Calciphylaxis in a haemodialysis patient: functional protein S deficiency?

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Case report

A 56-year-old woman with ESRF of unknown aetiology treated with haemodialysis in another centre from January 1983 was admitted for dialysis to our Hospital in November 1989. She had secondary hyperparathyroidism (intact PTH 433 pg/ml; normal range <65) and was taking 1,25-(OH)₂ D₃ (0.25 ug/day). The patient had been dialysed 3 times a week with bicarbonate dialysate containing 3 mEq/l of calcium and had been treated for hyperphosphataemia during these years with aluminium hydroxide. We discontinued aluminium hydroxide administration, and calcium carbonate was used as a phosphate binder. The patient had serum calcium concentrations ranging from 2.47 to 2.6 mmol/l (9.88-10.4 mg/dl; normal range 9-11 mg/dl) and serum phosphorus concentrations ranging from 1.42 to 2.0 mmol/l (4.4-6.2 mg/dl; normal range 2.7-4.5 mg/dl).

Secondary hyperparathyroidism increased progressively over the years. In December 1991, the intact PTH (1200 pg/ml) and serum alkaline phosphatase (1343 IU/l; normal range 98-280) levels were too elevated. Calcium carbonate continued to be effective for phosphorus control (< 1.93 mmol/l). The serum calcium level was normal, the free calcium was 1.17 mmol/l (4.7 mg/dl; normal range 4.25–5.05 mg/dl) and the calcium-phosphorus product was <6 mmol²/l². The 1,25 (OH)₂ D₃ level was 7 pg/ml (normal range 18–78 pg/ml). The bone radiographic study showed evidence of advanced renal osteodystrophy with severe diffuse calcifications in arteries of several sizes (abdominal aorta, iliacs, femorals, posterior tibials, and digitals). The desferrioxamine (DFO) test measured yearly was persistently positive. The patient repeatedly refused to be submitted to parathyroidectomy or bone biopsy.

In January 1992 she developed severe burning pain and violaceous skin lesions on both thighs and legs, which progressed to painful necrotic ulcerations (Figure 1). The patient was not taking β-blockers and the peripheral pulses were all palpable and symmetric. Arterial pressure was 120/80 mmHg. One month later...
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Fig. 1. Necrotic skin ulcerations on the thigh.

therapy was initiated for her severe secondary hyperparathyroidism with intermittent high oral doses of 1,25-(OH)2 D3 (Rocaltral tablets, Roche) of 4.0 μg given twice a week (Monday/Friday) at the end of each haemodialysis. The patient was dialysed 3 times a week with bicarbonate dialysate containing 2.5 mEq/l of calcium. She continued taking calcium carbonate (4–6 g/day) as a phosphate-binding agent.

A punch biopsy of the skin lesions in April 1992 showed dermal and epidermal necrosis, with numerous calcifications in subcutaneous interstitium, dermis, and vessels. Most vascular calcifications surrounded the whole vessel wall and some of them showed associated luminal thrombi. There was no evidence of fibrinoid necrosis or granulomatous inflammation (Figures 2 and 3).

In July 1992, an important functional prot S serum [7] deficiency (50%; normal range 105 ± 25%) was detected, which previously had not been investigated. Prot C activity, antithrombin III, von Willebrand factor antigen, platelet counts, prothrombin time, activated partial thromboplastin time, thrombin time, and fibrinogen were normal. The plasma protein, albumin and hepatic enzymes were also normal.

We began daily administration of a low-molecular-weight heparin (Fraxiparin, 15000 AXa Inst. Choay/s.c./day). The burning pain disappeared in 2 weeks and the necrotic ulcerations began slowly to improve, and after 4 months the cutaneous lesions were completely healed (Figure 4).

The intact PTH (1835 pg/ml) and the alkaline phosphatase (1500 IU/l) levels increased during treatment. The serum calcium was normal, the free calcium levels...
to patients with moderate hyperparathyroidism and to patients with severe hyperparathyroidism compared (data), we observed a lower functional prot S activity an epiphenomenon of this syndrome. However, functional prot S deficiency can occur secondary to severe hyperparathyroidism and extensive vascular calcifications in the vessels walls, subcutaneous interstitium and dermis were still observed, although in smaller quantities than in the initial biopsy. There was no evidence of luminal thrombi.

From this moment, no more skin lesions appeared. The 1,25-(OH)₂ D₃ dose was increased in March 1993 to 6.0 μg given twice a week (Monday/Friday) at the end of each haemodialysis session. In July 1993 the intact PTH decreased to 600 pg/ml, oscillating between 600 and 800 pg/ml in the following months. The serum alkaline phosphatase level ranged between 700 and 900 IU/l. The 1,25 (OH)₂ D₃ level oscillated between 20 and 24.3 pg/ml. The serum calcium was normal, the free calcium oscillated from 1.26 mmol/l (5.05 mg/dl) to 1.27 mmol/l (5.1 mg/dl) and the serum phosphorus was <2.09 mmol/l. In February 1993 the LMWH dose was decreased to 10 000 AXa Inst Choay/s.c./day, and discontinued in August of the same year.

The patient died of a cardiac arrest 6 months later. Permission for an autopsy could not be obtained.

Discussion

In this patient with calciphylaxis and severe hyperparathyroidism, we observed a remarkably favourable response to treatment with LMWH. Parathyroidectomy is the treatment of choice for such a patient. However, our patient refused to undergo this procedure and the discovery of a functional prot S deficiency suggested this alternative and fortunately successful treatment. It should be noted that the patient did not experience any negative reaction from the s.c. injections of this compound, which has been regarded as dangerous in cases of calciphylaxis [2]. Our data suggest that LMWH may be a useful treatment for patients with calciphylaxis, especially in the absence of treatable hyperparathyroidism and/or hyperphosphataemia. More data on functional prot S activity and response to LMWH in such patients are needed before this treatment can be advocated for general use in calciphylaxis.

The cause of functional prot S deficiency in our patient is unclear. It persisted after disappearance of the calciphylaxis, and therefore it is unlikely to be only an epiphenomenon of this syndrome. However, functional prot S deficiency may occur secondary to severe hyperparathyroidism and extensive vascular calcifications. In a recent comparative study (unpublished data), we observed a lower functional prot S activity in patients with severe hyperparathyroidism compared to patients with moderate hyperparathyroidism and to healthy controls. Prot S, a potentiator of the anticoagulant prot C, is synthesized in the liver and by endothelial cells. Approximately 60% is bound to complement factor C4 binding protein (C4 BP), and hence is inactive. The rest of prot S circulates unbound in the plasma and is the active cofactor for prot C. Functional prot S deficiency in patients with severe hyperparathyroidism might be explained by impaired endothelial cell function secondary to the severe calcifications. Alternatively it might be the consequence of an elevated C4 BP and thus a decreased free prot S level, as suggested by the data from Lai et al., who observed an elevated total prot S and decreased free prot S antigen level in haemodialysis patients [8]. Unfortunately, we did not measure total prot S or C4 BP.

A role for functional prot S deficiency in the pathogenesis of the syndrome of calciphylaxis is suggested by the presence of luminal fibrin thrombi without any inflammatory cell infiltration in dermal and hypodermal arteries in involved skin. In addition, the similarity of the clinical picture of calciphylaxis and warfarin skin necrosis in patients with prot S or prot C deficiency [9] seems to support the possibility that local thrombosis plays a role in calciphylaxis.

The functional prot S deficiency in our patient is in accordance with earlier observations. Mehta et al. [3] reported functional prot C deficiency in five haemodialysis patients with calciphylaxis. However, functional prot C was measured after parathyroidectomy, and during or after healing of lesions, except for one patient. Kant et al. [4] reported a low free prot S associated with relatively high levels of the C4 BP in two patients with skin necrosis receiving continuous ambulatory peritoneal dialysis (CAPD). Free prot S normalized when patient 2 was changed from peritoneal dialysis to haemodialysis and parathyroidectomy was performed. The authors attributed the free prot S deficiency to peritoneal dialysis associated losses which the patients were unable to compensate for by increased synthesis.

In summary, our haemodialysis patient with calciphylaxis in the setting of severe secondary hyperparathyroidism, severe vascular calcifications, and a functional prot S deficiency had a remarkably favourable response to treatment with LMWH. Although the pathogenesis of calciphylaxis remain to be elucidated, our data suggest that a reduced activity of prot S might contribute to the development of this life-threatening syndrome.

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