Perineural and Vascular Calcification in a Patient with Chronic Renal Failure

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Sir,
The term calciphylaxis, coined by Seyle in 1962 (1), traditionally describes an uncommon entity that usually presents with cutaneous necrosis due to small vessel calcification. As the original concept regarding risk factors for the disease has changed considerably in the past few years, we have recently suggested the term ‘cutaneous vascular calcification’ for this pathology, based on the study of associated diseases and clinicopathological features of 17 patients with calcification within the walls of cutaneous vessels (2). To date, however, calcium deposits in the perineurium have never been described in the setting of cutaneous vascular calcification.

We report here the finding of cutaneous vascular and perineural calcification in skin samples from a diabetic patient with chronic renal failure who developed extremely painful erythematous and violaceous lesions in the abdomen, thighs and foot.

CASE REPORT
A 67-year-old woman with a history of chronic renal failure due to diabetic nephropathy who was undergoing peritoneal dialysis was admitted for evaluation of an episode of dialysis fluid leak. She developed an erythematous plaque located in the infra-umbilical region. This lesion was extremely painful and progressively increased in size. Physical examination revealed a firm plaque of 20 × 10 cm in size, with violaceous coloration (Fig. 1). Similar painful lesions subsequently appeared on both thighs and purpuric reticulated macular lesions developed on the dorsal and lateral sides of the left foot. During the following days, necrotic areas appeared on the abdominal plaque, evolving into ulcerated lesions. Morphine did not achieve good control of the intense pain.

Blood cell count revealed microcytic anaemia and leucocytosis (26,420 leucocytes mm$^{-3}$) with marked neutrophilia (91%), and many metamyelocytes and myelocytes. The blood film showed marked anisocytosis, poikilocytes and abnormal haemoglobinization. Biochemical tests disclosed elevated parathormone levels (144 pg ml$^{-1}$; normal 10–75 pg ml$^{-1}$) with normal calcium and phosphate levels, low albumin (2.4 g dl$^{-1}$; normal 3.4–4.8 g dl$^{-1}$) and protein levels (6 g dl$^{-1}$; normal 6.6–8.7 g dl$^{-1}$) and elevated creatinine (3.5 mg dl$^{-1}$; normal 0.5–1.3 mg dl$^{-1}$), urea (58 mg dl$^{-1}$; normal 10–50 mg dl$^{-1}$), alkaline phosphatase (409 U l$^{-1}$; normal 91–258 U l$^{-1}$) and γ-glutamyltransferase levels (157 U l$^{-1}$; normal 7–32 U l$^{-1}$). Thyroid hormone levels were within normal range. Coagulation tests disclosed a shortened thromboplastin time (62.9%). Radiological studies of lower extremities and abdomen revealed arterial calcifications of the abdominal aorta and its branches, both iliac arteries and left femoropopliteal territory. An abdominal ultrasound study showed calcifications of the subcutaneous tissue.

Four biopsies were performed, two from the abdomen, one from the right thigh and one from the left foot. Periarterial calcification of small vessels located in the dermis and/or subcutaneous tissue was observed in all samples. The skin from abdomen and thigh also showed continuous circumferential calcium deposits in the perineurial sheaths of small dermal nerve twigs (Figs 2 and 3). The staining pattern of the perineurial sheaths was continuous. No alteration of the nerve fibres was observed. No extravascular calcifications were observed in any of the samples. Different grades of subcutaneous and eccrine gland necrosis could also be observed, without an inflammatory infiltrate.

The patient died 1 month after the onset of the cutaneous lesions due to massive gastrointestinal bleedings.

DISCUSSION
The presence of vascular calcification in patients with chronic renal failure is a well-known phenomenon. Clinically these patients usually develop extremely painful indurated areas and retiform purpura located on the medial thighs, buttocks and the lower part of the abdomen. Progression results in the development of central necrosis and ulceration (3). Our patient could be included in this group of patients. Histologically they are characterized by the presence of calcium deposition in the walls of small-to-medium diameter blood vessels of the dermis and subcutaneous fat followed by fibroblast proliferation and giant cell formation (3). Fibrosis, intimal hyperplasia and occasionally thrombosis of the vessel result (3).

Reports on calcification in human peripheral nerves are scarce. Paetau & Haltia (4) reported selective calcification of the perineurial sheaths in the sciatic nerve found in a necropsy of a 33-year-old woman who died from uraemia complicating juvenile diabetes. Histological studies showed that the outer layers of the perineurium were more heavily calcified, while the innermost layers often were free. In a later report (5) they concluded that the mineral deposits were definitely concentrated in the outer perineurium and composed mainly of calcium hydroxyapatite. Perineurial calcification has been verified in diabetes by Johnson et al. (6). VanLis et al. (7) studied sural nerve biopsies from 25 patients with different pathologies, mostly neuromuscular diseases. Calcium deposits were found in the perineurial sheaths of 20 individuals > 16 years of age, irrespective of the presence or absence of nerve fibre pathology. Fifteen of these patients suffered from neural pathology. The staining pattern of the perineurial sheaths was focal and deposits were located in the middle and outer layers of the...
perineurium. Anzil & Palmucci (8) found calcified globules in the perineurium of sural nerves from three patients suffering from polyneuropathies.

The pathogenesis of calcium deposits is unknown. VanLis et al. (7) suggested that the calcium deposits could be related to the function of the perineurium as a diffusion barrier, to degeneration of nerve fibres and probably also to the local presence of lipids in the perineurium.

We found perineurial calcification of the dermal nerves in two different locations in a diabetic patient with chronic renal failure. Probably the diabetes may act as a predisposing factor; however, this finding has not been described in such small nerves (4–6). The coexistence of perineurial and vascular calcification in our patient suggests that the pathogenic mechanisms may be similar. The precise mechanisms of vascular calcification are unclear. Perturbations of calcium, phosphate and parathyroid metabolism are not present in all cases and the pathogenesis is probably multifactorial (2). Several predisposing factors, such as renal disease, altered calcium-phosphorus metabolism, altered coagulation tests and damaged microcirculation may be implicated (2). Whether these factors may also promote perineurial calcification is difficult to assess, but perineurial calcification might explain the extremely painful lesions of our patient.

REFERENCES