis, eschars, or ulcers, and renal failure. If misdiagnosed as calciphylaxis, nephrogenic systemic fibrosis, or oxalosis secondary to chronic hemodialysis, appropriate treatment may be delayed.

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Correspondence: Brooke Grant Jeffy, MD, Division of Dermatology, University of Louisville School of Medicine, 310 E Broadway, Louisville, KY 40202 (brooke.jeffy@gmail.com).

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REFERENCES


Notable Notes

Sherlock Holmes and the Mysterious White Spots

Mr Sherlock Holmes was measuring the white spots dotting the body of the dark-haired, middle-aged man seated before us. The Royal Medical Society had asked Holmes to diagnose this puzzling skin malady. Holmes announced, “Watson, this is most interesting. All the lesions measure exactly 3/4 inch square, roughly the size of a large bean. Each spot has 2 white hairs within it.”

I wasn’t sure where Holmes was going with this. To me, the diagnosis was vitiligo of 7 days’ duration. I glanced at Holmes. Despite the passage of time, Holmes was still sharp of mind and could solve any crime or challenge placed before him.

“Watson, what you have here is a dermatologic condition not seen in over 2000 years!” All of a sudden, the patient yelled “I am being punished for my sins!” as he clutched a book close to his chest. I was stunned by this outburst, but Holmes calmly replied, “Elementary, my dear Watson. He wears a wedding band, no spouse, 27-year-old woman.”

I was flabbergasted. “Holmes, you don’t really think he is being punished with Biblical Leprosy?” “Watson, his guilty conscience was too much to bear. He snapped and believed he was being punished by God. In his delusion he created his own skin affliction.” “Holmes, I find all this very strange!” “Truth, Watson, is sometimes stranger than fiction.”

Holmes relaxed in his chair, deep in thought. It’s been 125 years since his first case, yet there was still no one better at solving crime than Sir Arthur Conan Doyle’s great detective, Mr Sherlock Holmes!

Leonard J. Hoenig, MD

Contact Dr Hoenig at 601 N Flamingo Rd, Ste 201, Pembroke Pines, FL 33028 (gooddocljh@yahoo.com).