Case report
Skin wounds associated with calciphylaxis in end-stage renal disease patients on dialysis

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Abstract
Calciphylaxis is a rare complication of chronic renal failure mostly with poor prognosis. Painful lesions on various skin surface areas are the most prominent feature of this serious disease. Subsequent infection of necrotic skin tissue is associated with the risk of sepsis. Pathophysiology is unclear, but several risk factors are known. The most important risk factor is impaired calcium-phosphate metabolism. Our paper describes two cases of different forms of calciphylaxis in patients with chronic renal failure. In the first case, pamidronate and cinacalcet were used for treatment. In the second described case, calciphylaxis was associated with secondary hyperparathyroidism and immediate subtotal parathyroidectomy was performed. Both patients were successfully treated, using systemic approach as well as dedicated local care for healing of skin wounds.

Introduction
Skin pathologies and wounds are common but often neglected complications in maintenance dialysis patients [1], contributing significantly to low functional ability and quality of life in these patients. In some conditions, such as in calcific uremic arteriopathy, which is known also as calciphylaxis, skin lesions may be fatal.

Estimated prevalence of calciphylaxis is about 1–5% of the dialysis population, which corresponds to 10 to 50 cases per million in the general population. Therefore, in general, the disease is very rare. However, calciphylaxis is a very severe disease. If unsuspected and unrecognized immediately, the outcome is often fatal.

Recent reviews are dedicated to this topic [2,3]. Briefly, diagnosis is based on clinical presentation—very painful single or multiple skin ulcerations of various surface areas, starting with dark-red skin color with subcutaneous indurations, continuing with necrosis of affected skin areas, which often becomes infected with multiresistant bacteria (Figs. 1–9).

Two clinical forms, differing in location of lesions, but also in prognosis, may be recognized: proximal with lesions on trunk or thigh (with worse prognosis) and distal, where lesions are located distally from knees or elbows.

Local wound therapy is mandatory, but must be associated with measures aiming to correct responsible factors (see described case reports below). However, this is not easy, as the pathogenesis is multiple and still not fully known and thus it is difficult to cover all factors. Moreover, a similar clinical picture may be associated, for example, with systemic vasculitis (exclusion should be based on appropriate serum immunological tests, definitive confirmation on skin histology).

There are no specific laboratory tests to diagnose calciphylaxis. However, calcium, phosphate, and parathyroid hormone should be assessed in all patients and any abnormality (both above and below target concentrations) must be considered as at least a provoking factor.

What is the role of mineral and bone metabolism disturbances associated with renal failure? Chronic kidney disease—mineral bone disorder (CKD-MBD) is a well-established secondary complication in kidney patients. Secondary hyperparathyroidism and/or vascular calcifications are a component of CKD-MBD, having the same background—disturbed phosphate and calcium
metabolism. Hyperphosphatemia is a component of uremic toxicity [4]. A concentration of phosphate higher than 2 mmol/L induces an active process of vascular media calcification [5,6]. Hyper- as well as hypoparathyroidism are associated with redistribution of calcium and phosphate from bone into soft tissue (vessels) [6]. All chronic hemodialysis patients are at risk of vascular disease and vascular calcification, a fact which is often neglected.

Calciphylaxis, as a unique syndrome of calcification associated with skin and surrounding tissue necrosis, is associated with several additional risk factors: female gender, obesity, diabetes mellitus; derangement of calcium-phosphate metabolism (also associated with some therapeutic approaches); some data also support low serum albumin, previous warfarin use, and other factors [1,2,7–10]. Their individual contribution must be carefully weighed in all patients, as it is very important for an appropriate therapeutic decision.

In cases of hyperparathyroidism, immediate parathyroidectomy is a method of choice, without any doubt. In others, careful handling of calcium and phosphate metabolism is a first step (stopping calcium supplementation, stopping calcium-based phosphate binders, stopping vitamin D metabolites and analogs; lowering calcium in dialysis fluid). Biphosphonate, cinacalcet hydrochloride, and also sodium-thiosulphate were used with promising success [11–13]. Hyperbaric oxygenotherapy was also used [14,15].

Here we present two cases of calciphylaxis. The aims are to demonstrate this rare but very serious disease and to point out the importance of the complex approach, based on appropriate local as well as systemic care. For more detailed information of the syndrome of calciphylaxis, we refer to recent comprehensive reviews [2,3].

Case report 1

A 70-y-old obese woman with a long-lasting history of arterial hypertension and history of diabetes mellitus 2 type since 1982 (on insulin therapy since 1996) was regularly followed up for chronic kidney disease since 1991. In 2001, after recurrent “erysipelas-like” lesions on her left lower extremity, she was placed on warfarin therapy. She started planned regular hemodialysis therapy in 2007. At that time, warfarin was stopped as it was a not-indicated drug.

In August 2007, a painful dark red-colored skin discoloration with palpable subcutaneous induration (Fig. 1) developed 1 wk after minor injury on the right thigh. Two other similar lesions occurred also on right thigh 2 wk later. Skin biopsy was indicated, but the result did not help to confirm or exclude calciphylaxis syndrome.

Concentrations of serum calcium and phosphate were within reference range. Intact parathyroid hormone (PTH) was 10.2 pmol/L, which was slightly below the recommended target for end-stage renal disease [16]. Serum albumin was 36 g/L and C-reactive protein was 27 mg/L.

During the next few weeks skin areas affected progressed and enlarged. Necrotic defects developed, being initially small and located centrally (Fig. 2), but continuously involved the whole affected areas (Fig. 3).

After 2 mo, cinacalcet administration was started (30 mg once daily). Shortly after, serum PTH decreased to 1 pmol/L, but no decrease of serum calcium was observed. Serum C-reactive protein rose to 50–100 mg/L. One month later, all three defects formed just one very large lesion, which was very painful (Fig. 4). Moreover, similar lesions occurred on the contralateral thigh, fortunately without necrosis. At the beginning of December, i.e., 4 mo after initial presentation, pus and further signs of bacterial infection were observed (Fig. 5). Serum CRP concentrations reached 150 mg/L. Systemic clindamycin therapy was started based on results of cultivation (a smear from wound). However, no improvement was observed. Therefore, at the end of December, a course of pamidronate was started (30 mg after

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**Fig. 1.** Early stage of calciphylaxis in case report 1: dark red-colored skin affection with palpable subcutaneous induration.

**Fig. 2.** Small centrally located necrotic defects.

**Fig. 3.** Necrotic defects affect previously dark red-colored skin area.

**Fig. 4.** Large necrotic defect.

**Fig. 5.** Pus and bacterial infection signs.
hemodialysis intravenously for 40 min, every third day; total dose 150 mg).

Dedicated local care was applied for the whole period. Necrotic lesions were removed repeatedly, as needed. In December, the first areas of new granulomatous tissue occurred (Fig. 6), indicating the first signs of the healing process. In March 2008, the infection was controlled and successful healing continued, with further formation of granulomatous tissue. After 9 mo of therapy, lesions were cured (Fig. 7).

**Case report 2**

A 60-y-old female with polycystic kidney disease was on regular dialysis treatment since 2001. In 1999 she suffered from myocarditis, which resulted in dilated cardiomyopathy, associated with secondary mitral regurgitation and chronic heart failure with low ejection fraction (25%). During regular dialysis, serum phosphorus concentration was not controlled properly, partly due to non-compliance with phosphate-binder therapy. Secondary hyperparathyroidism developed.

In October 2006, small (5–15 mm in diameter) petechia-like exanxema developed on both calves (Fig. 8). During the next month, small central necroses occurred. Skin biopsy confirmed suspected calciphylaxis.

Serum PTH was 45 pmol/L; serum predialysis phosphate concentration was 3.95 mmol/L. Serum calcium was 2.56 mmol/L, and phosphate-calcium product was 10.1. The patient was treated by paricalcitol three times 5 μg per week intravenously (into dialysis tubes) and used lanthanum carbonate 2.5 g/d.

Acute subtotal parathyroidectomy was performed as a vital procedure.

Shortly after surgery, PTH decreased to 18.0 pmol/L; serum phosphate normalized and calcium decreased slightly below reference range.

The skin lesion slowly healed. Most problematic was the defect, which occurred after skin biopsy (Fig. 9).

Full healing was completed 4 mo after parathyroidectomy. At the present time, chronic dialysis therapy continues and no more lesions developed.

**Discussion**

Our case reports demonstrate that calciphylaxis has different forms and many risk factors. Both cases had similarities as well as differences in provoking factors, clinical picture, and course of disease.

The first case represents a proximal location of calciphylaxis without association with hyperparathyroidism. Many other known risk factors were present: obesity [7], history of warfarin use [9], diabetes mellitus, and female gender [10]. However, parathyroid hormone elevation was not the case [2]. Skin lesions were first noticed by the patient and suspected to be hematomas (after small injury). During the following months, all stages of local lesions developed, from initial color change to deep and infected wounds.

Despite the very large affected areas and several risk prognostic factors (age, diabetes mellitus, obesity) and absence of hyperparathyroidism (which means that curative parathyroidectomy is
not applicable), skin wounds were successfully cured. We thus can confirm reports of others who used new therapeutic approaches (bifosfonates, cinacalcet, sodium-thiosulphate) [11–13]. Cinacalcet and pamidronate therapy, however, was started relatively late. Despite this, therapy was successful. The relative contribution of these measures to the final success is difficult to recognize, as the therapy was combined.

Our case demonstrated the need for a complex approach, both local as well as appropriate use of pharmacotherapy. Because sepsis is the primary cause of mortality in patients with calciphylaxis [2,7], it is very important to prevent wound infection. Therefore, we were very careful with local care, aiming to minimize wound injury. If needed, antibiotic administration should be started without delay.

The second case report documents distal calciphylaxis associated with secondary hyperparathyroidism, with the important pathogenetic role of hyperphosphatemia [2,5]. Due to extremely high phosphates, hyperparathyroidism was resistant to vitamin D receptor activation with paricalcitol (hyperphosphatemia as a factor of vitamin D activation resistance). However, we must admit that at the same time paricalcitol could contribute to elevated serum phosphorus (the calcemic and phosphatemic risk with paricalcitol is much lower than with calcitriol, but still some calcemic and phosphatemic action with paricalcitol remains).

Parathyroid hormone concentration, 45.0 pmol/L (450 pg/mL), itself would not be an indication for parathyroidectomy in secondary hyperparathyroidism in end-stage kidney patients. However, in association with calcification and, namely with calciphylaxis, parathyroidectomy is the method of choice with absolute indication. This was the case in our patient, in which this indication was absolute and with immediate need, despite some risk (cardiomyopathy). The benefit of parathyroidectomy in patients with calciphylaxis positively correlates with increasing PTH serum concentration [17,18].

Another aspect worth considering when discussing the outcome of patients with calciphylaxis is the skin biopsy. First, the result is not always representative and a diagnosis may be missed, as it was in our first case. Second, healing of the necrotic skin area after biopsy may be problematic, as demonstrated in our second patient.

Thanks to early diagnosis and early radical correction of mineral metabolism (parathyroidectomy with subsequent normalization of calcium and phosphate concentrations), initial small defects did not progress. However, their full healing took several months. Also in this case, dedicated and extremely careful local care was an inevitable component of complex therapy.

Care of patients with calciphylaxis should be comprehensive with cooperation of the nephrologist, surgeon, and wound therapy specialist. Local therapy is one of most important components in calciphylaxis treatment and without well-guided local care and healing, recovery is nearly impossible.

In conclusion, dialysis patients are prone to some specific complications. Calciphylaxis is one of them, being extremely important due to its severe prognosis. Specific attention must be paid to the diagnosis and correction of all provoking and contributing factors; those linked to CKD-MBD are crucial, but others factors may also play a role. Once suspected, specific pharmacologic and local care must be applied by dedicated staff. Moreover, urgent parathyroidectomy is indicated when calciphylaxis is associated with secondary hyperparathyroidism.

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