

## Calcific Uremic Arteriopathy

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A 50-year-old African-American woman presented to the emergency department with a painful, hand-sized area of discolored skin on the medial aspect of both thighs that had been present for 2 months. She reported having difficulty walking and experiencing weakness, dizziness, and pruritus. She had end-stage renal disease treated by hemodialysis for many years. Significant medications included calcium carbonate, calcitriol, and warfarin. Physical examination revealed bilateral painful erythematous lesions with central eschar (**Figure 1**). Results of laboratory testing included the following: calcium, 10.3 mg/dL; phosphorus, 6.4 mg/dL; alkaline phosphatase, 255 U/L; and intact parathyroid hormone, 1820 pg/mL. The patient was diagnosed with calcific uremic arteriopathy. Intravenous antibiotics were initiated, and the patient underwent urgent subtotal (3.5 gland) parathyroidectomy. Following surgery, the patient had decreased pain and erythema of the wounds, resolution of pruritus, and normalization of phosphorus and calcium levels.

**C**alcific uremic arteriopathy (CUA), also called calciphylaxis, is a disorder of small-vessel calcification associated with the development of progressive cutaneous plaques and ulcers due to ischemia. This painful condition occurs primarily in patients with chronic kidney disease and is seen especially in those with end-stage renal disease (ESRD) who are undergoing hemodialysis or peritoneal dialysis. The estimated prevalence of CUA in ESRD patients is 4.1%.<sup>1</sup> As the ESRD population continues to grow, this historically rare but serious disorder is likely to become more common. In a recent prospective case control study, the mortality rate at 6 months was 33% in patients with CUA who presented only with cutaneous plaques, and the mortality rate increased to 80% once ulceration developed.<sup>2</sup> Prevention is the mainstay treatment, but once patients with CUA seek medical care, quick recognition and aggressive multidisciplinary treatment are imperative.

### PATHOGENESIS

CUA was first described in 1962 by Selye,<sup>3</sup> who demonstrated calcium salt deposition in tissues of nephrectomized rats that were sensitized with vitamin D or parathyroid hormone and challenged with injections of iron or albumin. Gipstein et al<sup>4</sup> published the first case series in 1976, describing 11 patients with ESRD who developed medial calcinosis of the arteries and painful ischemic ulcers. Abnormal levels of calcium and phosphorus as well as abnormal bone metabolism in

uremia contribute to the development of CUA. In patients with ESRD, the mechanism of abnormal mineral and bone metabolism involves an increase in serum phosphorus, which contributes to increased secretion of parathyroid hormone. Severe derangements in mineral and bone metabolism occur as a result of secondary hyperparathyroidism, dietary changes, treatment of hyperphosphatemia and secondary hyperparathyroidism (with calcium-based phosphate binders in combination with calcitriol and other vitamin D analogues), and calcium absorption from dialysate.<sup>5</sup>

Factors other than the uremic milieu are believed to be involved in the development of CUA. Exposure to certain events or agents, considered sensitizers, has been associated with the development of CUA; possible sensitizers include parathyroid hormone, elevated vitamin D, hypercalcemia, hyperphosphatemia, iron dextran, blood transfusions, warfarin, corticosteroids, and trauma. Warfarin, a vitamin K antagonist, is believed to induce CUA by inhibiting the vitamin K-dependent  $\gamma$ -carboxylation of matrix Gla protein. This protein has been shown to inhibit calcification, and when it is inhibited, pathologic calcification occurs.<sup>6</sup> This mechanism could be related to ESRD because vitamin D is also a cofactor needed for  $\gamma$ -carboxylation of

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### TAKE HOME POINTS

- Calcific uremic arteriopathy (CUA) is seen primarily in patients with end-stage renal disease (ESRD) undergoing dialysis (prevalence, 4.1%).
- Mortality rates approach 80% when infection and sepsis develop.
- CUA is characterized by painful, cutaneous non-healing wounds in the abdominal and thigh region caused by small-vessel medial wall calcification with intimal proliferation.
- Hyperphosphatemia and a calcium–phosphorus product greater than  $55 \text{ mg}^2/\text{dL}^2$  in an ESRD patient with a suspicious lesion (resembling lentigo reticularis) suggests the diagnosis.
- Biopsy is helpful for definitive diagnosis but may be associated with development of a nonhealing ulcer.
- Treatment consists of discontinuing sensitizing agents such as warfarin, correcting calcium and phosphorus levels, frequent hemodialysis with low-calcium dialysate, and parathyroidectomy if severe secondary hyperparathyroidism exists.
- Frequent wound débridement, hyperbaric oxygen therapy, and antibiotics for infected lesions may be needed.

matrix Gla protein. In a recent case report, long-term steroid and methotrexate use were considered sensitizing agents that induced CUA in a patient without ESRD.<sup>7</sup> In contrast, there is a report of a patient with CUA improving with corticosteroid treatment; of note, this patient was not on chronic steroid treatment.<sup>8</sup>

Although high phosphorus and calcium levels may lead to supersaturation and deposition of calcium, another theory suggests that calcification of vessels is not purely a passive process driven by high serum phosphorus and calcium concentrations but is an active process mediated by vascular smooth muscle cells that develop a bone-forming phenotype from the uremic milieu. Using electron microscopy and immunostaining, bone matrix vesicles and bone matrix protein expression have been demonstrated in vascular specimens from patients with CUA.<sup>9,10</sup> In addition, these proteins are present before pathologic calcification develops.

### RISK FACTORS

Several risk factors for the development of CUA have been identified (Table 1). Due to the retrospec-



Figure 1. Calcific uremic arteriopathy lesion of the thigh.

tive nature of studies of CUA and the small size of reported case series, it is difficult to postulate specific risk factors and mechanisms for CUA, but recurring themes exist. Reviews show that ESRD patients with sustained serum phosphorus concentrations greater than  $6.5 \text{ mg/dL}$  and a calcium–phosphorus ( $\text{Ca} \times \text{P}$ ) product above  $55 \text{ mg}^2/\text{dL}^2$  are at high risk for developing CUA.<sup>11</sup> Protein malnutrition (ie, serum albumin level of approximately  $2 \text{ g/dL}$ ),<sup>11,12</sup> body mass index greater than  $30 \text{ kg/m}^2$ ,<sup>12</sup> and diabetes mellitus are risk factors for CUA in hemodialysis patients.<sup>13</sup> These factors are associated with decreased blood flow in areas where CUA commonly occurs, including the abdominal wall and pannus and subcutaneous tissue of the thigh. Alkaline phosphatase levels  $10 \text{ IU/L}$  above normal increased the risk of CUA by 19%.<sup>11</sup> Coates et al<sup>14</sup> reported a case series of 16 patients who presented with CUA over an 11-year period; 7 of these had been on warfarin therapy, and 7 had lost more than 10% body weight over the previous 6 months. The mechanism of warfarin-induced calcification has been described by Price et al.<sup>6</sup> Protein C and S deficiencies are the primary hypercoagulopathic risk factors and may be a factor in a subset of patients.<sup>15</sup>

Although CUA occurs most commonly in patients on hemodialysis or peritoneal dialysis, it has been reported to occur in conditions such as primary hyperparathyroidism, vitamin D intoxication, malignancy, and multiple myeloma.<sup>16</sup> The mechanism most likely involves abnormal calcium and phosphorus metabolism and vascular cell-mediated mineralization as previously discussed. In this context, vitamin D acts as a sensitizing agent for the development of CUA. In addition, rare cases of CUA not associated with ESRD have been reported with breast cancer, cholangiocarcinoma,

**Table 1.** Factors Associated with Development of Calcific Uremic Arteriopathy

End-stage renal disease
Hemodialysis
Calcium–phosphate product > 55 mg <sup>2</sup> /dL <sup>2</sup>
Prolonged hyperphosphatemia
Warfarin use
Diabetes mellitus
Obesity
Hypercoagulable states
Protein malnutrition
Caucasian race
Elevated alkaline phosphatase

and alcoholic cirrhosis.<sup>17</sup> These reports are most likely associated with abnormal calcium metabolism and derangements in parathyroid activity causing pathologic calcification.

### DIAGNOSIS

CUA has a high mortality rate, especially when secondary infection or wet gangrene occurs, as these lead to severe systemic sepsis and death.<sup>18</sup> Distal limb lesions are associated with a 23% mortality rate, while the more common thigh and abdominal wall lesions carry a 63% mortality rate.<sup>19</sup> Quick recognition and diagnosis of CUA can decrease morbidity and prolong survival. The clinical features of CUA resemble those of other significant diseases (**Table 2**), and it is important to consider every diagnosis in the differential to allow quick appropriate treatment. CUA is diagnosed based on the clinical examination. Laboratory evaluation and occasionally radiology can suggest the diagnosis; in equivocal cases, biopsy can establish the diagnosis.

### Presentation and History

A long history of ESRD and renal replacement therapy (ie, functional renal graft, hemodialysis, peritoneal dialysis) should raise suspicion for CUA in patients with painful cutaneous lesions or nodules. Renal insufficiency associated with chronic kidney disease can be associated with CUA.<sup>20,21</sup> A history of intensely painful lesions suddenly appearing and progressing quickly is characteristic. Trauma can precipitate the occurrence of CUA, and patients should be questioned about any trauma to the site of the lesion such as a scratch, insulin injection puncture, or bite.<sup>22</sup> Knowing the acute and chronic use of medication helps differentiate CUA from other conditions such as warfarin-induced skin necrosis. Patients should be questioned

**Table 2.** Differential Diagnosis of Calcific Uremic Arteriopathy

Peripheral vascular disease
Hypersensitivity vasculitis
Venous stasis
Disseminated intravascular necrosis
Warfarin-induced skin necrosis
Thromboembolic phenomena
Hypercoagulable diseases
Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis

regarding use of warfarin, iron dextran, blood transfusions, corticosteroids, vitamin D, and phosphate binders, all of which have been linked to CUA.<sup>23–27</sup>

### Physical Examination

Physical examination findings include firm cutaneous nodules and/or plaques with or without ulceration. Lesions appear mottled and bluish-purple to black and are exquisitely tender to the touch. Lesions may extend into the muscle and cause a myopathy.<sup>28</sup> Advanced stages exhibit full-thickness skin and subcutaneous necrosis with gangrene. Superinfection yields erythematous even purulent wounds, usually ending in sepsis and death. Plaques and ulcers primarily occur on areas of thick adipose tissue such as the thighs and abdomen; especially prone is a large pannus. To a lesser extent hand, foot, and ankle involvement is found.<sup>13,22</sup> CUA lesions can occur anywhere (a rare case presented with penile involvement),<sup>29</sup> and CUA rarely can present limited to visceral organs. Pulmonary and cardiac involvement has been reported.<sup>30,31</sup>

Palpating pulses, obtaining ankle-brachial indices, and looking for the reddish-brown staining with brawny edema will aid in differentiating CUA from peripheral vascular disease and venous stasis. Rarely will CUA involve the digits or inner ankles. Differentiating CUA from advanced vascular diseases is important as the acute management differs. Thromboembolism can be excluded with a thorough cardiac examination and angiography, as needed. Autoimmune vasculitides will have antibodies on fluoroscopic examination, while CUA does not.

### Laboratory and Radiologic Evaluation

Laboratory studies should include measurement of serum electrolytes. Hyperphosphatemia and a Ca × P product exceeding 55 mg<sup>2</sup>/dL<sup>2</sup> is suggestive of CUA, although not all patients will have this finding.<sup>5</sup> If hyperparathyroidism and an elevated Ca × P product are



**Figure 2.** Calcific uremic arteriopathy of abdominal wall on computed tomography scan.

found, then surgical parathyroidectomy may be needed. Coagulation factors including prothrombin time, activated partial thromboplastin time, and protein C and S levels are important to assess for hypercoagulopathy.<sup>25</sup> An autoimmune work-up may prove beneficial if the diagnosis is in question as autoimmune disorders, vasculitides, or dermatologic manifestations of diseases such as cryoglobulinemia can cause violaceous lesions and necrosis.<sup>32</sup> An elevated white blood cell count with a left shift on differential is an important sign of infection.

Radiologic tests are rarely helpful for definitive diagnosis but may help in equivocal cases. Plain radiographs or computed tomography may show calcifications (**Figure 2**), but this finding is nonspecific in older patients with diabetes and ESRD. A bone scan is positive in 97% of patients with CUA<sup>2</sup> and may be helpful in determining whether CUA is responding to treatment; however, Goldsmith<sup>33</sup> showed it was neither sensitive nor specific in establishing the initial diagnosis. The best imaging test to demonstrate small calcified vessels is xeroradiography.<sup>34</sup> This modality is very similar to mammography with its fine magnification, but clinical experience with and reproducibility of this test are lacking.

Wilmer et al<sup>35</sup> has shown in small studies that transcutaneous oxygen saturations can suggest the diagnosis of CUA. A skin oxygen saturation of less than 30 mm Hg on ambient air is characteristic of the ischemic nature of this disease.<sup>35</sup>

### Biopsy

A pathologic specimen obtained by core or incisional biopsy using sterile technique will establish the diagnosis in equivocal cases.<sup>33</sup> Specimens from the lesions show calcium deposition in small arterial (100  $\mu$ m) walls with intimal proliferation as well as lobular fat necrosis, calcifications, and infiltrate in neutrophils, lymphocytes, and macrophages.<sup>36</sup> However, because CUA lesions are inherently ischemic, there is a risk of the biopsy site not healing and becoming contaminated with bacteria, yielding superinfection.

### TREATMENT

Acute treatment of CUA is instituted by a multidisciplinary team and can be divided into nonoperative and operative treatment.

#### Nonoperative Therapy

As possible sensitizing agents, warfarin, corticosteroids, calcium or vitamin D supplementation, and intravenous iron therapy should be discontinued. Normalization of calcium and phosphate levels to low normal is key. Russell et al<sup>37</sup> accomplished this by increasing the dose and frequency of dialysis up to 4 hours 6 times per week, in addition to adjusting medications. Using low-calcium dialysate is very important. In addition, dietary restriction of phosphorus through low-protein diets (noncompliance is common) and the use of calcium-free phosphate binders are helpful. Sevelamer hydrochloride is effective in reducing both phosphorus and parathyroid hormone levels in addition to lowering the Ca  $\times$  P product.<sup>38</sup> Other calcium-free phosphate binders that use aluminum or magnesium are beneficial but carry a more severe side effect profile than sevelamer. Vitamin D supplementation with calcitriol is effective for correcting hyperparathyroidism, but it induces intestinal absorption of calcium and phosphorus. Newer analogues, such as paricalcitol and doxercalciferol, are recommended because they result in less intestinal absorption of calcium and phosphorus while maintaining a high affinity for negative feedback on the parathyroid gland.<sup>39</sup>

Correction of hypercoagulable states, vitamin K supplementation if deficiency is present, and, most importantly, avoiding or discontinuing warfarin are indicated.<sup>16</sup> Pain relief with appropriate analgesics is essential; large doses may be required. Lumbar sympathetic blockade has been shown to be beneficial for the exquisitely painful lesions.<sup>40</sup> Broad-spectrum antibiotics based on antibiograms are necessary when infection is present. Due to the ischemic nature of the lesions, nasal cannula oxygen and even hyperbaric oxygen can be used in the acute

setting to help heal wounds and decrease the amount of pain, although studies have had mixed results.<sup>41</sup>

Several treatments for CUA have been reported in the literature. Bisphosphonates are used to inhibit bone resorption, but at higher doses these agents inhibit bone mineralization. Researchers have prevented warfarin- and vitamin D-induced arterial calcification in rats using bisphosphonates, including ibandronate, alendronate, and etidronate.<sup>42,43</sup> They hypothesized that vascular cells having the phenotypic features of osteoclasts and osteoblasts initiate pathologic calcification. In a hemodialysis-dependent ESRD patient with skin ulcers due to CUA, administration of oral etidronate at a dose of 200 mg/day resulted in immediate resolution of fever and healing within days with improvement of infection.<sup>43</sup> In a patient with painful necrotic ulcers and necrosis, intravenous sodium thiosulfate 3 times weekly resolved pain after 2 weeks and allowed healing at 4 weeks.<sup>44</sup> Cinacalcet is a calcimimetic that has been used successfully to treat CUA in patients with secondary hyperparathyroidism.<sup>45</sup> It acts within hours by increasing the sensitivity of calcium-sensing receptors of the parathyroid gland, causing a reduction of parathyroid hormone, calcium, and phosphorus, stabilizing the parathyroid axis.<sup>45</sup>

### **Operative Treatment**

Surgical consultation is recommended for possible subtotal or total parathyroidectomy and serial wound débridement or amputation. No randomized trials are reported in the literature, but subtotal with or without reimplantation and total parathyroidectomy have been shown to decrease pain, increase wound healing, and decrease parathyroid hormone, calcium, and phosphorus levels in patients with CUA. Girotto et al<sup>46</sup> showed that when secondary hyperparathyroidism was present parathyroidectomy improved wound healing and increased survival versus nonoperative treatment; these results agreed with previous findings.<sup>4,47</sup> In a review of 16 patients treated for CUA, 7 patients with severe hyperparathyroidism, a Ca × P product greater than 70 mg<sup>2</sup>/dL<sup>2</sup>, and debilitating pain underwent subtotal parathyroidectomy in addition to intensive medical care received by every other patient; a survival advantage was observed in the parathyroidectomy group (14.8 months versus 6.3 months).<sup>48</sup> In conclusion, complete parathyroidectomy and subtotal parathyroidectomy are indicated for secondary hyperparathyroidism and the presence of CUA in addition to palliation of pain. We prefer to reserve 3.5-gland parathyroidectomy with or without reimplantation for patients with severe pain or those with an elevated Ca × P product.

Serial débridements of infected necrotic tissue by an experienced surgeon are warranted and aid in wound healing and treatment of sepsis. Amputation is associated with poor healing rates but may be necessary in patients with chronically infected wounds or the acutely septic patient with distal wounds.<sup>49</sup> Because CUA is an ischemic condition, revascularization procedures for peripheral vascular disease involving the extremities may prove beneficial.

### **Prevention**

Prevention of CUA is essential. Recommendations include maintaining a serum phosphorus level less than 5.5 mg/dL, calcium level less than 9.6 mg/dL, and a Ca × P product less than 55 mg<sup>2</sup>/dL<sup>2</sup>. Use of dialysate with a low concentration of calcium and calcium-free phosphate binders is encouraged.<sup>50</sup> The use of vitamin D analogues other than calcitriol and administering calcimimetics such as cinacalcet to control secondary hyperparathyroidism is beneficial. Avoiding warfarin in patients at risk for CUA by substituting alternative anticoagulants should be considered. Maintaining adequate diet to decrease phosphorus/protein intake and control diabetes and obesity help prevent CUA but can be difficult and fraught with noncompliance. Finally, avoiding the slightest trauma can help prevent serious infections.

### **CONCLUSION**

CUA presents as a painful ischemic cutaneous disease found primarily in ESRD patients. Abnormal calcium and phosphorus metabolism and parathyroid hormone feedback irregularities are involved in the development of this disease. Multiple risk factors exist, but most reports in the literature contain fewer than 20 patients, making definite assumptions difficult. Presentation is generally an obese, dialysis-dependent ESRD patient with abdominal or thigh wounds that resemble lentigo reticularis and may be gangrenous and necrotic. Treatment is multidisciplinary after other vascular, autoimmune, or thromboembolic phenomena have been ruled out. Cessation of sensitizers such as warfarin and avoidance of subcutaneous trauma is necessary. Decreasing calcium and phosphorus levels, treatment of hypercoagulable states, vitamin K repletion, and antibiotics as indicated are imperative. A surgical consult for parathyroidectomy is recommended when secondary hyperparathyroidism coexists or severe pain continues. Wound débridement and amputations are occasionally needed, although outcomes are characterized by poor healing. Appropriate dosing with analgesics is necessary for palliation of severe pain. **HP**

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