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An Alternate Explanation

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Abstract

A 48-year-old man with long-standing type 2 diabetes mellitus (recent glycated hemoglobin level, 6.5%) and chronic kidney disease (baseline creatinine level, 3.3 mg per deciliter [292 μmol per liter]; glomerular filtration rate, 24 ml per minute per 1.73 m^2 of body-surface area) presented to his primary care physician with a 3-month history of numbness, tingling, and faint violaceous discoloration of the tips of multiple fingers and toes. His physical examination showed reduced light-touch sensation in a glove-and-stocking distribution; the radial and pedal pulses were palpable. The vitamin B_{12} level was 260 pg per milliliter (192 pmol per liter; normal range, 190 to 950 pg per milliliter [140 to 701 pmol per liter]). He did not smoke tobacco, drink alcohol, or use illicit drugs. One month later, a nontraumatic wound developed on the left foot. The ankle–brachial index (ABI) was 1.2 on both sides (normal range, 0.91 to 1.3). Wound care was initiated for a presumed neuropathic ulcer.

Paresthesia and sensory deficits are characteristic of a small-fiber neuropathy. Diabetes mellitus is a common cause of distal sensory polyneuropathy. However, involvement of the

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hands in combination with symptoms in the feet that are confined to the toes is unusual. Other common causes of sensory neuropathy include alcohol use, vitamin deficiency, and use of certain medications; many sensory neuropathies are unexplained. A low-normal serum vitamin B_{12} level should prompt measurement of the methylmalonic acid level to more accurately evaluate vitamin B_{12} deficiency. The palpable peripheral pulses and the ABI of 1.2 suggest that macrovascular disease is not responsible for the symptoms in the fingers and toes. However, highly calcified arteries (which are common in the context of diabetes and chronic kidney disease) may be noncompressible and thus may lead to a false elevation in the ABI despite the presence of peripheral artery disease. The toe–brachial index (TBI) can be a more accurate measure of distal perfusion in the context of these diseases.

The discoloration in the fingers and toes could reflect a disruption in the microcirculation (e.g., vasospasm or cryoglobulinemia). Ulcers on the feet typically arise from arterial or venous insufficiency or neuropathy-related injury. The patient's chronic kidney disease was probably caused by his diabetes, but further evaluation is warranted to confirm that it is not part of a systemic process that would also explain the ulcerations and neuropathy (e.g., granulomatosis with polyangiitis).

Approximately 1 month after the left foot ulcer appeared, the patient was admitted to a hospital with acute dyspnea. His wife noted that he had frequently been somnolent and less active overall in the preceding weeks. He reported an exacerbation of chronic low back pain, for which he had been taking ibuprofen intermittently during the preceding month. His other medical history included hyperlipidemia and obesity (which had been treated with Roux-en-Y gastric bypass 13 years earlier). He was taking aspirin at a dose of 81 mg daily, atorvastatin at a dose of 40 mg daily, gabapentin at a dose of 200 mg three times daily, and a multivitamin. His father had type 2 diabetes mellitus, and his mother had advanced dementia.

The patient's oral temperature was 37.1°C, the heart rate 94 beats per minute, the blood pressure 92/50 mm Hg, the respiratory rate 28 breaths per minute, and the oxygen saturation 93% while he was breathing ambient air. Examination revealed pitting edema in both feet and an eschar that had formed over the initial ulcer on the left dorsal midfoot that extended to the tips of the first three toes with no surrounding erythema or induration.

The hemoglobin level was 6.8 g per deciliter (baseline level, 7.5); the white-cell count and platelet count were normal. The potassium level was 6 mmol per liter, and the creatinine level 5.6 mg per deciliter (495 μmol per liter) (estimated glomerular filtration rate, 12 ml per minute). The total bilirubin level was 1.1 mg per deciliter (18.8 μmol per liter; normal range, 0.3 to 1.2 mg per deciliter [5.1 to 20.5 μmol per liter]), the lactate dehydrogenase level 196 U per liter (normal range, 105 to 290), and the haptoglobin level 114 mg per deciliter (normal range, 50 to 200 mg per deciliter). The troponin T level was 0.03 ng per milliliter (normal range, 0 to 0.04). A blood smear was not obtained. Urinalysis showed 2+ protein. Two sequential sets of blood cultures were sterile. An electrocardiogram showed sinus rhythm. Renal ultrasonography ruled out a diagnosis of hydronephrosis. Hemodialysis was initiated for acute-on-chronic kidney injury with hypervolemia and hyperkalemia.

In addition to a progressive wound on the foot, the patient now has dyspnea, hypotension, and kidney injury. The dyspnea may be multifactorial and could be the result of progressive anemia and hypervolemia; additional possible causes, such as pulmonary embolism or cardiac tamponade, warrant urgent consideration. Hypotension arises from cardiovascular, distributive, or hypovolemic causes. Acute kidney injury could arise from hypotension of any cause, including sepsis (e.g., an infection originating from the foot ulcer), or from progressive glomerular injury, which is suggested by the presence of proteinuria. The results of renal ultrasonography make postrenal acute kidney injury unlikely. The patient's baseline anemia is probably attributable to anemia of chronic kidney disease, and the progression could reflect hemorrhage or hemolysis. Although hemolysis is unlikely on the basis of the laboratory test results, a peripheral-blood smear would be useful to rule out thrombotic microangiopathies, such as hemolytic–uremic syndrome or thrombotic thrombocytopenic purpura, that can lead to acute kidney injury. A cutaneous ulcer, digital ischemia, kidney injury, and (possible) neuropathy are compatible with a systemic vasculopathy.

Ultrasonography revealed a deep-vein thrombosis in the right femoral vein. A pulmonary embolism was identified on a ventilation–perfusion scan. A heparin infusion and warfarin treatment were initiated. The patient's worsening renal failure was attributed to his previous use of nonsteroidal antiinflammatory drugs. A renal biopsy was not performed because of the use of anticoagulant therapy. The next day, necrotic lesions developed on the fingers, toes, feet, and penis. Warfarin-induced skin necrosis was suspected. Warfarin treatment was discontinued, and apixaban was prescribed.

The development of deep-vein thrombosis and pulmonary embolism in the context of subacute illness may signal an underlying cancer or autoimmune vasculopathy with associated hypercoagulability. However, thrombosis could also result from subacute illness or inflammation and reduced mobility from the foot ulceration.

Warfarin-induced skin necrosis is a transient hypercoagulable state that is induced by vitamin K antagonism and leads to vascular occlusion and skin necrosis, but this process typically occurs after a few days of therapy. Other concerns, given the development of necrotic lesions despite the use of anticoagulation, include an underlying severe form of hypercoagulability (e.g., antiphospholipid syndrome) or a vasculitis (e.g., polyarteritis nodosa).

During the next 2 weeks, all the necrotic wounds remained dry except for the eschar on the left foot, which became malodorous, with an increased amount of drainage and edema in the surrounding area. A wound culture grew *Pseudomonas aeruginosa*. Despite treatment with intravenous antibiotic agents, the amount of drainage from the wound and the depth of the wound increased. Urgent source control necessitated a left below-knee amputation. No angiographic studies were performed. Two weeks after the operation, he was discharged home with a plan to receive wound care and complete a 3-month course of apixaban. Follow-up was arranged with his primary care physician and a vascular medicine specialist.

Two months after hospital discharge and 5 months after the patient's initial presentation to his primary care physician, he was evaluated in a vascular medicine clinic. He reported the

gradual development of multiple painless wounds after discharge. He had a large nonhealing eschar on the left knee. Three toes of the right foot were necrotic, and an autoamputation of the second toe had occurred; there was also a necrotic wound on the right heel. Three fingers of the right hand were necrotic, with sparing of the thumb and fifth digit, and four fingers of the left hand were necrotic, with sparing of the thumb (Fig. 1). Radial and pedal pulses were nonpalpable.

Multiple mechanisms can lead to end-organ ischemia, including atherosclerosis, embolism, thrombosis, dissection, vasospasm, and vasculitis. Among these conditions, embolism, thrombosis, and vasculitis are the most likely to occur in this widespread distribution over a subacute time course.

It would be uncharacteristic of an endovascular infection to affect nearly every digit in the absence of sepsis with disseminated intravascular coagulation, and sepsis would be unlikely to occur over the course of several months without fever, leukocytosis, or bacteremia. It is conceivable that a noninfectious embolic process, such as cholesterol emboli or atrial myxoma, has injured both the kidneys and distal vascular beds. With the presence of severe kidney injury and diffuse microvascular occlusion, calciphylaxis (also known as calcific uremic arteriolopathy) should be considered, although associated skin lesions are typically painful, unlike those that developed in this patient. Along with evaluations for anemia, neuropathy, kidney injury, and hypercoagulability, echocardiography and histopathological examination of a surgical specimen of the amputated leg would be informative.

After a 3-month course of apixaban, an evaluation for thrombophilia was performed. The prothrombin 20210A mutation was not detected; protein C and protein S activity was 114% and 116%, respectively (normal range, 70 to 150); the blood level of total homocysteine was 10 μmol per liter (normal range, 5 to 15); the factor V Leiden mutation was not detected; the blood level of lipo-protein(a) was 17 mg per deciliter (normal range, 5 to 29); and antithrombin III activity was 91% (normal range, 80 to 130). Testing for lupus anticoagulant, β_2-glycoprotein 1 antibodies, anticardiolipin antibodies, cryoglobulins, antinuclear antibodies, and perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies was negative, as was testing for anti–double-stranded DNA, anti-Smith, anti–Scl-70, anti–RNA polymerase III, and anti–U1-ribonucleoprotein antibodies. Complement levels were normal. Venous thromboembolism was attributed to the patient's limited activity level in the context of gangrenous lesions.

A transthoracic echocardiogram did not show masses or vegetations. The ABI and TBI were above the upper limit of the normal range, findings that were attributed to noncompressible arteries in the legs and feet. Pulse-volume recordings showed dampened monophasic waveforms at all levels of both legs below the thighs. On duplex ultrasonography, diffuse disruption of sound waves occurred as a result of acoustic shadowing from arterial calcification. Computed tomographic (CT) angiography of the abdomen and legs revealed extensive arterial calcification in both legs without evidence of atherosclerosis (Fig. 2). One month after the patient's vascular medicine appointment, there was significant proximal expansion of the necrotic area of his right foot, and he underwent a right below-knee amputation.

The ABI and TBI testing, duplex ultrasonography, and CT angiography collectively indicate diffuse severe arterial calcification. Chronic kidney disease and diabetes place him at risk for atherosclerotic disease, but no evidence of atherosclerosis was observed on imaging studies.

A disorder involving widespread arterial calcification and thrombosis is the most likely cause of his generalized ischemia and necrosis. Negative autoimmune serologic testing and thrombophilia assays make an autoimmune vasculitis or inherited thrombophilia unlikely.

Histopathological examination of a surgical specimen of the right below-knee amputation revealed dense medial arterial calcification with no calcium deposition in the capillary walls of the dermis or subcutis (Fig. 3). There was no evidence of vasculitis, thrombosis, or atherosclerosis. The blood calcium level was 9.0 mg per deciliter (normal range, 8.5 to 10.2), and the phosphate level 4.3 mg per deciliter (normal range, 3.5 to 4.7). The magnesium, 25-hydroxyvitamin D, and parathyroid hormone (PTH) levels were normal.

The combination of extensive medial arterial calcification, widespread necrosis (possibly resulting from warfarin use), and advanced chronic kidney disease is characteristic of calciphylaxis. However, the presence of wounds in nonadipose tissue, the absence of pain, and the normal levels of calcium, phosphorus, and PTH are atypical. Furthermore, the surgical specimen does not show microvascular thrombosis — a condition that partially mediates the necrosis associated with calciphylaxis, although thrombosis can be scattered and transient. Patients with advanced chronic kidney disease and diabetes can have medial arterial calcification that is distinct from the intimal calcification that occurs with atherosclerosis but is still a contributor to critical limb ischemia.

Progressive necrosis of the fingers and further limb loss continued, including autoamputation of multiple fingers on each hand. Given that the clinical findings were inconsistent with calciphylaxis, an alternative diagnosis was pursued. Whole-genome sequencing of the arterial tissue revealed a missense mutation in *NT5E* (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) that leads to a deficiency of CD73, an enzyme that has a central role in phosphate metabolism and tissue calcification. The patient received a diagnosis of arterial calcification due to deficiency of CD73, also known as ACDC.

He was treated with wound care and infusions of the calcium chelator sodium thiosulfate during hemodialysis on the basis of reports of benefit of this agent in patients with vascular calcification, although not specifically in those with ACDC. Subsequently, all his open wounds began to heal, and his nonnecrotic digits were salvaged (Fig. S2). One year later, all the wounds had healed, and no new wounds had appeared. The patient continued to receive infusions of sodium thiosulfate during each hemodialysis session.

COMMENTARY

This patient presented with peripheral wounds and limb ischemia that rapidly evolved to digit and limb loss. The identification of extensive vascular calcification without atherosclerosis reframed the differential diagnosis. After calciphylaxis was ruled out, genomic testing led to the diagnosis of arterial calcification due to deficiency of CD73.

Peripheral artery disease causes luminal narrowing of the arteries, impairs perfusion to the arms and legs, and can lead to critical limb ischemia. Peripheral artery disease is most commonly caused by atherosclerosis and intimal calcification, which may culminate in plaque rupture and thrombosis. Patients with risk factors for atherogenesis, including diabetes, hyperlipidemia, hypertension, smoking, and chronic kidney disease, are especially susceptible to peripheral artery disease and its clinical sequelae. However, there is growing recognition that a nonatherosclerotic mechanism — medial arterial calcification — may also cause vessel occlusion.[1]

The molecular mechanisms that drive medial arterial calcification are distinct from the pathways that drive atherosclerotic plaque calcification, although both phenotypes are associated with thrombotic events.[1] The hemodynamic consequences of vascular calcification stem from a loss of elasticity of the blood vessels,[2] which can lead to ischemia, end-organ dysfunction, and tissue necrosis.[3] In the current patient, noncompressible blood vessels in the legs, acoustic shadowing on duplex ultrasonography, and CT angiographic findings pointed to severe vascular calcification. The rapid and severe development of wounds suggested that the patient's peripheral artery disease differed from atherosclerosis-associated arterial calcification.

An early consideration was calciphylaxis, a rare disorder that is characterized by vascular calcification and is most frequently observed in patients with end-stage renal disease[4] and is associated with hyperparathyroidism,[5] although cases have been reported in patients with normal kidney function and normal levels of calcium, phosphate, and PTH. Typically, skin lesions start as a violaceous rash and progress to painful necrotic ulcers in central areas of high adipose-tissue distribution.[5,6] Histopathological findings include calcification of small and medium-sized arteries, calcium deposition in the capillary walls of the dermis and subcutis, and microvascular thrombosis.

In this patient, the absence of pain; the localization of wounds to the hands, legs, and feet; and the normal PTH level led health providers to consider alternative causes. Furthermore, histologic evaluation of the surgical specimen from the right below-knee amputation showed dense medial arterial calcification of thick-walled vessels but no typical manifestations of calciphylaxis, such as calcium deposition or microvascular thrombosis in the dermis or subcutaneous adipose tissue.

Whole-genome sequencing identified a missense mutation in *NT5E* (c.1126→G, p.Thr376Ala),[7] one of several sequence variants that are known to cause ACDC. *NT5E* encodes CD73, which converts adenosine monophosphate to adenosine and inorganic phosphate. Loss-of-function mutations resulting in low CD73 levels lead to decreased adenosine production and increased tissue-nonspecific alkaline phosphatase activity, with resulting increased signaling of down-stream mediators that stimulate ectopic calcification[8,9] (Fig. 4).

ACDC is a rare, autosomal recessive, adult-onset genetic disorder that causes periarticular calcifications and calcification of the peripheral arteries (iliac, femoral, and tibial) with sparing of larger central arteries such as the aorta and carotid and coronary arteries.[10,11]

Histologic analysis of tissue from patients with ACDC reveals calcification of the medial arterial layer that is distinct from the intimal calcification that accompanies atherosclerosis.

Clinical manifestations of ACDC include arthralgias in the hands and feet, wounds, claudication, and critical limb ischemia.[10,12] In early case series, most patients were reported to be between 20 and 50 years of age and were reported to have normal kidney function, normal blood glucose levels, and normal calcium, phosphate, and PTH levels.

This patient had marked improvement in the ischemic process after he began receiving infusions of the calcium chelator sodium thiosulfate. The by-product of the reaction of sodium thiosulfate with excess calcium is readily cleared from the body. An observational study involving patients with calciphylaxis showed a lower incidence of death among those who received sodium thiosulfate than the incidence reported on the basis of historical data among patients who had not received sodium thiosulfate, as well as a reduction in lesion size associated with its use.[13] The efficacy of sodium thiosulfate in this patient suggests that agents that affect calcium metabolism may be useful in the treatment of rapidly progressive disorders of calcification. Bisphosphonates are competitive inhibitors of tissue-nonspecific alkaline phosphatase activity and are currently under investigation as a treatment for ACDC (ClinicalTrials.gov number, NCT01585402).

Earlier recognition of this patient's vascular disease that was caused by a disorder of vascular calcification could have led to earlier administration of sodium thiosulfate and may have resulted in limb salvage. In the context of a wound in a leg or foot, a normal ABI result is insufficient to rule out peripheral artery disease and should be combined with the use of pulse-volume recordings and waveform analysis, which can reveal vascular insufficiency. The development of gangrenous lesions during hospitalization warranted angiographic evaluation to investigate their cause and to ensure adequate perfusion to the newly developed wounds.

This case highlights the fact that pathways other than atherosclerosis can lead to critical limb ischemia. For this patient, gene sequencing directed the clinicians to an alternate diagnosis — ACDC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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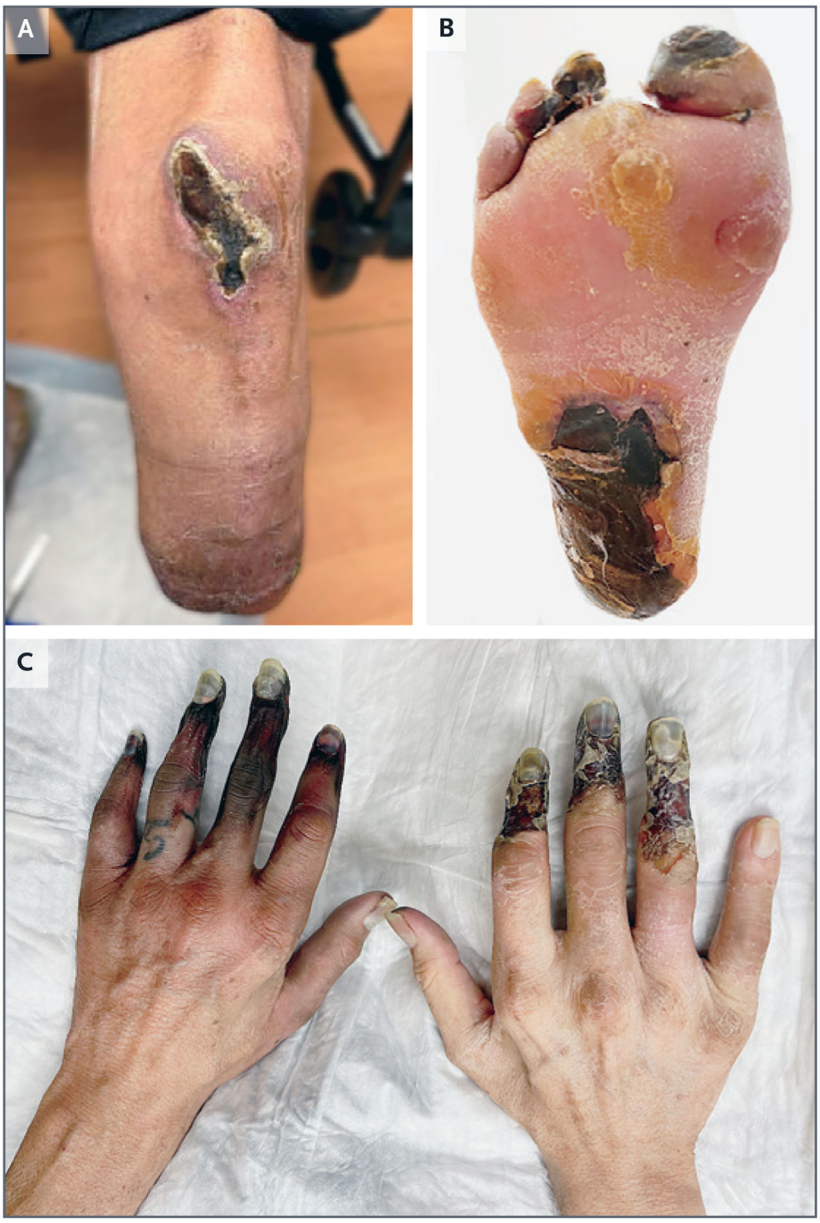

Figure 1. Photographs of Nonhealing and Necrotic Wounds.
Shown are clinical photographs of a nonhealing wound near the area of the left below-knee amputation (Panel A), necrotic wounds on the right heel and toes (Panel B), and necrotic wounds on the fingers of both hands (Panel C).

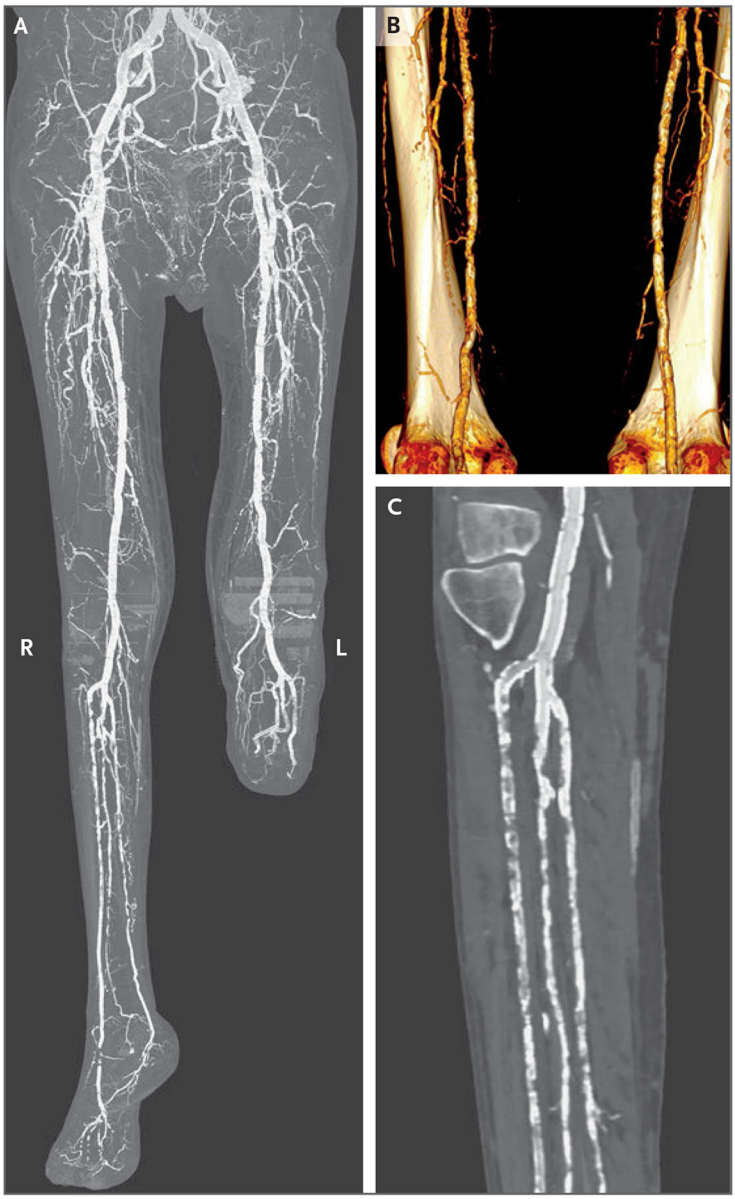

Figure 2. CT Angiography with Runoff.

Panel A shows a two-dimensional maximum-intensity projection image of both legs (after the left below-knee amputation). Panel B shows a three-dimensional reconstruction of both superficial femoral arteries. Panel C shows a two-dimensional image of the right popliteal and below-knee arteries. L denotes left, and R right.

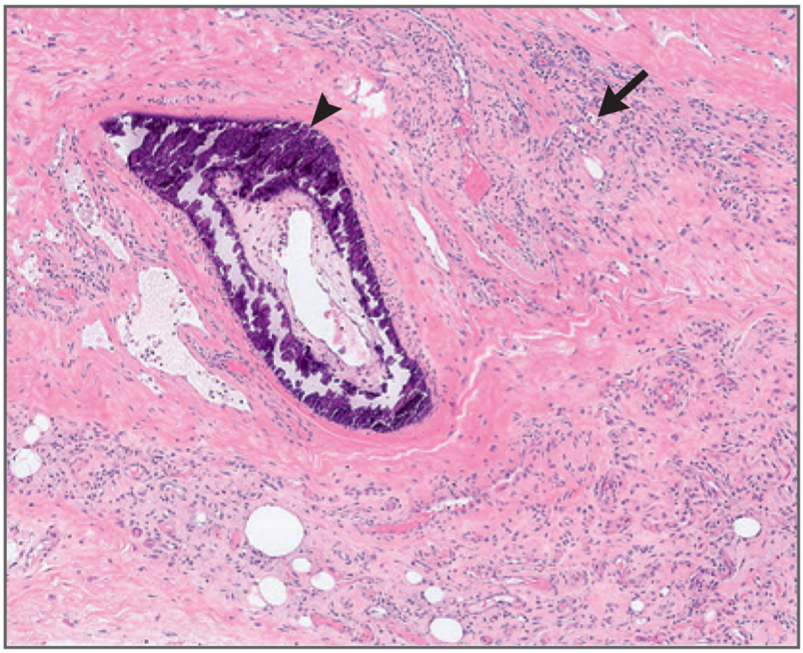

Figure 3. Biopsy Specimen of the Right Below-Knee Amputation.
Hematoxylin and eosin staining shows reactive capillary proliferation (arrow) and medial calcification in thick-walled vessels (arrowhead). (Image courtesy of Ryanne A. Brown, M.D.)

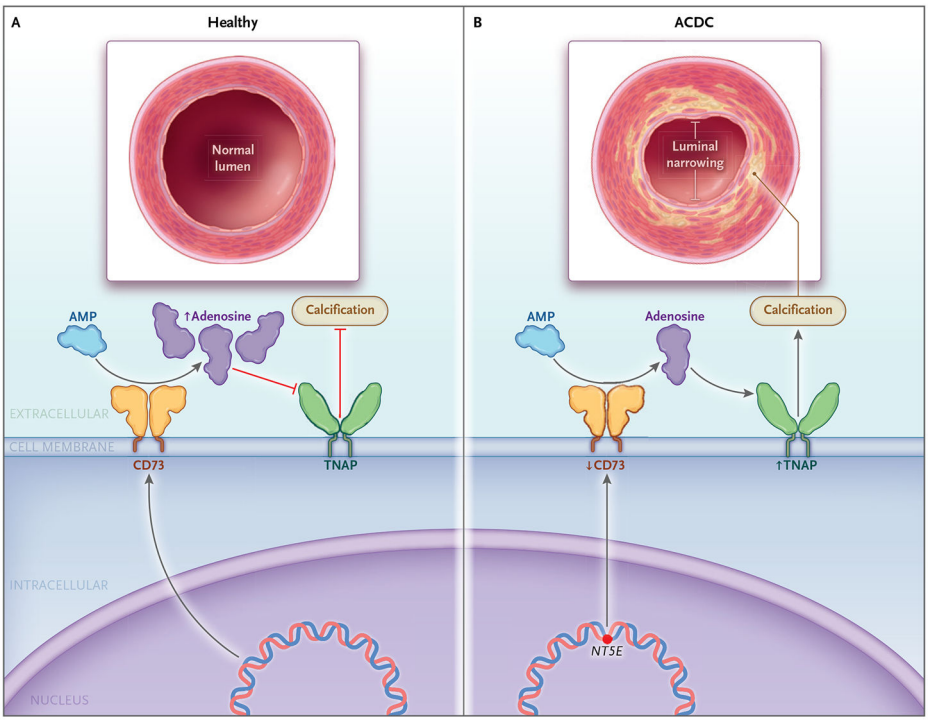

Figure 4. Ectopic Calcification in Arterial Calcification Due to Deficiency of CD73 (ACDC).
Shown is a depiction of the signaling cascade that leads to ectopic calcification in ACDC. Arrows show the change in CD73 and tissue-nonspecific alkaline phosphatase (TNAP) levels in ACDC. AMP denotes adenosine monophosphate.