Digital gangrene and pneumatosis intestinalis associated with calciphylaxis

Qingwen Kawaji, MSc,[a] Erik Brian Eller, MD,[b] Jerry Yee, MD,[c] *and* Judith C. Lin, MD, MBA,[a] *Detroit, Mich*

ABSTRACT

Reports of calciphylaxis or calcific uremic arteriolopathy associated with acral and gastrointestinal involvement are rare. We describe a 36-year-old white woman with end-stage renal disease on hemodialysis after failed kidney and pancreas transplantation who developed dry gangrene of bilateral digits, osteomyelitis, and small bowel ischemia within several months of each presentation. She had multiple débridements of a septic right ankle. Computed tomography angiography showed severe vascular calcification and pneumatosis intestinalis. She underwent intestinal resection for gangrenous small bowel. A multidisciplinary approach with aggressive medical and surgical management may improve survival. Our case and the literature confirm the high morbidity of patients with calciphylaxis and vascular complications. Careful follow-up remains necessary for diagnosis and management to prevent complication, infection, and death. (J Vasc Surg Cases and Innovative Techniques 2018;4:133-5.)

CASE REPORT

A 36-year-old woman with history of type 1 diabetes mellitus, end-stage renal disease on hemodialysis, hypertension, osteomyelitis, and pancreas and kidney transplantation, with subsequent failure of the kidney transplant, underwent right triple arthrodesis with a right midtarsal arthrodesis and an Achilles tendon lengthening in 2014. Six months before her last hospitalization, she developed a septic right ankle and underwent removal of the hardware for a Charcot midfoot. She had a 6-week course of intravenous ertapenem for *Streptococcus mitis* and *Klebsiella pneumoniae*. She underwent placement of a right ankle spatial frame for loss of bone and antibiotic beads for persistent infection from *Klebsiella oxytoca* and *Enterococcus faecalis* (Fig 1). Additional wound culture showed *Stenotrophomonas (Xanthomonas) maltophilia*. She declined amputation of her right foot.

The patient developed a 3-month history of intermittent paresthesia, worsening pallor, and eventual dry gangrene of the fingers (Fig 2). The vascular surgery service was consulted for evaluation of painful, gangrenous hands and left foot. Ankle-brachial index showed incompressible vessels with absent perfusion of the digits and toes. Computed tomography (CT) angiography (Fig 3) showed circumferential calcified atherosclerotic disease of the ulnar, radial, and interosseous arteries and mesenteric vessels. Significant laboratory studies showed low glomerular filtration rate of 11 mL/min/1.73 m^2, elevated parathyroid level of 28 pg/mL, and high phosphorus level of 5.6 mg/dL. The diagnosis of calciphylaxis was determined on the basis of clinical presentation.

Two months later, the patient presented to the emergency department with a 2-day history of diffuse abdominal pain associated with nausea, vomiting, nonbloody diarrhea, fever, and chills. CT of the abdomen revealed extensive small bowel pneumatosis involving multiple bowel loops, suggestive of ischemic causes. The superior mesenteric artery demonstrated dense, circumferential atherosclerosis with circumferential calcification at the distal branches. The patient underwent resection of 130 cm of necrotic small bowel and second-look laparotomy. Pathologic examination showed transmural ischemic necrosis with ulceration, perforation, and acute peritonitis. She was discharged home 2 weeks later.

Six months after her initial presentation of septic arthritis, 3 months after digital gangrene, and 2 months after ischemic bowel, the patient developed leukocytosis, hypotension, and decubitus ulcer. She was readmitted for infection of the right foot, treated with antibiotics, and discharged 2 weeks before her death at home on December 30, 2017. Consent for publication was obtained from the patient before her death.

DISCUSSION

Also known as calcific uremic arteriolopathy, calciphylaxis was first characterized by Selye et al[1] in 1961 as a hypersensitivity reaction in rodents resulting in calcification of skin and skeletal muscles. It is a devastating disease with an estimated prevalence of 4.1% in hemodialysis patients and mortality of 60% within 1 year due to infections.[2,3] The mechanism of arterial calcification is a dynamic and active process that shares common grounds with normal bone mineralization.[4] Under the influence of β-glycerophosphate, smooth muscle cells can undergo osteoblastic differentiation, resulting in a favorable environment for mineralization.[4] Calcification

From the Division of Vascular Surgery,[a] Department of Orthopedic Surgery,[b] and Division of Nephrology,[c] Henry Ford Hospital.

Author conflict of interest: none.

Correspondence: Judith C. Lin, MD, MBA, Division of Vascular Surgery, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202 (e-mail: jlin1@hfhs.org).

The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2468-4287

https://doi.org/10.1016/j.jvscit.2018.02.007

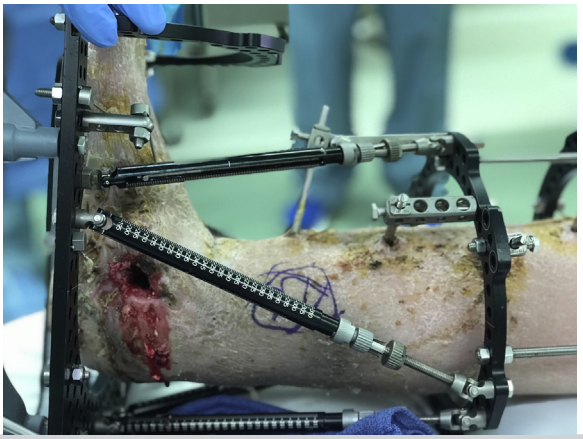

Fig 1. Placement of right ankle spatial frame for loss of bone and heel gangrene.

Fig 2. Dry gangrene of multiple fingers.

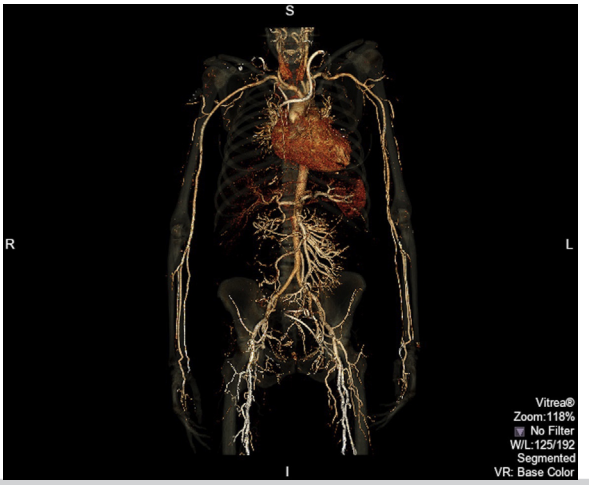

Fig 3. Computed tomography (CT) angiography showed circumferential calcified atherosclerotic disease of arteries in the upper extremities and mesenteric vessels.

occurs in the intimal layer, leading to atherosclerotic plaque and a decreased luminal area, and in the medial layer, resulting in loss of arterial compliance.[5] Histologic features include small- and medium-vessel medial calcification with intimal calcium deposits associated with dermal angioplasia and thrombosis. There is no histologic difference between patients with and patients without chronic kidney disease.[4]

Common presentation of calciphylaxis includes painful and nonhealing wounds that can result in black eschar and secondary superinfection.[6] Most commonly, these lesions occur in adipose-rich areas, such as trunk, buttocks, and thighs, although acral and penile involvement has also been reported.[7-9] Ocular, cardiovascular, pulmonary, and gastrointestinal system complications are extremely rare, with fewer than 10 reported cases of gastrointestinal involvement in calciphylaxis.[7,8,10-13] Risk factors for calciphylaxis include hyperparathyroidism, elevated calcium-phosphorus product, chronic kidney disease, diabetes, female sex, warfarin use, and obesity.[9]

Diagnosis of calciphylaxis is clinically supported by skin biopsy as the "gold standard." However, normal findings on skin biopsy do not rule out calciphylaxis because only 18% of 56 biopsy specimens from confirmed patients showed classic features of calcification of the arterioles.[2] Hayashi[6] proposed the use of histopathologic findings for calciphylaxis only if three of the clinical findings are not present: chronic hemodialysis or glomerular filtration rate <15 mL/min/1.73 m^2; more than two painful and nontreatable skin ulcers; and ulcers on trunk, extremities, or penis.

The high mortality rate of calciphylaxis is most often associated with infection of nonhealing wounds leading to sepsis, with 1-year survival <50% and 2-year survival <20%.[2] Gastrointestinal involvement of calciphylaxis is extremely rare with grim outcome.[7,8,10-13] A case report described a 63-year-old woman who presented with skin lesions of bilateral calves, single-digit discoloration of the left hand, and abdominal pain, with CT confirming colonic perforation.[12] Another case report described a 66-year-old woman with black necrotic eschar on bilateral lower extremities, lower gastrointestinal bleed, and rectal necrosis.[13] The patients of both cases died of sepsis and multiorgan failure. Although skin biopsy may confirm diagnosis of calciphylaxis, we advise clinicians to use caution regarding skin biopsy and invasive treatments because of poor healing and increased risk of sepsis.[6]

Current mainstays of treatment are mostly supportive, including pain control, wound care, intravenous sodium thiosulfate, correction of calcium and phosphorus levels, bisphosphonates, vitamin K, and full-intensity anticoagulation.[2] Patecki et al[9] recommended bone biopsy in patients with calciphylaxis to dictate therapy after determination of the level of bone turnover. The benefit of kidney transplantation in calciphylaxis remains unclear, and diverging results after renal transplantation have been reported.[2] An observational study proposed that intralesional sodium thiosulfate injections rather than

intravenous infusions may be an effective treatment of skin lesions due to calciphylaxis; however, this recommendation was based on four patients, and a case report showed that needle injections led to abscess formation and worsening of skin lesions.[14] Hyperbaric oxygen therapy (HBOT) is associated with better wound healing and extended survival time in >50% of patients with an average of 44 treatments; diabetes was the only factor that significantly influenced wound healing and mortality.[15] Use of sodium thiosulfate with HBOT has also been suggested to have a synergistic effect, but concrete data are needed for recommendation.[16] The role of revascularization for wound healing in calciphylaxis is insufficiently studied with no definitive recommendations. Furthermore, vascular procedures are a negative determinant of survival in patients with calciphylaxis.[17]

Multiple studies suggest that treatment of calciphylaxis is multimodal, and early initiation of such therapies is instrumental in achieving the best patient outcome.[2,6,16] Finally, because of the high mortality and morbidity associated with calciphylaxis, it is important to initiate early conversations of disease prognosis and approach to therapy with patients and their families so that their priorities can be factored in when management is being planned.[2] Finally, it is important to address end-of-life issues with such patients because of the high mortality and morbidity associated with calciphylaxis.

CONCLUSIONS

This patient has multiple risk factors and clinical presentation for calciphylaxis. Noninvasive arterial studies and CT angiography demonstrating incompressible vessels and vascular calcifications further solidify the diagnosis of calcific uremic arteriolopathy. HBOT and sodium thiosulfate may be considered viable therapies. A multidisciplinary approach with aggressive medical and surgical management may improve survival. Our case and the literature confirm the high morbidity of patients with calciphylaxis and vascular complications. Careful follow-up remains necessary for diagnosis and management to prevent complication, infection, and death.

REFERENCES

1. Selye H, Gentile G, Prioreschi P. Cutaneous molt induced by calciphylaxis in the rat. Science 1961;134:1876-7.
2. Jeong HS, Dominguez AR. Calciphylaxis: controversies in pathogenesis, diagnosis and treatment. Am J Med Sci 2016;351:217-27.
3. Angelis M, Wong LL, Myers SA, Wong LM. Calciphylaxis in patients on hemodialysis: a prevalence study. Surgery 1997;122:1083-9; discussion: 1089-90.
4. Chen TY, Lehman JS, Gibson LE, Lohse CM, El-Azhary RA. Histopathology of calciphylaxis: cohort study with clinical correlations. Am J Dermatopathol 2017;39:795-802.
5. Block GA. Control of serum phosphorus: implications for coronary artery calcification and calcific uremic arteriolopathy (calciphylaxis). Curr Opin Nephrol Hypertens 2001;10:741-7.
6. Hayashi M. Calciphylaxis: diagnosis and clinical features. Clin Exp Nephrol 2013;17:498-503.
7. Igaki N, Moriguchi R, Hirota Y, Sakai M, Akiyama H, Tamada F, et al. Calciphylaxis in a patient with end-stage renal disease secondary to systemic lupus erythematosus associated with acral gangrene and mesenteric ischemia. Intern Med 2001;40:1232-7.
8. Komurcu HF, Basar E, Kucuksahin O, Uz E, Orhun Yavuz HS, Anlar O. Bilateral optic neuropathy, acral gangrene and visceral ischaemia as a rare presentation of calciphylaxis: a case report. J Pak Med Assoc 2016;66:1324-6.
9. Patecki M, Lehmann G, Bräsen JH, Schmitz J, Bertram A, Berthold LD, et al. A case report of severe calciphylaxis—suggested approach for diagnosis and treatment. BMC Nephrol 2017;18:137.
10. Brown DF, Denney CF, Burns DK. Systemic calciphylaxis associated with massive gastrointestinal hemorrhage. Arch Pathol Lab Med 1998;122:656-9.
11. Volpini K, Kinonen C. Abdominal catastrophe in a 43-year-old female with end stage renal disease. Semin Dial 2011;24:79-82.
12. Rivera-Nieves J, Bamias G, Alfert J, Bickston SJ, Moskaluk CA, Cominelli F. Intestinal ischemia and peripheral gangrene in a patient with chronic renal failure. Gastroenterology 2002;122:495-9.
13. Gupta N, Haq KF, Mahajan S, Nagpal P, Doshi B. Gastrointestinal bleeding secondary to calciphylaxis. Am J Case Rep 2015;16:818-22.
14. Strazzula L, Nigwekar SU, Steele D, Tsiaras W, Sise M, Bis S, et al. Intralesional sodium thiosulfate for the treatment of calciphylaxis. JAMA Dermatol 2013;149:946-9.
15. An J, Devaney B, Ooi KY, Ford S, Frawley G, Menahem S. Hyperbaric oxygen in the treatment of calciphylaxis: a case series and literature review. Nephrology 2015;20:444-50.
16. Rogers NM, Coates PT. Calcific uremic arteriolopathy—the argument for hyperbaric oxygen and sodium thiosulfate. Semin Dial 2010;23:38-42.
17. Lal G, Nowell AG, Liao J, Sugg SL, Weigel RJ, Howe JR. Determinants of survival in patients with calciphylaxis: a multivariate analysis. Surgery 2009;146:1028-34.

Submitted Dec 2, 2017; accepted Feb 11, 2018.