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CLINICAL QUIZ

Rare etiology of severe calf pain and induration in a child with end-stage renal disease: Answers

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Answers

1. Frontal and lateral X-rays of left lower limb shows a thick, high-density area involving almost the entire subcutaneous tissue of the leg, in keeping with calcification (Fig. 1). Subperiosteal bone resorption is noted in the proximal femur and tibia, in keeping with renal osteodystrophy. Neck ultrasound (Fig. 2) reveals well-defined, hypoechoic, oval nodule posterior to the right thyroid lobe, in keeping with enlarged right parathyroid gland.
2. Calciphylaxis, a rare complication of bone mineral disease in CKD.
3. Sodium thiosulphate, cinacalcet, pamidronate, and intensified dialysis regimen.

Discussion

Calciphylaxis is a rare but life-threatening complication of end-stage renal disease (ESRD). Its pathogenesis is poorly understood and hypothesized to occur in two stages. The first stage involves vascular injury, which is followed by sensitization of the areas supplied tissue to ischemia. The second stage is additional vascular damage, which may be triggered by clinical events such as local trauma, hypotension, or thrombosis, and leads to the development of an ischemic infarct, dystrophic calcification, or ulceration [1]. Risk factors of calciphylaxis are ESRD, dialysis treatment, hyperphosphatemia, hypercalcemia, increased calcium–phosphate product, increased levels of parathyroid hormone (PTH), vitamin D supplementation, malnutrition, low plasma albumin, and inflammation [2]. The EVOLVE trial, a large-scale interventional study, suggested that high PTH levels or hyperparathyroidism may be associated with calciphylaxis [3].

Clinical presentation and course of disease can vary. Gokalp et al. reported a 8-year-old-child with calciphylaxis with ESRD who presented with widespread necrotic ulcers and purple, non-ulcerating plaques [4]. Valentini et al. reported a patient with calciphylaxis who died 9 months following presentation [5]. In our index case, clinical diagnosis of calciphylaxis was made based on clinical presentation of violaceous skin plaques in an ESRD patient, extremely high PTH and calcium phosphorus product, and supporting radiological picture. Skin biopsy was avoided because of the risk of creating an ulcer.

No specific treatment guidelines are available in the literature. Various treatment strategies for treating calciphylaxis have been tried so far. Dharnidharka et al. studied three children 12–21 years old with calciphylaxis on dialysis and successfully treated with sodium thiosulphate [6]. Jahangiri et al. treated a 21-month-old-child with end-stage renal failure who responded to pamidronate [7]. The treatment goal was to maintain calcium, phosphorous, and PTH in the normal or close-to-normal range. Our patient was managed as follows:

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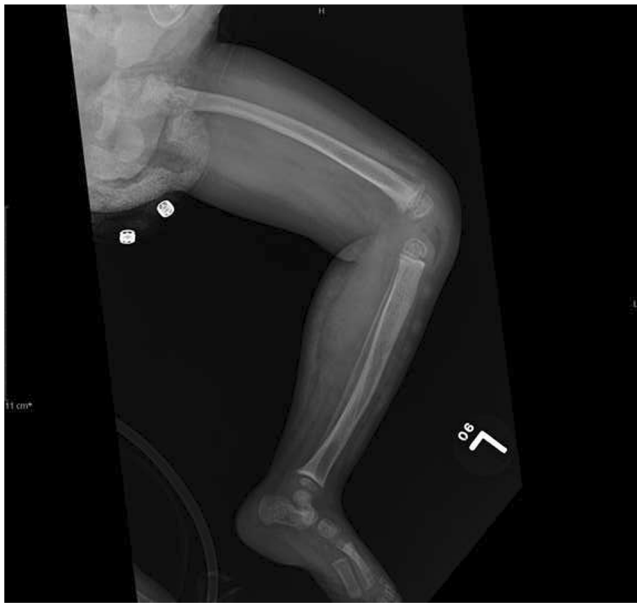
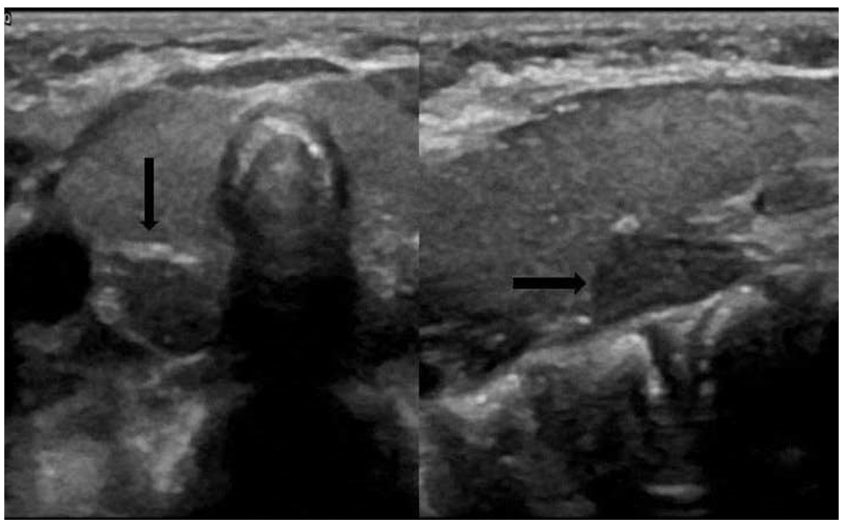


Fig. 1 X ray of left lower limb

1. Intensification of dialysis regimen and optimization of chronic kidney disease parameters. Low-calcium dialysate was used, along with longer dwell time and increased number of cycles. Albumin infusions were given to optimize serum albumin level. Phosphate restriction in diet and phosphate binders were started to lower the calcium phosphorous product.
2. Sodium thiosulphate (STS). STS prevents precipitation and calcium-deposit formation by binding calcium to form calcium thiosulfate, a highly soluble calcium salt. It also has an antioxidant effect that may reverse endothelial dysfunction .The potential side effects include nausea, vomiting, rhinorrhea, sinus congestion, prolonged QT interval, headache, weakness, sodium overload, and increased anion-gap metabolic acidosis [1]. Our patient received four doses of sodium thiosulfate 12.5 g IV infusion over 4–h twice weekly. Optimal dosage and duration needs to be determined.
3. Pamidronate: The rationale for using pamidronate was to decrease bone demineralization, with an additional benefit of inhibition of macrophage activity and local proinflammatory cytokine production [8]. The patient received four infusions of 5 mg each, given weekly. Long-term use was avoided, as it may have detrimental effects on uremic bone.
4. Cinacalcet: Cinacalcet targets the calcium-sensing receptor of the parathyroid gland, increasing its sensitivity to circulating calcium. Cinacalcet lowers PTH levels and improves calcium–phosphorous homeostasis. It is indicated for treating secondary hyperparathyroidism in ESRD [9]. In our patient, target ionized calcium was kept between 0.8 and 1 mmol/L.
5. Effective pain management with analgesics was required for the first week until the child became pain free. Skin erythema resolved, and the hard, calcified calf muscle became supple; calcification size was reduced after 3 weeks, and the patient was able to walk again.

No consensus guidelines regarding treatment and specific pediatric dosage for the above medications are available so far and thus may be area for future interest. Owing to rare occurrence of calciphylaxis and deficits of understanding the disease, German (2007) and UK (2012) calciphylaxis registries

Fig. 2 Ultrasound of the neck



may be good resources for evaluating long-term outcomes and management [10]. Early diagnosis and management, before the appearance of skin ulceration, may be associated with better outcomes.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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