# Painful Retiform Purpura in a Peritoneal Dialysis Patient

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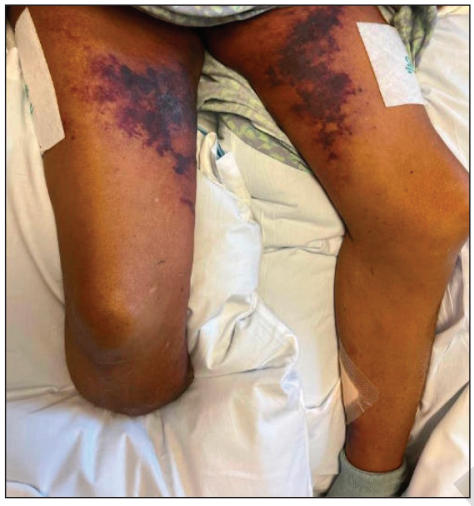

A 72-year-old woman presented to the emergency department with concerns of confusion and lethargy during a session of peritoneal dialysis, which she had been receiving for the last 2 years for end-stage renal disease. She had a history of type 2 diabetes mellitus, diabetic retinopathy, hypertension, coronary artery disease, and peripheral vascular disease preceding a recent right below-knee amputation. A review of systems was positive for a rash on the thighs of several weeks' duration that was preceded by several days of burning pain in the same distribution. Physical examination revealed retiform purpura with irregular contours and interspersed white stellate patterns scattered across the superomedial thighs, right lower back, and left lower abdomen. An initial laboratory workup revealed an elevated creatinine level of 5.03 mg/dL (reference range, 0.6–1.1 mg/dL; baseline level, 3.0 mg/dL) and mild leukocytosis (12.5 cells/mm$^3$ [reference range, 4.5–11.0 cells/mm$^3$]). Dermatology was consulted, and a 4-mm punch biopsy was obtained from the left medial thigh. Nephrology, infectious disease, and wound care consultations also were placed.

## WHAT'S YOUR **DIAGNOSIS?**

a. calcific uremic arteriolopathy
b. cryoglobulinemia
c. erythema ab igne
d. livedo reticularis from antiphospholipid syndrome
e. polyarteritis nodosa

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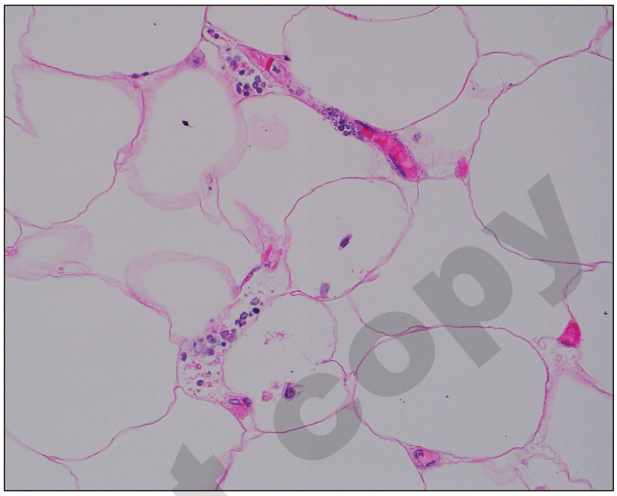
# THE **DIAGNOSIS:** Calcific Uremic Arteriolopathy

Computed tomography of the abdomen and pelvis with contrast revealed a right complex renal cyst with peripheral calcification; computed tomography of the head without contrast revealed atherosclerotic changes with calcification of the intracranial arteries, vertebral basilar arteries, and bilateral branches of the ophthalmic artery. Histopathology revealed occlusive vasculopathy with epidermal ischemic changes as well as dermal and subcutaneous vascular congestion and small thrombi. Within the subcutis, there were tiny stippled calcium deposits within very small vascular lumina (Figure). The combination of clinical and histological findings was highly suggestive of calcific uremic arteriolopathy, and the patient was transitioned to hemodialysis against a low-calcium bath to avoid hypercalcemia. Unfortunately, she developed complications related to sepsis and experienced worsening mentation. After a discussion with palliative care, the patient was transitioned to comfort measures and discharged home on hospice 1 week after the biopsy at her family's request.



Tiny stippled calcium deposits within very small vascular lumina characteristic of calcific uremic arteriolopathy (H&E, original magnification ×400).

Calcific uremic arteriolopathy (also known as calciphylaxis) is a rare, life-threatening syndrome of widespread vascular calcification leading to microvascular occlusion within the dermis and subcutaneous tissues.[1] Clinically, it typically manifests as severely painful, purpuric skin lesions that evolve through phases of blistering, ulceration, and ultimately visible skin necrosis.[2] The pain likely is a consequence of ischemia and nociceptive activation and often may precede any visibly apparent skin lesions.[3] Risk factors associated with the development of this condition include female sex; history of diabetes mellitus, obesity, rapid weight loss, or end-stage renal disease; abnormalities in calcium and phosphorus homeostasis; and vitamin K deficiency.[1,3] It is more prevalent in patients on peritoneal dialysis compared to hemodialysis.[4]

Calciphylaxis is diagnosed with combined clinical and histopathological evidence. Laboratory test abnormalities are not specific for disease; therefore, skin biopsy is the standard confirmatory test, though its practice is contentious due to the risk for nonhealing ulceration and increasing risk for infection.[1] Findings suggestive of disease include focal to diffuse calcification (intravascular, extravascular, or perieccrine), superficial fat calcium deposition, mid panniculus calcium deposition, mid panniculus vascular thrombi, and focal to diffuse angioplasia.[5] The hallmark feature is diffuse calcification of small capillaries in adipose tissue.[6]

The mortality rate associated with this disease is high—a 6-month mortality rate of 27% to 43% has been reported from the time of diagnosis[7-9]—which often is related to subsequent superimposed infections patients acquire from necrotic skin tissue.[2] The disease also carries high morbidity, with patients experiencing frequent hospitalizations related to pain, infections, and nonhealing wounds.[6] There is no standard treatment, and trials have been limited to small sample sizes. A multidisciplinary treatment approach is essential to maximize outcomes, which includes wound care, risk factor modification, analgesia, and symptomatic management strategies.[1,2,6]

Some pharmacologic agents have received noteworthy attention in treating calciphylaxis, including sodium thiosulfate (STS), bisphosphonates, and vitamin K supplementation.[1] The strongest evidence supporting the use of STS comes from 2 trials involving 53 and 27 dialysis patients, with complete remission in 14 (26%) and 14 (52%) patients, respectively.[10,11] However, these trials did not include control groups to compare outcomes, and mortality rates were similarly high among partial responders and nonresponders compared with patients not treated with STS. A 2018 systematic review failed to assess the efficacy of STS alone for the treatment of calciphylaxis but suggested there may be a future role for it, with 251 of 358 patients (70.1%) responding to therapy.[12]

Erythema ab igne is a cutaneous reaction related to long-term heat exposure, often from electronic devices such as laptops, heating pads, space heaters, or hot-water bottles.[13,14] Clinically, this rash appears as an erythematous, purpuric, or hyperpigmented reticular dermatosis that is below the clinical threshold to define a thermal burn.[13] Lesions often are seen on the anterior thighs or across the abdomen.[15] There usually are no long-term clinical sequelae; however, rare malignant transformation

has been documented in cases of atrophy or nonhealing ulceration.[16] Treatment is supportive with removal of the offending agent, but hyperpigmentation may persist for months to years.[14]

Livedo reticularis is a cutaneous pattern of mottled violaceous or hyperpigmented changes that often signifies underlying vascular dermal changes.[17] It can be seen in various pathologic states, including vasculitis, autoimmune disease, connective tissue disease, neurologic disease, infection, or malignancy, or it can be drug induced.[18] There are no pathognomonic microscopic changes, as the histology will drastically differ based on the etiology. Workup can be extensive; cues to the underlying pathology should be sought based on the patient's history and concurrent presenting symptoms. Livedo reticularis is the most common dermatologic finding in patients with antiphospholipid syndrome, and workup should include antiphospholipid antibodies (eg, lupus anticoagulant, anticardiolipin, anti–beta-2-glycoproteins) as well as lupus testing (eg, antinuclear antibodies, anti–double-stranded DNA).[19] Treatment is targeted at the underlying disease process.

Cryoglobulinemia is a disease characterized by abnormal serum immunoglobulins that precipitate at cold temperatures and is further subcategorized by the type of complexes that are deposited.[20] Type I represents purely monoclonal cryoglobulins, type III purely polyclonal, and type II a mixed picture. Clinical manifestations arise from excessive deposition of these proteins in the skin, joints, peripheral vasculature, and kidneys leading to purpuric skin lesions, chronic ulceration, arthralgia, and glomerulonephritis. Cutaneous findings may include erythematous to purpuric macular or papular changes with or without the presence of ulceration, infarction, or hemorrhagic crusting.[21] Systemic disease often underlies a diagnosis, and further investigation for hepatitis C virus, connective tissue disease, and hematologic malignancies should be considered.[20] Treatment is targeted at underlying systemic disease, such as antiviral treatment for hepatitis or chemotherapeutic regimens for hematologic disease.[22]

Polyarteritis nodosa is a systemic necrotizing vasculitis that typically involves small- to medium-sized arteries. Cutaneous manifestations often include subcutaneous nodules, livedo reticularis, and ulcerations most found on the lower extremities.[23] Systemic symptoms including fever, myalgia, arthralgia, and neuropathy often are present. Characteristic histopathology findings include inflammation and destruction of medium-sized arteries at the junctional zone of the dermis and subcutis along with microaneurysms along the vessels.[24] Treatment is based on the severity of disease, with localized cutaneous disease often being controlled with topical steroids and anti-inflammatory agents, while more widespread disease requires immunosuppression with systemic steroids, hydroxychloroquine, azathioprine, methotrexate, mycophenolate mofetil, or intravenous immunoglobulins.[23]

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