Low-Dose Tissue Plasminogen Activator for Calciphylaxis

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The patient had been receiving peritoneal dialysis for approximately 1 year for end-stage renal disease. His medical history included recurrent deep venous thrombosis, chronic active hepatitis C, obstructive sleep apnea, and hypertension. His serum albumin level was decreased at 1.9 g/dL (normal, 3.4-4.8 g/dL) and the serum calcium level was 9.1 mg/dL (2.3 mmol/L) (corrected, 10.8 mg/dL [2.7 mmol/L]; normal, 8.9-10.1 mg/dL [2.2-2.5 mmol/L]). The serum phosphorus and parathyroid hormone levels were increased at 5.2 mg/dL (1.7 mmol/L) (normal, 2.5-4.5 mg/dL [0.8-1.5 mmol/L]) and 8.5 pmol/L (normal, 1.0-5.2 pmol/L), respectively. The calcium-phosphate product was 47.2 mg²/dL² (corrected, 56.0 mg²/dL²).

A 75-year-old man with end-stage renal disease presented with a 6-month history of nonhealing, markedly painful, necrotic ulcerations of the lower extremities (Figure 1A). The ulceration progressed in spite of multiple treatments elsewhere that included intensive wound care with wet-to-dry dressings, topical becaplermin, surgical debridement, and Unna boot dressings. A skin biopsy specimen demonstrated intravascular and extravascular calcification with pannicular necrosis and fibrin thrombi in dermal blood vessels consistent with calciphylaxis (Figure 2).

Figure 1. A, Ulcers before treatment (note inflamed, necrotic ulceration on lower extremity). B, Appearance of ulcers immediately after treatment. C, Appearance of ulcers 6 months after treatment with tissue plasminogen activator.
Coagulation screening tests demonstrated the following: low factor II activity at 35% (normal, 70%-130%), low factor VII activity at 48% (normal, 60%-125% and 70%-130%, respectively), a normal protein S antigen and activity level, and an increased level of fibrinogen at 671 mg/dL (19.7 µmol/L) (normal, 160-340 mg/dL [4.7-10.0 µmol/L]. These coagulation abnormalities were interpreted as being consistent with vitamin K deficiency or warfarin effect. However, the patient was not taking warfarin, and the vitamin K level was not determined. Prothrombin and factor V Leiden mutations were not detected. Findings were negative for antineutrophilic cytoplasmic antibodies (cANCA and pANCA), cryoglobulins, and cryofibrinogens.

**THERAPEUTIC CHALLENGE**

The patient presented with signs and symptoms consistent with calciphylaxis. The mortality rate varies with the distribution of involvement, with reported mortality rates ranging from 23% (distal) to 63% (proximal).1 Treatments reported beneficial for calciphylaxis include parathyroidectomy,1-3 low-molecular-weight heparin,4 wound debridement,2 hyperbaric oxygen,5,6 intensive wound care, and increased frequency of hemodialysis.7

In our patient, wound debridement and intensive local wound care had not led to improvement. Parathyroidectomy was not performed in view of its uncertain benefit because of the patient’s minimally increased level of parathyroid hormone. Hyperbaric oxygen treatment was not available.

**SOLUTION**

Because vascular occlusion may be a primary mechanism leading to the cutaneous necrosis associated with calciphylaxis,8,9 we elected to institute thrombolytic therapy in our patient. Low-dose tissue plasminogen activator (tPA; alteplase) was administered according to the protocol used for other cutaneous vaso-occlusive disorders (Table).10,11 The patient was hospitalized and given a daily 10-mg dose of alteplase intravenously for 14 days, followed by warfarin anticoagulation maintenance therapy. Also, the dialysis was intensified; the patient received hemodialysis daily for 1 week until the serum level of phosphorus normalized; then, he was maintained on hemodialysis 3 times weekly. Bedside debridement of the ulcers was performed daily as tolerated.

After completion of the tPA protocol (2 weeks after hospitalization), the ulcerated areas were markedly improved and less painful (Figure 1B). After discharge, the patient continued to receive wound care with daily whirlpool and periodic debridement. In addition, beginning at 6 weeks after discharge, skin grafts with the skin substitute Apligraf (Novartis, Basel, Switzerland) were placed on the larger areas of ulceration, with 4 total dressings applied over a 2-month period. Six months after tPA treatment, the patient had superficial erosions on the right and left anterior tibias, but otherwise the ulcers had healed completely (Figure 1C).
Thrombolytic therapy was considered a reasonable treatment choice for our patient for the following reasons: (1) there was clinical and laboratory evidence of a hypercoagulable state (history of multiple deep venous thromboses, low protein C level, and low antithrombin III level), and a hypercoagulable state has been reported in several patients with calciphylaxis;22-26, (2) fibrin thrombi were observed on histopathologic examination; (3) anticoagulation therapy has been reported effective in patients with calciphylaxis;4, (4) we postulated that calciphylaxis may be considered an occlusive vasculopathy (with clinical resemblance to warfarin-induced skin necrosis or type I cryoglobulinemia); and (5) we have found that low-dose tPA is effective in the treatment of other coagulopathic disorders of the cutaneous microvasculature (eg, livedoid vasculopathy27,28 and antiphospholipid antibody syndrome). To our knowledge, therapies directed at clot lysis have not been used for calciphylaxis.

Tissue plasminogen activator has found wide use in reducing morbidity and mortality in thrombosis-associated myocardial infarction, pulmonary embolism, and stroke.17 We postulated that a mechanism similar to that occurring in atherosclerotic disease may mediate the pathogenesis of calciphylaxis, wherein progressive, calcific narrowing of the cutaneous microvasculature ultimately leads to thrombotic vascular occlusion and downstream tissue necrosis.

The explanation for the coagulopathy in our patient is unclear, but it may be secondary to poor nutrition, end-stage renal disease, or long-term hemodialysis or it may be multifactorial. Vitamin K deficiency has been observed in patients with chronic renal failure,18 in patients receiving long-term hemodialysis,19 and in patients with calciphylaxis.20,21

Thrombolytic therapy appeared to be effective in our patient. Paradoxically, oral anticoagulation with warfarin has been reported to be a risk factor for the development of calciphylaxis.4,22 This risk may be secondary to low vitamin K–dependent anticoagulation factors (eg, protein C and protein S). However, vitamin K replacement was associated with progression of calciphylaxis and mortality in a patient with calciphylaxis and a documented low serum level of vitamin K.20

Most treatments of calciphylaxis have centered on restoring calcium and phosphate homeostasis. Theoretically, this may prevent further calcification of the cutaneous microvasculature, which is thought to precede thrombus formation.23 These therapies have included parathyroidectomy (surgical and ethanol ablation), alteration of ionic concentrations in the dialysate, and oral phosphate binders.

Good wound care was likely a vital therapeutic component leading to healing in our patient. Regardless of the cause of cutaneous ulceration, debridement of necrotic tissue by surgery, whirlpool, or wet dressings is often necessary to allow for wound reepithelialization. Moreover, restoration of a normal phosphorus level after intensive dialysis may have contributed to our patient’s improvement.

Because tPA therapy carries the risk of potential hemorrhage-associated morbidity and mortality, patients must

### REFERENCES


Clinicians, local and regional societies, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Submit 4 double-spaced copies of the manuscript with right margins nonjustified and 4 sets of the illustrations. Photomicrographs and illustrations must be clear and submitted as positive color transparencies (35-mm slides) or black-and-white prints. Do not submit color prints unless accompanied by original transparencies. Material should be accompanied by the required copyright transfer statement, as noted in “Instructions for Authors.” Material for this section should be submitted to George J. Hruza, MD, Laser and Dermatologic Surgery Center Inc, 14377 Woodlake Dr, Suite 111, St Louis, MO 63017.