Pivotal Role of Paricalcitol in the Treatment of Calcific Uremic Arteriolopathy in the Presence of a Parathyroid Adenoma

Vassilis Vargemezis, MD, PhD,[1] Vassilios Liakopoulos, MD, PhD,[1] Pelagia Kriki, MD,[1] Stylianos Panagoutsos, MD, PhD,[1] Maria Leontsini, MD, PhD,[2] Ploumis Passadakis, MD, PhD,[1] and Elias Thodis, MD, PhD[1]

Calcific uremic arteriolopathy, or calciphylaxis, is a serious and life-threatening complication of end-stage renal disease. Its pathogenesis is not yet fully elucidated and treatment is controversial. In the presence of severe hyperparathyroidism, parathyroidectomy should be considered. We report a case of a woman on maintenance hemodialysis therapy with calciphylaxis and parathyroid adenoma who refused to undergo parathyroidectomy. She was treated successfully with a combination of noncalcium phosphate binders, cinacalcet, and paricalcitol. Subcutaneous plaques disappeared, and the necrotic lesion was healed. Discontinuation of paricalcitol led to an increase in serum parathyroid hormone levels and reappearance of the patient's symptoms, whereas its reintroduction resulted in complete remission of the clinical picture. Paricalcitol, a less calcemic vitamin D analogue, is also a selective vitamin D receptor activator with a number of nonclassic actions (such as inhibition of inflammation and ossification-calcification) that could prove beneficial in cases of calciphylaxis.
Am J Kidney Dis 55:144-147.

INDEX WORDS: Calcific uremic arteriolopathy; cinacalcet; paricalcitol; parathyroid adenoma.

Calcific uremic arteriolopathy (CUA), previously termed calciphylaxis, severe and progressive ischemic necrosis of the skin and adipose tissue, is an uncommon and life-threatening complication associated with end-stage renal disease.

Its prevalence varies from 1% to 4% in dialysis patients.[1] It most frequently affects the lower limbs and is associated with increased mortality, which in the case of proximal CUA may be as high as 87%.[2]

The exact pathogenetic mechanisms of CUA have not been fully elucidated.[3,4] Treatment of CUA is controversial. Parathyroidectomy has been advocated as a potent treatment, although its importance has been questioned by the report of cases of CUA in the absence of hyperparathyroidism.[3] Cinacalcet, a novel calcimimetic agent, has been reported to suppress parathyroid hormone (PTH) secretion and was shown to be beneficial in cases of CUA.[5-7] However, use of vitamin D or its analogues in the treatment of CUA has been questioned.[4]

We report a case in which paricalcitol (a vitamin D analogue) had a pivotal role in the treatment of CUA in a dialysis patient with parathyroid adenoma.

CASE REPORT

In January 2008, a 57-year-old white woman with end-stage renal disease caused by immunoglobulin A nephropathy on maintenance hemodialysis therapy in another unit was evaluated for pain in the right leg and an ischemic lesion of the right calf.

The patient presented with a 3 × 2.6-cm ischemic necrotic lesion on the inner surface of the right calf and painful subcutaneous plaques of different sizes on the inner and outer sides of both thighs (Fig 1). She was not febrile and had normal vital signs. Peripheral pulses were palpable and symmetrical. The patient was not obese (body mass index, 24.5 kg/m^2), and laboratory data showed the following values: calcium (Ca), 10.9 mg/dL (2.72 mmol/L); phosphorus (P), 7 mg/dL (2.26 mmol/L); intact PTH (iPTH), 1,800 pg/mL (1,800 ng/L; normal value, 10 to 65 pg/mL [ng/L]); albumin, 3.8 g/dL (38 g/L); C-reactive protein (CRP), 15 mg/dL; and alkaline phosphatase, 100 IU/L. Wound swab cultures were negative.

The patient was on thrice-weekly hemodialysis therapy for 6 years. In March 2007, she underwent aortic valve replacement surgery and was on systemic anticoagulation therapy with warfarin. She also was using Ca carbonate. The pain in the area of the plaques and the necrotizing lesion was

From the [1]Department of Nephrology, Medical School, Democritus University of Thrace, Alexandroupolis; and [2]Department of Renal Pathology, Hippokration General Hospital, Thessaloniki, Greece.

Received December 16, 2008. Accepted in revised form March 27, 2009. Originally published online as doi:10.1053/j.ajkd.2009.03.015 on June 1, 2009.

Address correspondence to Vassilis Vargemezis, MD, PhD, Professor of Nephrology, Department of Nephrology, Medical School, Democritus University of Thrace, University Hospital of Alexandroupolis, Alexandroupolis, 68100, Greece. E-mail: vargem@otenet.gr

0272-6386/09/5501-0020$36.00/0
doi:10.1053/j.ajkd.2009.03.015

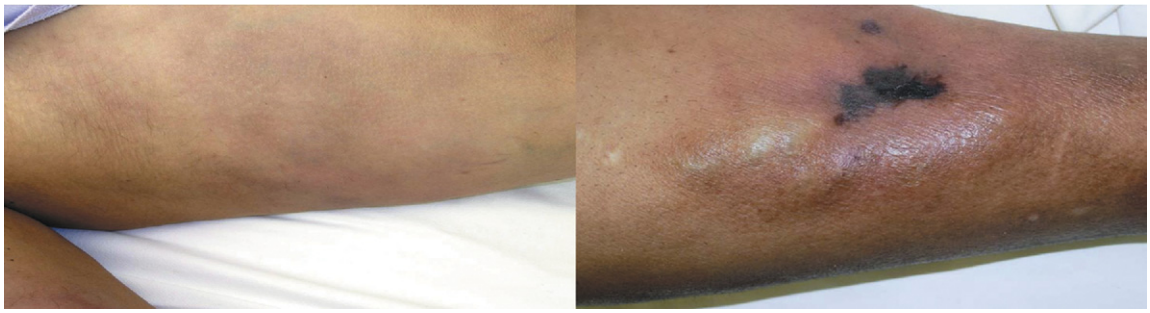

Figure 1. (Left) Painful subcutaneous plaque of the left thigh and (right) necrotic lesion of the right calf.

severe and became more intense during dialysis, requiring analgesic therapy with paracetamol and opioids.

A technetium-99m (^{99m}Tc)-sestamibi scan was compatible with parathyroid hyperplasia and an adenoma of the right upper parathyroid gland (Fig 2). Results of the biopsy of the ulcer and an adjacent subcutaneous plaque were characteristic of CUA (extensive intimal hyperplasia, medial vascular calcification, arteriolar and subcutaneous fat calcification, and thrombi in capillaries). Parathyroidectomy was suggested, but because of the patient's refusal, conservative management was the only option.

Treatment included rigorous wound care, discontinuation of warfarin therapy with initiation of low-molecular-weight heparin, additional dialysis sessions (although the severe pain that the patient experienced made these sessions difficult to perform), decreasing the dialysate Ca to 1.5 mEq/L (0.75 mmol/L), and substitution of Ca carbonate with lanthanum carbonate. Treatment with intravenous paricalcitol (12.5 mg 3 times weekly) and oral cinacalcet, 30 mg once daily, also was initiated.

One month later, the patient's clinical picture improved significantly. Her laboratory tests showed the following values: iPTH, 407 pg/mL (407 ng/L); Ca, 9.8 mg/dL (2.45 mmol/L); and P, 6.3 mg/dL (2.03 mmol/L). At 6 months, serum chemistry results showed an iPTH level of 375 pg/mL (375 ng/L), Ca level of 9.5 mg/dL (2.37 mmol/L), P level of 6.6 mg/dL (2.13 mmol/L), and CRP level of 0.8 mg/dL. In the meantime, the patient experienced only 1 episode of hypercalcemia, for which the intravenous paricalcitol dose was decreased to 10 mg 3 times weekly and cinacalcet dose was increased to 60 mg once daily.

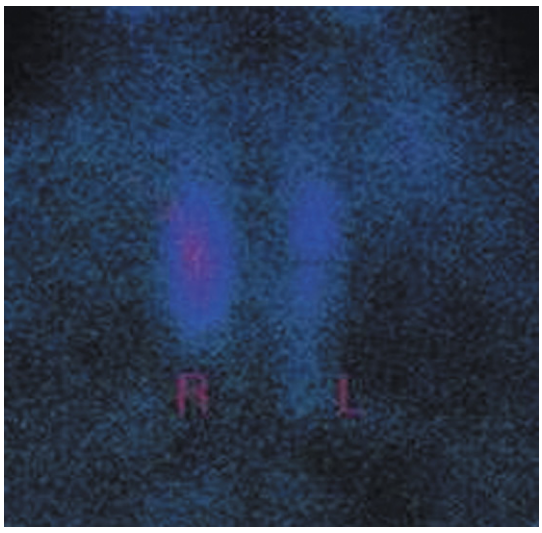

Figure 2. Adenoma of the right upper parathyroid gland.

Remission of the skin lesions and subcutaneous plaques was observed after 1 month of treatment, and at 6 months, they had disappeared. A new ^{99m}Tc-sestamibi scan showed the same adenoma of the right upper parathyroid gland. Parathyroidectomy was suggested again to the patient, but she refused.

The patient was sent to her previous dialysis unit with instructions to follow the same treatment. However, 1 month later, paricalcitol therapy was stopped by her attending nephrologists. The patient again developed erythema in both thighs, started to experience dysthesia and pain in the legs and thighs, and came to our unit for reevaluation. She was using cinacalcet, 60 mg once daily, and lanthanum carbonate, 1.5 g 3 times daily. Serum iPTH level was 900 pg/mL (900 ng/L), Ca level was 11 mg/dL (2.74 mmol/L), P level was 7 mg/dL (2.26 mmol/L), and CRP level was 4 mg/dL. Paricalcitol, 10 mg intravenously 3 times weekly, was added, and 1 month later, the patient's laboratory tests showed the following values: iPTH, 300 pg/mL (300 ng/L); Ca, 9.8 mg/dL (2.44 mmol/L); P, 5.5 mg/dL (1.77 mmol/L); and CRP, 0.5 mg/dL. The pain disappeared and her condition remains stable until now.

DISCUSSION

CUA represents a serious complication of end-stage renal disease, with detrimental effects on patient survival and quality of life. Risk factors include female sex, white race, obesity, diabetes, liver disease, local trauma, hypotension, hypoalbuminemia, increased serum calcium-phosphorus product, hyperparathyroidism, malnutrition, protein S and C deficiencies, and use of warfarin anticoagulants.[8,9]

The pathogenesis of CUA is poorly understood. Multiple pathways have been proposed,