
Calciophylaxis: Comparison of radiologic imaging and histopathology



Charles L. Halasz, MD,^{a,b} David P. Munger, MD,^c Heather Frimmer, MD,^c
Michael Dicorato, MD,^d and Sandra Wainwright, MD^e
New York, New York; and Norwalk and Greenwich, Connecticut

Background: The current gold standard for diagnosis of calciophylaxis is a skin biopsy specimen demonstrating calcification of small-caliber arteries or arterioles.

Objective: The aim of this study is to compare diameters of calcified vessels seen in skin biopsy specimens and radiology images of patients with calciophylaxis.

Methods: We conducted a retrospective study of patients with known calciophylaxis from 2009 to 2016 at a community hospital who had both skin biopsy specimens and radiology images taken as part of their routine care. Vascular calcification was compared in skin biopsy specimens and radiology images.

Results: Seven patients were identified. Small-vessel calcification as fine as 0.1 to 0.3 mm was identified on plain films in 3 patients; 0.1 to 0.2 mm by mammography in 3 patients, and 0.1 to 0.2 mm by computed tomography imaging in 1 patient, nearly as fine a resolution as on histopathology.

Limitations: This was a single-center study with limited sample size.

Conclusion: Radiologic imaging might enable more rapid diagnosis of calciophylaxis when skin biopsy specimen is pending or not available. (J Am Acad Dermatol 2017;77:241-6.)

Key words: calcific uremic arteriopathy; calciophylaxis; mammography; radiologic imaging.

Calciophylaxis, also termed “calcific uremic arteriopathy,” is a serious complication well known to nephrologists, dermatologists, and wound-care specialists consulting on hospital patients, but relatively unknown to other specialties. It presents with painful indurated violaceous skin lesions that ulcerate, often with an overlying jagged black eschar. Older estimates of the incidence rate in patients on dialysis for chronic renal failure have ranged from 1% to 4%.^{1,2} Newer estimates suggest a rate below 1% although with a trend upward.³⁻⁵ Calciophylaxis can also present in nonuremic patients with milder renal dysfunction.^{6,7} A diagnosis of calciophylaxis carries a 1-year mortality of 45% to 80%.⁸ The mortality is 2.5 to 3 times higher in patients with calciophylaxis than in the general hemodialysis population.⁵ Although usually

requiring a skin biopsy specimen for confirmation of the diagnosis, radiography can assist in early diagnosis of this condition. In this study we compare calcification of small vessels as measured by histopathology and by radiology as described below and summarized in Table I.

METHODS

Diameters of calcified vessels seen in skin biopsy specimens and radiology images of patients with calciophylaxis at a community hospital who had these studies done as part of their routine care during 2009 to 2016 were compared. Records of 7 patients with calciophylaxis were located. Six of the 7 patients had histopathology confirming the diagnosis. One (case 2) had a lower extremity amputation and calciophylaxis involving the penis, and further skin

From the Department of Dermatology, Columbia University Medical Center, New York^a; Departments of Medicine,^b Radiology,^c and Pathology,^d Norwalk Hospital; and Department of Hyperbaric Medicine and Wound Healing, Greenwich Hospital.^e

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Reprint requests: Charles L. Halasz, MD, Department of Medicine, Norwalk Hospital, 149 East Ave, Suite 20, Norwalk, CT 06851.

E-mail: ch1@cumc.columbia.edu.

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biopsy specimen was thought to be contraindicated. His diagnosis was confirmed by mammographic imaging. This retrospective study was approved by the Norwalk Hospital Institutional Review Board.

RESULTS

Patients ranged in age from 29 to 76 years. Four were male, and 3 were female. Five had diabetes. All had chronic kidney disease. Six were on hemodialysis and had an elevated calcium-phosphate product. Three were anticoagulated with warfarin, 1 with low-molecular-weight heparin, and 2 with platelet inhibitors. Five patients received intravenous thiosulfate, and 3 received hyperbaric oxygen. Wounds were debrided. Six of the patients improved, and 1 was transferred to hospice care.

Three patients had mammographic imaging specifically ordered to identify fine vascular calcification adjacent to skin ulceration, thereby facilitating rapid confirmation of the clinical diagnosis. Additional radiographic imaging reviewed retrospectively for identification of vascular calcification included 1 patient with computed tomography (CT) of the extremities, and 4 patients with plain film radiography of the hand, foot, ankle, or distal extremities. Diameters of the smallest calcified vessels measured on skin biopsy specimens ranged from 0.04 to 0.3 mm. Resolution of calcified vessels by radiologic imaging was nearly as fine, with smallest vessels visualized at 0.1 to 0.3 mm. Results are reported in detail in Table I. Clinical and radiologic images are presented in Figs 1-3 and Supplementary Figs 1-3 (available at <http://www.jaad.org>).

DISCUSSION

Calciophylaxis can be regarded as a kind of calcific sclerosis of the tunica media of the microvasculature. Small arteries and arterioles are the major determinant of peripheral arterial resistance⁹ and it is speculated that these vessels, when calcified, are unable to vasodilate in response to pressure or other stresses, with consequent ischemia and necrosis of involved skin, resulting in calciophylaxis.¹⁰ Fischer and Morris¹¹ reported that involved arterioles have luminal diameters of 0.02 to 0.6 mm with most

measuring about 0.1 mm. In the experience of the authors, calcified vessels this small are not commonly identified in radiographs of elderly patients. One study of 131 renal transplant recipients found extensive small-vessel calcification on plain radiographs (mainly of the hands) in 12 patients.¹²

All developed severe complications, including gangrene and myositis with mortality reported in 9. Interestingly, a muscle biopsy specimen of one is depicted and shows microcalcification of the tunica media. However, systematic studies evaluating the extent of medial calcification of the microcirculation have not been performed to date.¹³

Another pattern of calcification affecting larger arteries is termed "Monckeberg medial calcific sclerosis" and involves the muscular tunica media. Monckeberg medial calcific sclerosis is a common incidental finding seen in radiographs, described as "rail-

road," "tram tracks," or "pipstem" calcification, particularly of older patients and those with chronic kidney disease or diabetes.^{11,13,14} The prevalence of Monckeberg medial calcific sclerosis in adults between age 45 and 75 years was estimated to be 13.3% in males, and 6.9% in females when calculated by ankle-brachial index greater than 1.3.¹⁵ The prevalence of calcification of larger arteries in patients awaiting renal transplantation evaluated by plain film radiography of the pelvis, thigh, or both was reported to be 39.5%.¹⁶ In a study of Finnish diabetics between ages 45 and 64 years, calcification of the femoral artery was noted in 41.5% of patients.¹⁷ An additional pattern of vascular calcification, patchy calcification of the tunica intima of larger arteries, is associated with atherosclerosis.^{18,19}

The main differential diagnosis of calciophylaxis includes atherosclerotic disease, cholesterol embolism, nephrogenic systemic fibrosis, oxalate vasculopathy, purpura fulminans, vasculitis, and warfarin necrosis.⁸ Normally confirmation of the clinical diagnosis requires a skin biopsy specimen demonstrating calcification of small arteries and arterioles with microthrombi sometimes noted, along with interstitial tissue calcium deposition, and resultant inflammation and ischemic necrosis.⁸ However, this procedure entails a risk of bleeding,

CAPSULE SUMMARY

- The diagnosis of calciophylaxis in patients presenting with painful cutaneous ulcers is typically confirmed by a skin biopsy demonstrating small vessel calcification.
- In a series of 7 patients, commonly used radiologic imaging techniques including plain films, mammography, and computerized tomography scans visualized fine vessel calcification comparable to histopathology.
- Collaborating with radiology colleagues to identify small vessel calcification that might otherwise be overlooked can assist in early diagnosis of calciophylaxis.

Table I. Summary of cases

Patient	Age; sex; medical history	Creatinine mg/dL (reference range <1.3)	Anticoagulation	Ca-Phos product mg ² /dL ² (reference range <55)	Treatment	Pathology specimen location	Calcification pathology diameter, mm	Radiology image and location	Calcification radiology diameter, mm
1	69 y; F; CKD, DM, obesity, CAD	2.8	Ticagrelor	42.1	Na ₂ S ₂ O ₃	Right hip	0.2-0.3	Mammogram right hip	0.2-0.3
2	64 y; M; CKD, DM, hemodialysis	10.7	Aspirin	66.8	Na ₂ S ₂ O ₃ and HBO	Below left knee amputation	Larger vessels (anterior and posterior tibial arteries)	Mammogram right leg	0.1-0.3
3	59 y; M; CKD, hemodialysis	3.9	Warfarin	78.6	HBO	Right leg	0.15-0.25	Plain film legs	0.8-1.6
4	76 y; M; CKD, DM, hemodialysis	5.7	Warfarin	84.6	Hospice	Right thigh	0.1	Plain film left foot	0.3-0.4
5	65 y; F; CKD, DM, COPD, DVT hemodialysis	8.4	Enoxaparin	90.5	Na ₂ S ₂ O ₃	Right buttock and thigh	0.05-0.12	Plain film feet	0.2-0.4
6	29 y; F; CKD, DM hemodialysis	10.3	None	89.2	Na ₂ S ₂ O ₃ and HBO	Left arm	0.15	CT lower extremities Plain film left foot	0.1-0.2 0.2
7	52 y; M; CKD, hemodialysis	11.8	Warfarin	63.0	Na ₂ S ₂ O ₃	Right leg	0.04-0.09	Mammogram right leg Plain film feet	0.2 0.7-0.8

CAD, Coronary artery disease; Ca-Phos product, calcium-phosphate product; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DM, diabetes mellitus; DVT, deep vein thrombosis; F, female; HBO, hyperbaric oxygen; M, male; Na₂S₂O₃, sodium thiosulfate.

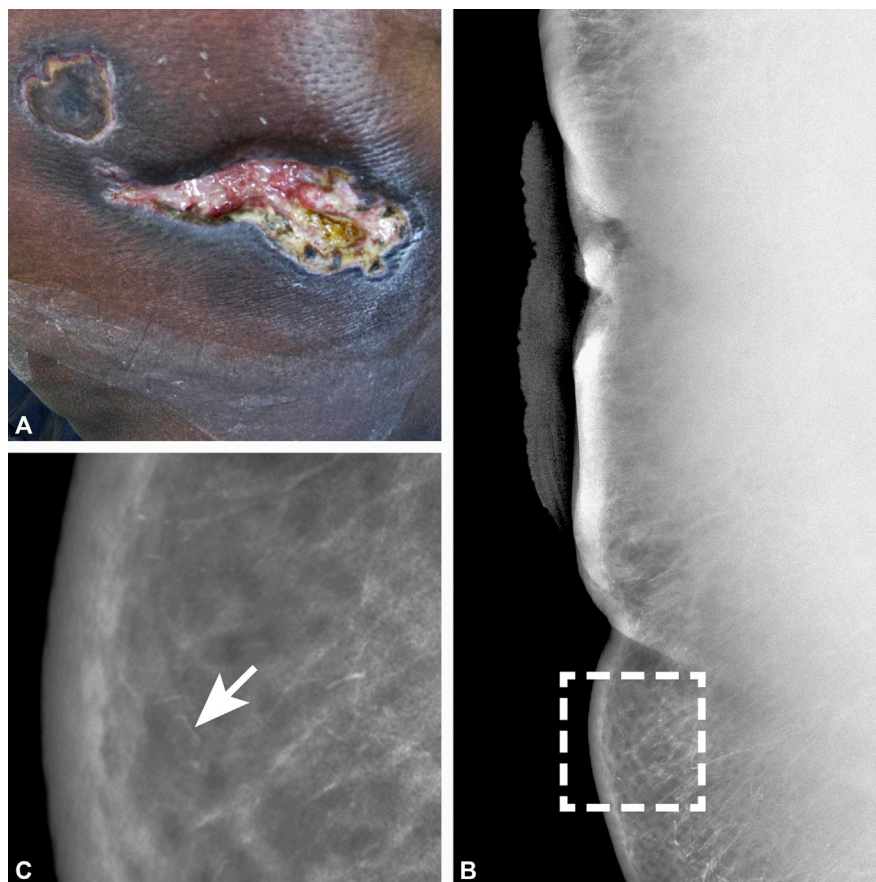


Fig 1. Calciphylaxis. Patient 1. **A**, Right buttock ulcer. **B**, Mediolateral mammographic image of the soft tissues of the left gluteal area. **C**, Zoomed-in image from the full mammogram. Smallest vessel diameters ranged from 0.2 to 0.3 mm (*arrow*).



Fig 2. Calciphylaxis. Patient 2. **A**, Right calf ulcer. **B**, Necrosis of tip of penis. **C**, Mediolateral mammographic image obtained from the right ankle posterior soft tissues. **D**, Zoomed-in image. Smallest vessel diameters ranged from 0.1 to 0.3 mm (*arrow*).

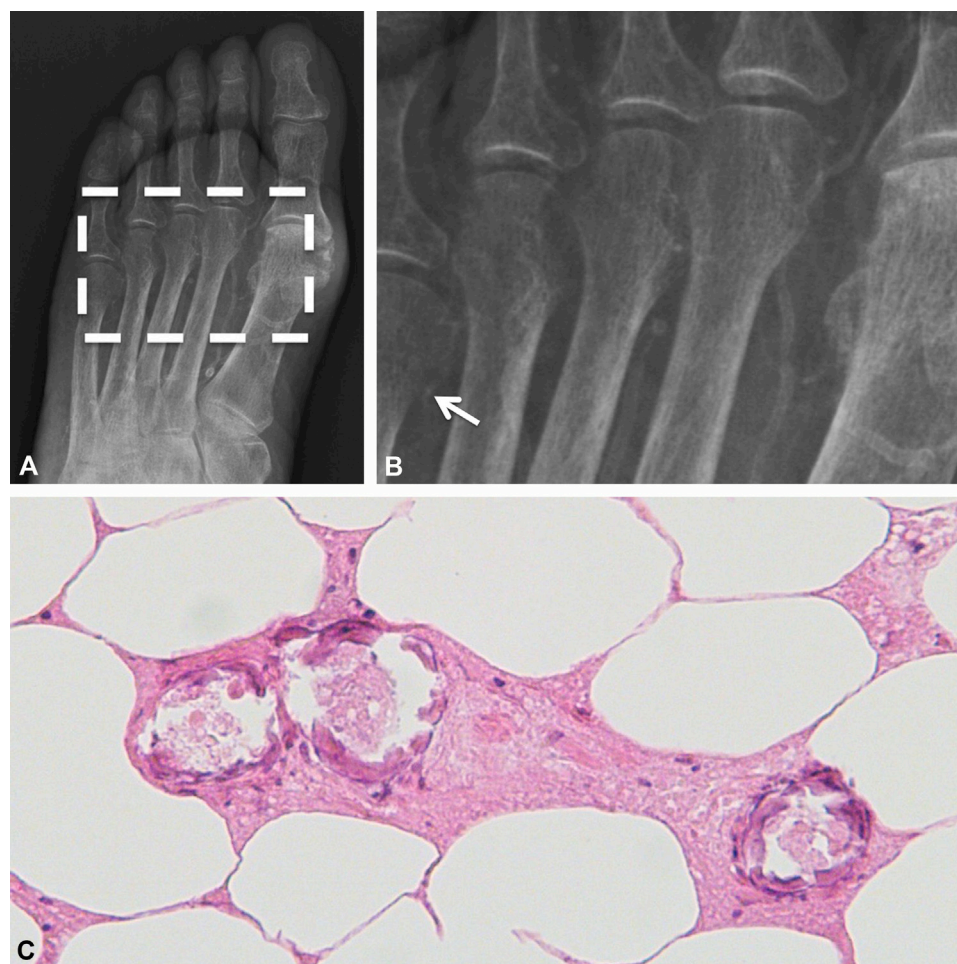


Fig 3. Calciphylaxis. Patient 5. **A**, Anteroposterior radiograph of the left foot. **B**, Zoomed-in image from the full radiograph. Smallest vessel diameters ranged from 0.2 to 0.4 mm (arrow). **C**, Histopathology demonstrated calcification of vessels 0.05 to 0.12 mm. (Original magnification: $\times 200$.)

poor healing of the biopsy site, and even extension of necrosis.²⁰ When calciphylaxis involves the penis (as in patient 2), biopsy specimen may even be contraindicated.²¹ Therefore some authors have sought noninvasive radiologic methods to visualize the hallmark vessel calcification seen in calciphylaxis.²²

A number of radiologic techniques can be used to detect small-vessel calcification. A plain film demonstrating calcification of arteries and a netlike pattern of calcification can suggest calciphylaxis.²³ Mammography using low-energy ~ 30 kV radiation can detect calcification as small as 0.13 mm.²⁴ This resolution is said to be superior to that of plain films or CT scan.²⁴ Another radiologic technique (not used in the current study) is bone scintigraphy using technetium 99m label.^{25,26} This can demonstrate calcium not only in the subcutaneous tissue, but in other organs such as the lung, heart, and kidney.

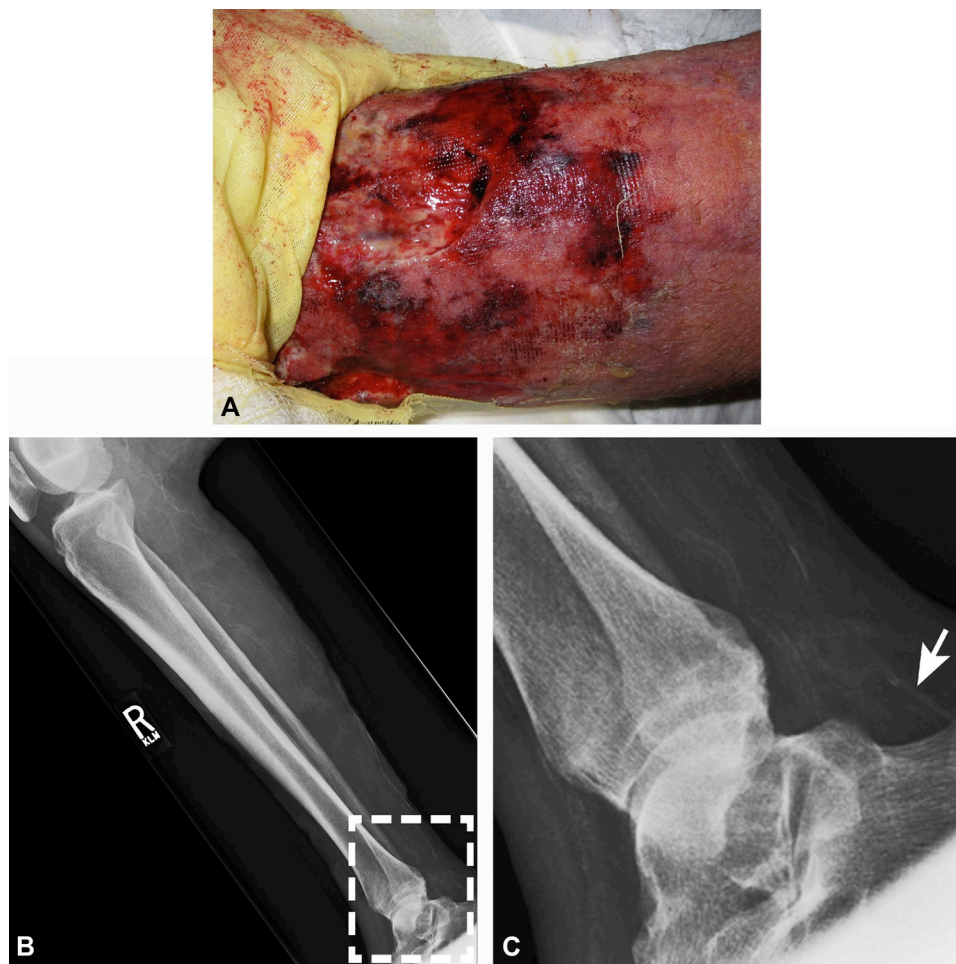
In our series of patients (summarized in Table I), various common imaging techniques used in their routine care, reviewed retrospectively, confirmed the presence of arteriolar calcification with resolution of as little as 0.1 to 0.3 mm diameter, nearly equal to that of histopathology. Mammography was particularly useful in visualizing calcification in 3 cases where the involved tissue site was thick, limiting the resolution of plain films. Plain films and CT imaging of thinner parts of the body (the heel, foot, or leg in patients 3 to 7, areas not clinically involved with calciphylaxis) also visualized calcification of vessels less than 1 mm, most in the same 0.1- to 0.3-mm range. This is probably the case because calciphylaxis is actually a systemic disease with vessel calcification not limited to the locus of ulcer formation.⁶

Limitations of the current study include the small number of patients studied and the retrospective nature comparing calcified vessel diameters using

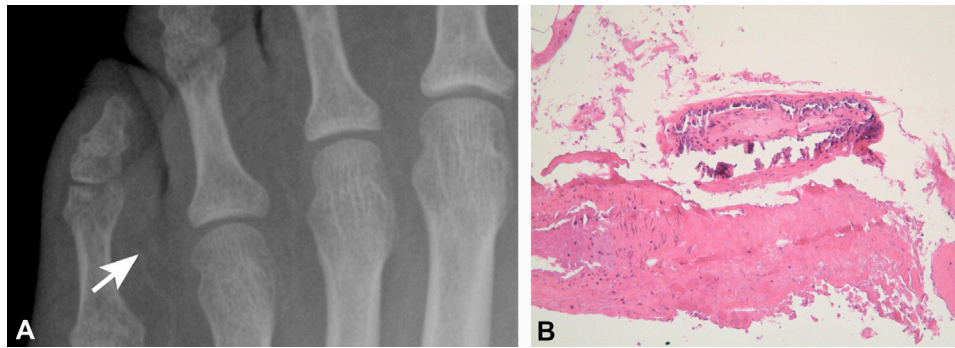
a variety of radiologic techniques against histopathology. Further studies are clearly needed to determine which radiology study (plain film, mammogram, CT scan, or scintigraphy) is optimal in diagnosing calciphylaxis. In the meantime, we found that consultation with radiology colleagues can reveal small arterial and arteriolar calcification less than 1 mm potentially hastening the diagnosis of calciphylaxis before tissue pathology results are available.

REFERENCES

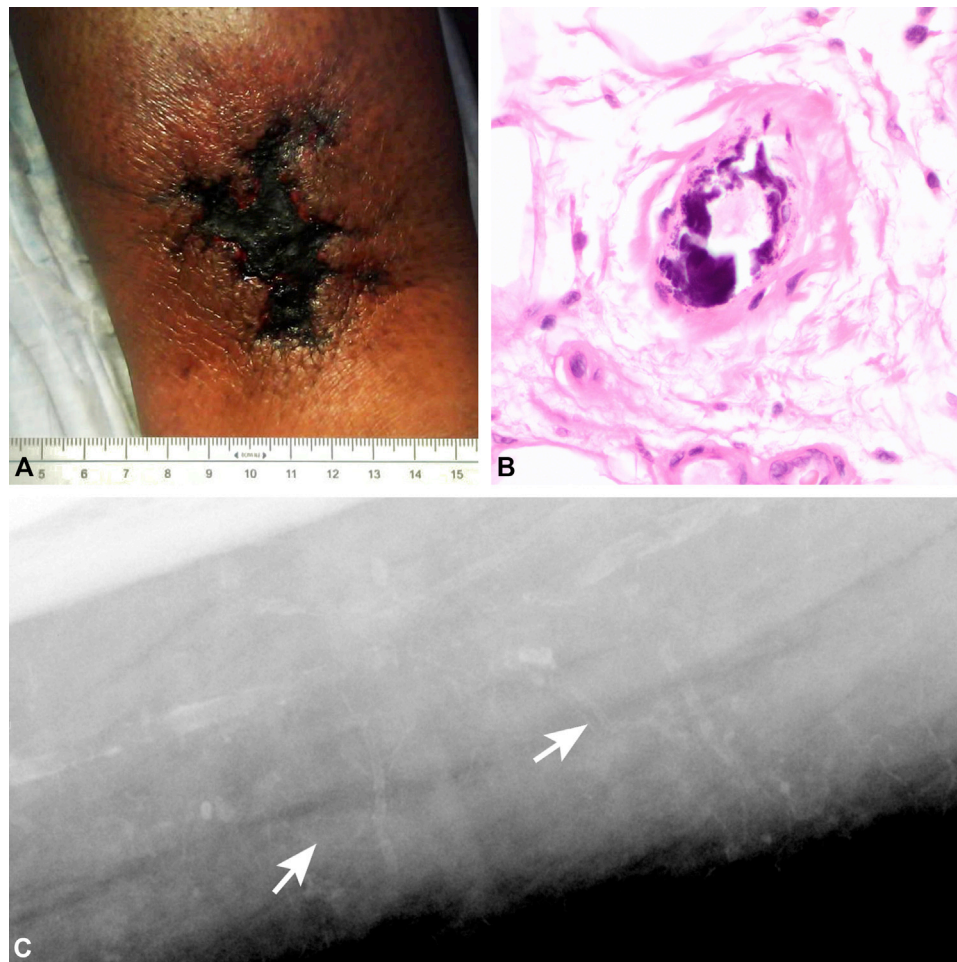
- Levin A, Mehta R, Goldstein MB. Mathematical formulation to help identify the patient at risk of ischemic tissue necrosis- a potentially lethal complication of chronic renal failure. *Am J Nephrol*. 1993;13:448-453.
- Angelis M, Wong LL, Myers SA, et al. Calciphylaxis in patients on hemodialysis: a prevalence study. *Surgery*. 1997;122: 1083-1090.
- Ketteler M, Biggar PH, Brandenburg VM, et al. Epidemiology, pathophysiology, and therapy of calciphylaxis. *Dtsch Arztebl*. 2007;104(50):A-3481-3485.
- Brandenburg VM, Kramann R, Specht P, et al. Calciphylaxis in CKD and beyond. *Nephrol Dial Transplant*. 2012;27:1314-1318.
- Nigwekar SU, Solici CA, Ankers E, et al. Quantifying a rare disease in administrative data: the example of calciphylaxis. *J Gen Intern Med*. 2014;29(Suppl 3):S724-S731.
- Nigwekar SU, Wolf M, Sterns RH, et al. Calciphylaxis from nonuremic causes: a systematic review. *Clin J Am Soc Nephrol*. 2012;3:1139-1143.
- Maroz N, Mohandes S, Field H, et al. Calciphylaxis in patients with preserved kidney function. *J Am Coll Clin Wound Spec*. 2015;6:24-28.
- Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: risk factors, diagnosis, and treatment. *Am J Kidney Dis*. 2015;66: 133-146.
- Martinez-Lemus LA. The dynamic structure of arterioles. *Basic Clin Pharmacol Toxicol*. 2012;110:5-11.
- Coates T, Kirkland GS, Dymock RB, et al. Cutaneous necrosis from calcific uremic arteriolopathy. *Am J Kidney Dis*. 1998;32: 384-391.
- Fischer AH, Morris DJ. Pathogenesis of calciphylaxis: study of three cases with literature review. *Hum Pathol*. 1995;26: 1055-1064.
- Peterson R. Small vessel calcification and its relationship to secondary hyperparathyroidism in the renal homotransplant patient. *Radiology*. 1978;126:627-633.
- Lanzer P, Boehm M, Sorribas V, et al. Medial vascular calcification revisited: review and perspectives. *Eur Heart J*. 2014;35:1515-1525.
- Tolle M, Reshetnik A, Schuchardt M, et al. Arteriosclerosis and vascular calcification: causes, clinical assessment and therapy. *Eur J Clin Invest*. 2015;45:976-985.
- Kroger K, Stang A, Kondratieva J, et al. Prevalence of peripheral arterial disease- results of the Heinz Nixdorf recall study. *Eur J Epidemiol*. 2006;21:279-285.
- Aitken E, Ramjug S, Buist L, et al. The prognostic significance of iliac vessel calcification in renal transplantation. *Transplant Proc*. 2012;44:2925-2931.
- Lehto S, Niskanen L, Suhonen M, et al. Medial artery calcification, a neglected harbinger of cardiovascular complications in non-insulin-dependent diabetes. *Arterioscler Thromb Vasc Biol*. 1996;16:978-983.
- Amann K. Media calcification and intima calcification are distinct entities in chronic kidney disease. *Clin J Am Soc Nephrol*. 2008;3:1599-1605.
- Parfitt AM. Soft-tissue calcification in uremia. *Arch Intern Med*. 1969;124:544-556.
- Latus J, Kimmel M, Ott G, Ting E, Alscher MD, Braun N. Early stages of calciphylaxis: are skin biopsies the answer? *Case Rep Dermatol*. 2011;3(3):201-205.
- Cimmino CB, Costable RA. Biopsy is contraindicated in the management of penile calciphylaxis. *J Sex Med*. 2014;11(10): 2611-2617.
- Bonchak JG, Park KK, Vethanayagamony T, et al. Calciphylaxis: a case series and the role of radiology in diagnosis. *Int J Dermatol*. 2016;55:e275-e279.
- Shmidt E, Murthy NS, Knudsen JM, et al. Net-like pattern of calcification on plain soft-tissue radiographs in patients with calciphylaxis. *J Am Acad Dermatol*. 2012;67: 1296-1301.
- Bleibel W, Hazar B, Herman R. A case report comparing various radiological tests in the diagnosis of calcific uremic arteriolopathy. *Am J Kidney Dis*. 2006;48:659-661.
- Koch Nagueira PC, Giuliani C, Ray N, Saïd MH, Cochat P. Calcifying panniculitis in a child after renal transplantation. *Nephrol Dial Transplant*. 1997;12:216-218.
- Paul S, Rabito C, Vedak P, Nigwekar SU, Kroshinsky D. The role of bone scintigraphy in the diagnosis of calciphylaxis. *JAMA Dermatol*. 2017;153:101-103.



Supplementary Fig 1. Calciphylaxis. Patient 3. **A**, Right leg ulcer. **B**, Radiographic image of right leg. **C**, Zoomed-in image shows vessel calcification 0.8 to 1.6 mm in diameter (*arrow*).



Supplementary Fig 2. Calciphylaxis. Patient 6. **A**, Plain film of left foot with vessel calcification 0.2 mm in diameter (*arrow*). **B**, Histopathologic image with vessel calcification and thrombosis, and surrounding tissue necrosis. (Original magnification: $\times 100$.)



Supplementary Fig 3. Calciphylaxis. Patient 7. **A**, Ulcer on right calf. **B**, Histopathology showing calcification of 0.04-mm vessel. (Original magnification: $\times 400$.) **C**, Mammographic image of right calf showing calcified vessels, with smallest diameters 0.2 mm (*arrows*).