CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 7-2007: A 59-Year-Old Woman with Diabetic Renal Disease and Nonhealing Skin Ulcers

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PRESENTATION OF CASE

Dr. Maha R. Farhat (Medicine): A 59-year-old woman was admitted to the hospital because of a nonhealing ulcer on the right heel and painful ulcers on the right thigh and hip.

The patient had been morbidly obese since early childhood; she had had type 2 diabetes mellitus and hypertension for 30 years and chronic renal insufficiency for 6. Painless ulcers had developed on the plantar surfaces of both heels 6 years earlier; those on the left side had healed with wound care and decreased weight bearing, but those on the right recurred when she resumed weight bearing. Four years before admission, she became unable to walk because of the ulcers, and moved to a long-term care facility. The chronic renal insufficiency progressed, and hemodialysis was begun 8 months before admission.

Three months before admission, a large area of purple discoloration and tenderness appeared along the back of her right lower thigh. This area subsequently ulcerated. Two months before admission, an ulcer developed over the greater trochanter of the right hip. Computed tomographic (CT) scanning of the thigh performed 3 months before admission was interpreted as showing cellulitis. Ultrasound imaging of the right leg was negative for deep venous thrombosis.

At approximately the same time, an ulcer on the right heel that had been present for about 2 years enlarged despite local care and attempts at primary closure. Approximately 2 months before admission, cultures of this ulcer yielded growth of *Pseudomonas aeruginosa* that was susceptible to ciprofloxacin and gentamicin, and intravenous therapy with these agents was started. Approximately 1 month before admission, a limited bone scan suggested the presence of osteomyelitis of the right calcaneus. Noninvasive vascular studies revealed an ankle–brachial index of 0.83 on the right and 0.90 on the left (normal, >0.96). Right calcaneal resection and placement of a vacuum-assisted closure dressing were performed 3 weeks before admission. Cultures of the resected bone grew the same species of *P. aeruginosa*, as well as *Escherichia coli*. Ciprofloxacin and gentamicin were continued.

On follow-up examinations, the heel ulcer did not improve; it became painful,

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with a purulent discharge, and an area of redness and swelling developed around it. The ulcers on the right hip and thigh increased in size. She was referred to the vascular-surgery clinic of this hospital 10 days before admission. At that time, there was an ulcer, 3 cm deep, on the right hip; a black, necrotic area, 15 cm by 15 cm, on the right posterior thigh; and a decubitus ulcer, 5 cm by 5 cm, on the right heel with exposed bone. None of the ulcers were purulent. Noninvasive vascular study of both legs was recommended. During the next 10 days, her physicians became increasingly concerned about sepsis from the foot ulcer, and she was sent to the emergency department of this hospital.

On examination, her vital signs were normal and the right lower leg was painful on any movement; the ulcers were unchanged. Examination by vascular ultrasound imaging was limited because of pain but revealed right distal popliteal-artery and tibial-artery disease with poor perfusion of the right foot. She was admitted to the hospital for a below-the-knee amputation of the right leg.

She did not have fever, chills, or sweats. She had diabetic retinopathy, neuropathy, and carotid and coronary atherosclerosis; carotid endarterectomy had been performed in the past because of transient ischemic attacks. She had had episodes of congestive heart failure with pulmonary edema but had no history of venous or arterial thromboses. She had no known allergies. She was unmarried, had a 16-year-old daughter, and had worked as a teacher until becoming disabled because of the ulcers. She had a 5-pack-year history of cigarette smoking, but had stopped smoking 5 years before admission. She did not drink alcohol or use illicit drugs. Her medications, in addition to the antibiotics, included simvastatin, furosemide, lisinopril, metoprolol, insulin, calcium carbonate, sevelamer, famotidine, gabapentin, narcotics for the pain from her ulcers, and laxatives.

On examination, the patient was an obese woman who was lethargic but arousable and oriented. She was in moderate discomfort from pain in her right leg. The axillary temperature was 37.4°C, the blood pressure 137/58 mm Hg, and the pulse regular at 72 beats per minute. Auscultation of the lungs and heart were normal; the abdomen was obese, with no tenderness or organomegaly. The carotid and radial pulses were normal. The left dorsalis pedis pulse was diminished, and the right was not palpable. An ulcer, 5 cm by 5 cm, overlying the trochanter of the right hip exposed the subcutaneous tissue without purulence or erythema. On the right posteromedial thigh, an exquisitely tender and violaceous indurated area, 15 cm by 15 cm, with black, dry ulcerations and surrounding tender erythema, extended from the popliteal fossa two thirds of the way up the thigh. An ulcer, 5 cm by 5 cm, on the right heel had cyanotic margins and a foul-smelling purulent base that exposed bone. An area of erythema that was tender to palpation spread from the heel about two thirds of the way up the lower leg. Laboratory test results are shown in Table 1.

During the evening, a repeated examination disclosed that the area of erythema on the lower leg now extended to the knee. The patient continued to have severe pain of the calf and posterior aspect of the thigh. A procedure was performed early the next morning.

DIFFERENTIAL DIAGNOSIS

Dr. Hasan Bazari: May we see the imaging studies?

Dr. Michael R. Jaff: The noninvasive vascular studies were performed with blood-pressure cuffs placed at the thigh, calf, ankle, foot, and toe levels. This examination tells us two things: the blood pressure at several levels of the leg, and the qualitative volume of arterial blood flowing to each level. These data are used to predict not only the presence and severity of peripheral arterial disease but also the segments of artery involved. The right thigh was not studied because of the ulceration. A normal plethysmographic pulse-volume recording is seen at the transmetatarsal region of the left foot (Fig. 1), with a rapid upstroke, rapid downstroke, dicrotic notch, and return to baseline.

The reported ankle–brachial indexes of 0.83 on the right and 0.90 on the left suggest minimal peripheral arterial disease. However, the arteries of the legs had diffuse calcification of the medial arterial layer, so that inflating the blood pressure cuff will not close the lumen, allowing for continuous arterial Doppler signals. In this setting, the ankle–brachial index is unreliable and cannot be used to determine the presence or severity of peripheral arterial disease. The plethysmographic waveforms, however, show significant peripheral arterial disease of both the femoral and the popliteal arteries at multiple levels of the right leg

and at the level of the ankle, the metatarsals, and the digits (Fig. 1).

Dr. Bazari: This 59-year-old woman with obesity, type 2 diabetes mellitus, hypertension, and end-stage renal disease presented with ulcers on her legs and feet and concern for sepsis. A chronic ulcer on the right heel was complicated by osteomyelitis and *P. aeruginosa* infection. During the three months before admission, new lesions developed, which were described as areas of purple discoloration and tenderness that appeared on the hip and thigh, and subsequently turned black and ulcerated. Her vital signs were stable on admission, but spreading erythema and pain associated with the heel ulcer suggested progression of infection. The laboratory tests showed a low albumin level and a high globulin level. She had anemia of chronic kidney disease as expected. I am aware of the diagnosis in this case, but the differential diagnosis was initially broad.

Table 1. Results of Laboratory Tests on Admission.*

Variable	Normal Range (Adults)	Value in Patient
White-cell count (per mm^3)	4500–11,000	13,000
Hematocrit (%)	36.0–46.0	32.5
Platelet count (per mm^3)	150,000–350,000	509,000
Polymorphonuclear leukocytes (%)	40–70	81
Prothrombin time (sec)	11.3–13.3	14.7
Activated partial-thromboplastin time (sec)	22.1–35.1	28.1
Plasma sodium (mmol/liter)	135–145	139
Plasma carbon dioxide (mmol/liter)	23.0–31.9	24.9
Calcium (mg/dl)	8.5–10.5	9.1
Phosphorus (mg/dl)	2.6–4.5	2.5
Magnesium (mmol/liter)	0.7–1.0	1.2
Urea nitrogen (mg/dl)	8–25	27
Creatinine (mg/dl)	0.6–1.5	4.4
Albumin (g/dl)	3.3–5.0	2.4
Globulin (g/dl)	2.6–4.1	4.8

* To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to milliequivalents per liter, divide by 0.5. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

ULCERS ON THE LEGS AND FEET

The ulcers on the legs and feet may be related to this patient's chronic diseases or may have another cause. The differential diagnosis for ulcers on the legs and feet is shown in Table 2.[1]

VASCULAR AND THROMBOTIC DISEASES

Ulcers due to arterial insufficiency typically occur on the toes, the heels, and the anterior shin and extend over the malleoli. Thromboangiitis obliterans (Buerger's disease) is a thrombotic disease seen in young male smokers that leads to limb loss if there is delay in cessation of smoking; this patient does not fit the demographic for Buerger's disease.[2] Atheroembolic disease can cause ulcers in the legs, especially in the setting of peripheral arterial disease; embolization characteristically occurs after a vascular procedure, such as angiography or cardiac or vascular surgery.[3] This patient clearly had peripheral arterial disease, which was probably a major factor in the heel ulceration.

Venous ulcerations typically occur above the lateral or medial malleoli. The patients usually have a history of venous insufficiency, stasis dermatitis, and a history of deep venous thrombosis. The distribution of this patient's ulcers is not characteristic of venous ulcers, there is no history of deep venous thrombosis, and there are no cutaneous findings to suggest venous stasis. Vasculitis and the antiphospholipid-antibody syndrome are unlikely in this patient, since she has no history of autoimmune disease and no systemic features of a vasculitis. I would have considered obtaining a hypercoagulable screen in the evaluation of this patient. Disseminated intravascular coagulation can lead to ischemia and loss of the arms and the legs; this typically occurs with disseminated infection or shock and would not be compatible with this patient's course.

Heparin-induced thrombocytopenia is caused by antibodies against complexes of platelet factor 4 and heparin and is increasingly recognized as a cause of thrombosis leading to loss of limbs. This disorder is associated with both venous and arterial thrombi.[4] I would have inquired whether heparin products had been used as prophylaxis or treatment in this patient. Skin necrosis can occur in patients with an underlying genetic or acquired deficiency in protein C or protein S who begin therapy with warfarin.

NEUROPATHIC ULCERS

Neuropathic ulcers occur under the metatarsal head, over the toe joints, under the heel, on the inner side of the first metatarsal head, and over the malleoli. We are not told about the neurologic

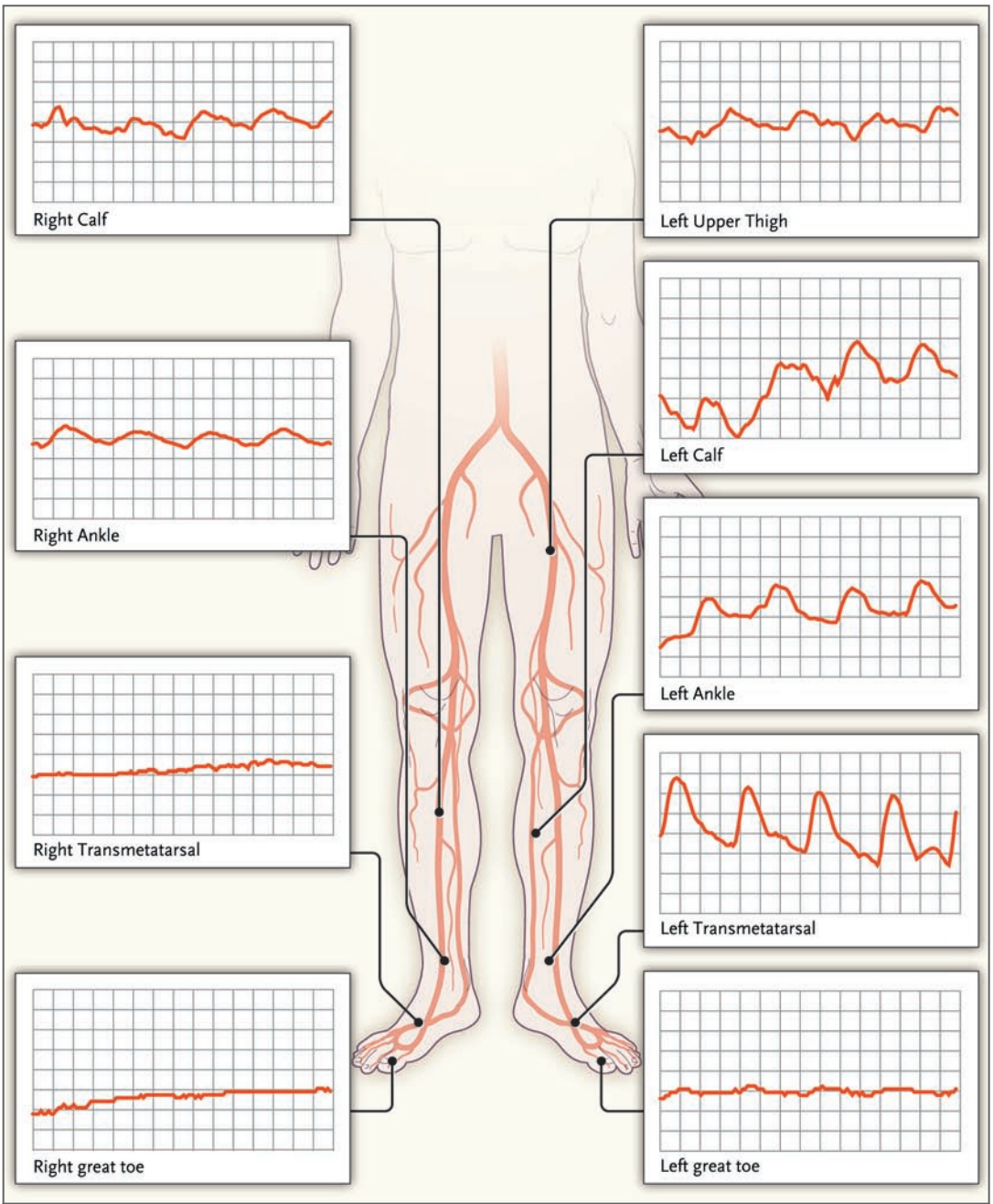

Figure 1. Vascular Studies of the Legs.

Plethysmographic pulse-volume recordings at five levels of the legs show multilevel peripheral arterial disease, which is more severe on the right than on the left. The normal deflection represents a waveform similar to an intraarterial pressure waveform, with a rapid upstroke, narrow waveform, rapid downstroke, dicrotic notch, and then completion of the waveform as it bows down to the baseline; the tracing from the left calf is closer to normal than that from the right calf. As peripheral arterial disease worsens, the dicrotic notch is lost, the waveform widens, and the amplitude decreases. Plethysmography of the digits shows complete loss of pulsatility at the level of the right great toe, suggesting advanced ischemia at the foot and toes.

examination, but this patient probably had diabetic neuropathy. The ulcers on this patient's heels are typical of neuropathic ulcers.

INFECTIONS

Osteomyelitis is clearly established in this case by the radiologic and microbiologic findings. Although osteomyelitis can be a cause of ulceration, in this case it is a consequence of the ulceration rather than a primary cause. The patient was treated with ciprofloxacin and gentamicin for a prolonged period, but the wound did not heal. Indolent infections such as tuberculosis can cause chronic nonhealing ulcers, and in immunosuppressed patients, fungal infections such as cryptococcus and coccidioidomycosis can lead to skin lesions that ulcerate. If these organisms had caused the heel ulcer, they probably would have been found at the time of this patient's recent surgery.

OTHER DISORDERS

Necrobiosis lipoidica diabeticorum produces skin lesions that typically occur over the pretibial area and heal with shallow hypopigmented scars. Erythema nodosum is a form of panniculitis that is often associated with underlying systemic diseases such as sarcoidosis and inflammatory bowel disease. Weber–Christian disease is another panniculitide and is sometimes associated with pancreatic disease. Pyoderma gangrenosum is associated with inflammatory bowel disease and cancer, neither of which this patient had; it typically presents as a single, purple, furunculoid abscess on the trunk that ulcerates.[5] The ulcers have a characteristic heaped-up border, unlike our patient's ulcers. None of these disorders are likely to explain the ulcer on the heel, but necrobiosis lipoidica or Weber–Christian disease could be considered for the more recent ulcers on the hip and thigh. However, although the patient has diabetes, the location of these lesions and their size and painfulness is atypical of necrobiosis lipoidica, and she has no history of pancreatic disease to suggest Weber–Christian disease.

CALCIPHYLAXIS

The ulcers on this patient's thigh and hip, which appeared spontaneously and without trauma, are characteristic of calciphylaxis, or calcific uremic arteriopathy, as shown in another patient in Figure 2. The lesions associated with calciphylaxis are characteristically exquisitely tender and plaque-like, with a dusky or purple discoloration, and progress to ulceration with the formation of eschars.[6] In a patient who receives dialysis, the appearance of progressive cutaneous lesions that are painful and ulcerate should invoke the diagnosis of calciphylaxis.

Patients with renal disease often have arterial, ocular, periarticular, soft-tissue, and visceral calcifications — these do not represent calciphylaxis.[7] Calciphylaxis is a poorly understood disorder, predominantly of the skin, that has characteristic calcifications in the media of small to medium-size blood vessels of the dermis and subcutaneous fat and is associated with ischemia and skin necrosis.[8] The relationship between uremia

Table 2. Differential Diagnosis of Ulcers on the Legs and Feet.

Vascular diseases
Arterial disease
Thromboangiitis obliterans (Buerger's disease)
Cholesterol embolization
Venous disease with stasis
Lymphedema
Antiphospholipid-antibody syndrome
Vasculitis
Cryoglobulinemia
Wegener's granulomatosis
Rheumatoid arthritis
Disseminated intravascular coagulation
Heparin-induced thrombocytopenia
Warfarin-induced skin necrosis
Neuropathic ulcers
Infections
Osteomyelitis
Necrotizing fasciitis with organisms such as clostridia, group A streptococcus, and *Vibrio vulnificus*
Tuberculosis
Fungal infections
Cryptococcus neoformans
Coccidioides immitis
Hematologic disorders
Polycythemia vera
Essential thrombocythemia
Therapy with hydroxyurea
Necrobiosis lipoidica diabeticorum
Pyoderma gangrenosum
Sweet's syndrome
Erythema nodosum
Cancer (squamous-cell carcinoma)
Calciphylaxis

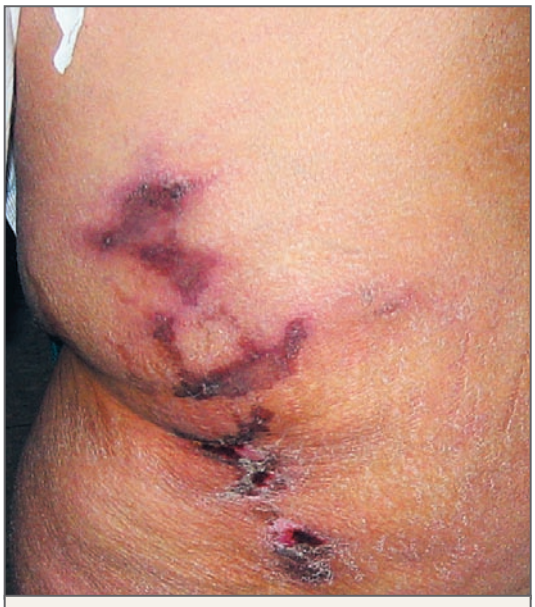

Figure 2. Calciphylaxis in Another Patient, Showing Irregular Areas of Dusky, Purplish Discoloration on the Skin of the Flank.

and vascular calcification was first described in 1898 by Bryant and White.[9] The term calciphylaxis was originally coined by Selye,[10] who showed that deposition of calcium occurred in the tissues of rats that were sensitized with vitamin D analogues, parathyroid hormone, and nephrotoxic insults when they were challenged with iron, other metal salts, glucocorticoids, or physical trauma.

DIAGNOSIS OF CALCIPHYLAXIS

Calciphylaxis is rare, although the prevalence in one study was 4.1% of patients receiving long-term hemodialysis.[11] It is more common in women and girls than in men and boys (male:female ratio, 1:3); the age range is 6 months to 83 years.[12] Most patients have some degree of kidney disease, although calciphylaxis has been reported in patients with cirrhosis,[13] Crohn's disease,[14] hyperparathyroidism,[15] and cancer.[16] The clinical features include hyperparathyroidism (in 80% of patients), hypercalcemia (in 20%), hyperphosphatemia (in 68%), and elevations in the calcium–phosphate product (in 33%).[17] About a third of the patients have had renal transplants.[18] The use of calcium-based phosphate binders and the use of vitamin D products to suppress the parathyroid hormone levels lead to higher levels of both calcium and calcium–phosphate products, causing premature vascular calcifications in patients with end-stage renal disease.[7]

The presence of hypercalcemia, hyperphosphatemia, elevations in the calcium–phosphate product, hyperparathyroidism, and exposure to calcium and vitamin D products should raise the suspicion of calciphylaxis. However, it is possible that the clinical syndrome may present well after the optimal confluence of conditions for the initiation of calciphylaxis, and the measurements at the time of clinical presentation may not represent the conditions required for initiation of the syndrome. This patient's serum calcium level was normal at 9.1 mg per deciliter (2.28 mmol per liter), but because of her albumin level of 2.4 g per deciliter, the ionized calcium level was probably at the upper limit of normal. She was also receiving calcium and vitamin D supplementation while she was receiving dialysis. She had a moderately elevated parathyroid hormone level. Some patients have low levels of protein C,[19] protein S,[20] or both,[13] which may promote calciphylaxis by inducing a hypercoagulable state.

Clinical suspicion is the single most important feature of the diagnosis, and once one has seen a case, the evolution of the disease is unforgettable. The gold standard for the diagnosis of calciphylaxis is a biopsy of one of the lesions. Bone scanning has been recommended as an alternative to biopsy.[21,22] It is unclear whether bone scans are as specifically diagnostic as a biopsy is, but they can be used when there is concern that a biopsy could lead to the formation of ulcers.

SUMMARY

In summary, the ulcer on this patient's foot and those on the hip and thigh have characteristics that suggest two different causes. The heel ulcers probably began as neuropathic ulcers. The presence of severe arterial insufficiency, in addition to probable diabetic small-vessel disease and uremia, all contributed to the persistence of the ulcer on the right heel. Finally, this ulcer was complicated by osteomyelitis caused by two organisms, one of which — *P. aeruginosa* — is particularly virulent and was difficult to eradicate, probably because of the patient's compromised vascular status. In contrast, the lesions on the hip and thigh, which developed several months after the patient began hemodialysis, are typical of calciphylaxis.

The procedures performed at the end of the

protocol were a guillotine amputation of the distal third of the right lower leg, done as an emergency because of the apparent progression of infection, and débridement of the ulcer on the right thigh.

CLINICAL DIAGNOSIS

Ischemic ulcer of the heel due to atherosclerotic vascular disease.

Decubitus ulcers of the hip and thigh.

DR. HASAN BAZARI'S DIAGNOSIS

Calciphylaxis, causing ulcers on the hip and thigh.

Ischemic ulcer on the heel, with secondary osteomyelitis, due to diabetic nephropathy and atherosclerotic and diabetic vascular disease.

PATHOLOGICAL DISCUSSION

Dr. Shaofeng Yan: Histologic examination of the amputation specimen of the right lower leg showed cutaneous ulceration of the heel with necrosis of collagen, muscle, and subcutaneous fat, as well as osteomyelitis. There was severe atherosclerosis of large vessels, as well as Monckeberg's medial calcific sclerosis (Fig. 3A). These findings are common in patients with diabetes and can arise independently in the same or anatomically similar arterial segments.[23,24] Both lesions compromise perfusion — the intimal atheroma by occlusion of the lumen, and the medial calcification by limiting distensibility.

The amputation of the right leg was followed during the ensuing days and weeks by two revisions of the amputation; three débridements of skin, soft tissue, and fascia of the right thigh; and finally, 6 weeks after admission, an above-the-knee amputation of the right leg. Histologic examination of both the amputation specimens and the lesion on the right thigh showed extensive areas of fat necrosis without marked acute inflammation. There is deeply basophilic amorphous material consistent with calcium deposition within the small arteries in the septa (Fig. 3B) and lobules (Fig. 3C) of the subcutaneous fat, highlighted by von Kossa's stain (Fig. 3D). Microthrombi were present within the small vessels (Fig. 3E). These features are diagnostic of calciphylaxis.

Calciphylaxis is a small-vessel vasculopathy characterized by mural calcification, intimal pro-

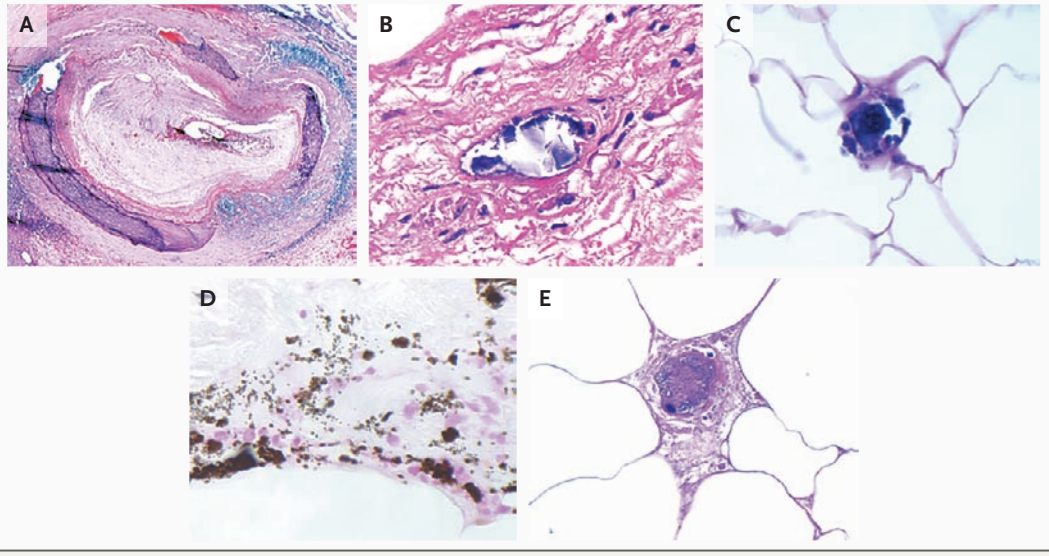

Figure 3. Histologic Examination of Specimens from Amputation of the Right Leg and Débridement.

A large artery from the guillotine below-the-knee amputation of the right leg (Panel A) shows severe atheroma and Monckeberg's medial calcific sclerosis (hematoxylin and eosin). Basophilic calcium deposition is evident within a small artery in the septum of subcutaneous fat (Panel B, hematoxylin and eosin). Panel C shows calcium deposition within a small artery in a lobule of subcutaneous fat (hematoxylin and eosin). Calcium deposits are highlighted as fine, dark granules within the septum tissue (Panel D, von Kossa's stain). Microthrombi are present within a small artery (Panel E, hematoxylin and eosin).

liferation, and microthrombosis. It commonly affects small arteries, ranging from 40 to 600 μm, with the average size approximately 100 μm.[25] The pathological differential diagnosis of calciphylaxis includes dystrophic calcification, calcinosis cutis, and medial calcific sclerosis. Calcinosis cutis is characterized by calcification in skin tissue but not in vessels. Dystrophic calcification involves calcification of injured tissue in association with normal serum calcium and phosphate levels, whereas in cases of calciphylaxis, calcium deposition can occur in areas without an abundant inflammatory-cell infiltrate.[26] Medial calcific sclerosis affects larger vessels than those affected by calciphylaxis.

DISCUSSION OF MANAGEMENT

Dr. Bazari: The management of calciphylaxis is based on assumptions about its causes; however, since no particular combination of factors reliably predicts the development of calciphylaxis, the effectiveness of all treatments remains unproved. When elevated levels of calcium, phosphate, and calcium–phosphate product are present, sevelamer hydrochloride should be substituted for calcium-based phosphate binders,[27] dietary phosphate intake and calcium in the dialysis bath should be reduced, and vitamin D products both in medications and in dialysis supplements should be eliminated. The role of parathyroidectomy remains controversial.[12,28,29] Calcimimetic agents can be used to control parathyroid hormone secretion. Bisphosphonates,[30] sodium thiosulfate, tissue plasminogen activator, and hyperbaric-oxygen therapy have all been used with some success.[21,31-34]

Sepsis is the leading cause of death in patients with calciphylaxis. Meticulous and aggressive management of wounds, use of antibiotics, and resection of necrotic tissue are key parts of the treatment, as they were in this patient.

Dr. Michael Mannstadt: Endocrinology was asked to consider the possible benefit of parathyroidectomy in this patient. Her serum calcium and phosphorus levels were normal. The elevation of intact parathyroid hormone was mild for the degree of renal insufficiency. Both 25-hydroxyvitamin D (a marker of vitamin D stores) and 1,25-dihydroxyvitamin D (the active metabolite of vitamin D) were within the normal range. Most reports of clinical improvement after parathyroidectomy have involved patients with markedly elevated parathyroid hormone levels, and even in that group it was not possible to predict who might benefit.[35] Moreover, parathyroidectomy in this patient could precipitate severe adynamic bone disease and complicate efforts to control the calcium–phosphate metabolism. Our recommendation was to continue efforts to tightly control the calcium–phosphate product, continue sodium thisosulfate,[21] avoid vitamin D analogues[22] and warfarin,[36,37] and consider hyperbaric-oxygen therapy.[33] The patient declined to undergo hyperbaric-oxygen therapy because of claustrophobia.

During her hospital stay, the patient's parathyroid hormone levels fluctuated, probably in response to fluctuating calcium levels around the time of her hemodialysis, but were as high as 466 pg per milliliter. Therapy was initiated with oral cinacalcet, a calcimimetic agent approved for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease who receive dialysis and also for the treatment of patients with parathyroid cancer.[38] Cinacalcet activates the calcium-sensing receptor expressed by parathyroid cells and in so doing mimics the action of calcium to suppress secretion of parathyroid hormone, enabling control of hypersecretion at normal or even low blood levels of ionized calcium.[39,40] The drug has an acceptable side-effect profile, and the patient was able to take 30 mg of cinacalcet without appreciable side effects. Subsequent levels of parathyroid hormone remained only slightly elevated.

Dr. Farhat: Calcium and vitamin D supplements were stopped, and sodium thiosulfate was added to her dialysate during hemodialysis three times a week. Several repeated débridements were performed, as were medical applications of maggots to the wounds and the placement of a vacuum-assisted closure dressing. Her wounds eventually showed evidence of healing, and after 3 months in the hospital, she was discharged to a rehabilitation facility. She was making good progress in regaining strength and physical mobility.

ANATOMICAL DIAGNOSIS

Calciphylaxis, extensive, involving the right leg.

Atherosclerotic vascular disease with ischemic ulcer on the heel and osteomyelitis.

Dr. Jaff reports receiving lecture fees from Bristol-Myers Squibb and Sanofi. No other potential conflict of interest relevant to this article was reported.

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