

Successful Treatment of Calciphylaxis With Pamidronate

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Calciphylaxis is a complication of chronic kidney disease characterized by necrotic lesion in the skin. Histological examination reveals microcalcification of medium-sized blood vessels. We report on a 21-month-old girl with end-stage renal disease with severe calcium-phosphate imbalance. Calciphylaxis process started when she received calcium gluconate intravenously the day before the surgery to correct hypocalcemia and continued progressively despite peritoneal dialysis and forced stopping calcium-containing medication. Pamidronate, 0.5 mg/kg/d, was administered for 6 days and then once a week for 5 weeks. After 1 week, the skin lesion started to heal and circulation improved, and after 6 weeks, all skin lesions completely recovered. Pamidronate was effective to stop calciphylaxis in this case with advanced renal insufficiency and severe calcium-phosphate imbalance. Medical or surgical debridement are not suggested and lesions might recover without scar by pamidronate.

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INTRODUCTION

Calciphylaxis is a rare but fatal complication of chronic kidney disease, seen in 1% to 4% of patients. It is characterized by vascular calcification, thrombosis, and necrotic lesions in the skin.¹ However the exact mechanism is unclear, it seems an imbalance of promoting and inhibitory factors of calcification attribute to the development of calciphylaxis. The presence of some risk factors such as end-stage renal disease (ESRD), hypercoagulability state, inflammatory status, female sex, obesity, and administration of vitamin D and calcium-based phosphate binders predispose the patients to calciphylaxis. To the best of our knowledge, there is no report on successful management of calciphylaxis in children with ESRD.²⁻⁴ We report on a successful therapy of a calciphylaxis due to chronic kidney failure with pamidronate.

CASE REPORT

A 21-month-old girl with ESRD due to diffuse

mesengeal sclerosis was referred for implantation of a Tenckhoff catheter. She was the first child of a nonconsanguineous marriage who presented with edema at the age of 10 days. She had been under standard therapy for congenital nephrotic syndrome. Physical examination was unremarkable except for the developmental delay. Laboratory tests results on admission were as follows: blood urea nitrogen, 150 mg/dL; serum creatinine, 5 mg/dL; serum uric acid, 10 mg/dL; serum calcium, 4.5 mg/dL; serum phosphate, 13.6 mg/dL; alkaline phosphatase, 1017 IU; parathyroid hormone, 700 pmol/L; vitamin D, 21 ng/mL; triglyceride, 560 mg/dL; total cholesterol, 400 mg/dL; C-reactive protein, 17 mg/L; hemoglobin, 10 mg/dL; and erythrocyte sedimentation rate, 94 mm/h.

She received intravenous calcium gluconate (elemental calcium, 540 mg/d) the day before surgery to correct hypocalcemia. The following day she became febrile and irritable, and had scant cough. Subsequently, a pink line appeared along superficial median vein of the left forearm.

Radiography of the wrist showed no evidence of calcium leakage. Conservative therapy including ibuprofen and cephalosporin was started. Intravenous calcium was stopped, oral calcium supplement (elemental calcium, 145 mg/d) in addition to calcium carbonate (elemental calcium, 200 mg/d) as phosphate binder were administered. On the 3rd day, the fever rose to 40°C, a superficial ill-defined erythematous lesion appeared on the plantar surface of the left wrist that progressed to a subcutaneous warm hard tender nodule, and a blister appeared on the right wrist. The following day, the left wrist became tremendously painful and swollen. Then, high-grade fever appeared and the severity of cough increased. Leukocytosis was documented (leukocyte count, $22.4 \times 10^9/L$; polymorphonuclear cells, 75%).

Antibiotic therapy was changed into tazocin and clindamycin. The next day, massive gastrointestinal bleeding was started. Upper endoscopy revealed the source of bleeding to be mucosal membrane of the mouth. Tenckhoff catheter for peritoneal dialysis was implanted surgically. Peritoneal dialysis was started with dwell volume of 50 mL every 60 minutes for 24 hours. Aluminum hydroxide, 15 mL/d, was given orally. Hourly peritoneal dialysis continued and all calcium-containing medications were stopped. Sevelamer was started and supplementary nutrition was encouraged. The blister of the right wrist progressed to skin necrosis (Figure 1). The skin became tender and erythematous by any venous puncture or utilizing adhesive band. The new blood laboratory test showed calcium level of 6.8 mg/dL; phosphate, 6.8 mg/dL; creatinine, 6.6 mg/dL; and hemoglobin, 7.4 mg/dL. Color Doppler ultrasonography of the forearm vessels revealed biphasic waves in favor of inflammation. Forearm radiographies showed soft tissue calcification.

Surgical debridement of the necrotic tissue of the right wrist was done (Figure 2). The dwell volume increased to 100 mL every 2 hours. Wound care on the surface of the surgical debridement was regular-forced irrigation with normal saline, and treated with hydrocolloid, alginate, and silver-containing absorbent dressing, but the lesion seemed to have no sign of recovery, the extent of dead tissue was been increasing, and tissue circulation was very poor. The nodule of the left wrist enlarged and became violaceous and severely tender. Because of



Figure 1. The clinical courses of lesions on the right and left wrists are shown. Surgical debridement was done on the right wrist but the left hand was kept as control under pamidronate therapy.

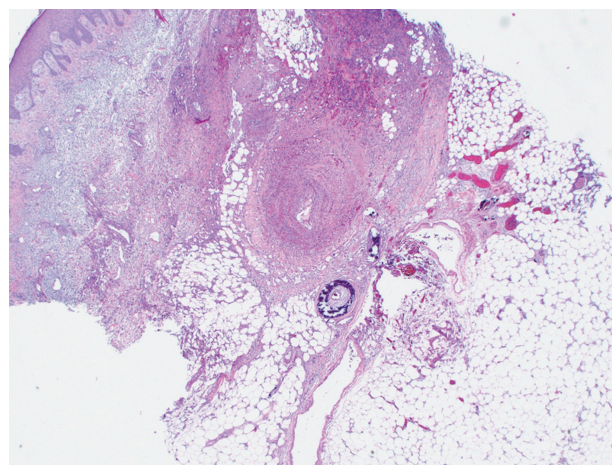


Figure 2. Pathologic examination of debridement skin showed extensive necrosis and calcium deposition and calcification in the arterial wall. There was also intimal proliferation and luminal narrowing. Hypodermis showed fat necrosis and panniculitis.

poor circulation, no further surgical debridement was done. Therefore, the left wrist and both ankles were kept as control. Pamidronate, 0.5 mg/kg/d, was administered for 6 days, then every other day. After the 8th dose, the patient became irritable and had constipation and sterile culture-negative peritonitis developed (leukocyte count, $0.4 \times 10^9/L$; polymorphonuclear cells, 5%; lymphocytes, 95%) that recovered spontaneously by increasing the interval of pamidronate injection to once a week. The lesion fully recovered in 45 days after the first injection of pamidronate. She was being followed for more than 48 months since she discharged from hospital. On the last follow-up visit, she was on peritoneal dialysis with no sign of tissue calcification.

DISCUSSION

To the best of our knowledge, this is the first successful management of an infant with ESRD complicated with systemic calciphylaxis with bisphosphonate. All of the other reported cases had a fatal course or severe morbidity with progression to gangrene and losing the extremities.^{5,6} With all managements including substitution of sevelamer and low-calcium-content peritoneal dialysis fluid,² low-molecular-weight heparin and pentoxifyllin,⁷ aluminum hydroxide, patient survival was poor and treatment was ineffective.¹

Calciphylaxis consists of vascular calcification, thrombosis, and skin necrosis. It has poor outcome and occur both in ESRD and in non-uremic conditions. Various risk factors are proposed as the etiology of the disease, including calcium products, hyperlipidemia, warfarin, hypercoagulability, female sex, and obesity. The underlying pathophysiology is still unknown but the imbalance of calcium-phosphate product, reduction of calcification inhibitors inclusive fetuin-A and Max-Ga protein, and inflammation play some roles.⁸ The etiology of calciphylaxis in our patient was multi-factorial. She had ESRD due to congenital nephrotic syndrome that required dialysis, had severe calcium-phosphate imbalance (severe hyperphosphatemia), received intravenous calcium and oral calcium carbonate and calcium gluconate, and suffered from hyperlipidemia, trauma, cachexia, and malnutrition.

There is no definite treatment for calciphylaxis as the disease is rare and the data is based on case series and not clinical trials. Wound debridement has

been suggested. But our patient demonstrated that the best strategy was to keep the wound naturally closed. Surgical or chemical debridement is highly possible to increase the risk of infection. In addition, the repair of poorly vascular perfusion exposed wounded tissue is highly risky. Discontinuation of calcium containing medications and vitamin D is the main core of therapy. The very low level of calcium in our case in addition to the history of convulsion postponed this step of therapy and the patient received firstly intravenous calcium and then oral calcium that both aggravated the clinical course of calciphylaxis. Drastic reduction of phosphate is obligatory by hemodialysis, but it was unavailable for this small-sized child in our setting. The only available modality for this size was continuous ambulatory peritoneal dialysis that slowly eliminated phosphate. Some studies suggested sodium thiosulfate as an anti-oxidant and a potent chelator of tissue calcification in uremic patients. The other recommended but not proved therapies are hyperbaric oxygen and *Lucilia sericata* larvae, none of which were available in our country.⁹ Bisphosphonate is another therapy that has been used successfully for treatment of calciphylaxis mostly in adult ESRD patients.¹⁰

Tissue calcification has been shown to be over a simple calcium-phosphate precipitation. The presence of transdifferentiation to chondrocyte either in the intima or medial layer of vessels is an insight to an active bone formation in vascular calcification of uremic patients.¹¹ The efficacy of bisphosphonate on bone mineral disorder in chronic kidney disease (CKD) and dialysis patients are challenging.¹² Bisphosphonate is widely used in hypercalcemia,^{13,14} osteoporosis, etc. Its main role is to inhibit osteoclastic activity and promote osteoblast function.^{4,15} However, its prescription in children with CKD might not be without risk of aggravating preexisting adynamic bone disease and longitudinal growth impairment. Its risks and benefits should be balanced before utilization in CKD and dialysis patients.¹⁶

Given the available modalities of treatment, we had no choice except to start pamidronate in our patient to stop the calciphylaxis and accelerate the healing process. Before pamidronate exposure, the exposed wound of the child showed very sluggish perfusion with no sign of recovery. The figure of both wrists with and without surgical

intervention demonstrated that wound debridement should not be recommended and bisphosphonate and supportive care would be essential to help the patient transit from acute deadly stage to recovery phase. However, the study about the efficacy and safety of pamidronate in higher CKD stages is lacking, and clinical trials are suggested to provide more solid evidence for implication of pamidronate in this group.

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CONFLICT OF INTEREST

None declared.

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