Tumoural calcinosis associated with subclavian vein occlusion and hypercalcaemia in a haemodialysis patient

Sir,

Tumoural calcinosis (TC), which is a major form of extraskeletal calcification, is composed of hydroxyapatite crystals and located in periarticular areas. It is a rare presentation in patients with end-stage renal disease (ESRD). TC behaves as a large-sized tumour, has a tendency to recur after surgical removal, and can progressively enlarge enough to encase the adjacent structure [1,2]. However, encasement of vessels has not yet been reported in the literature. Here we report an ESRD patient who presented with TC, resulting from persistent hyperphosphataemia and a high serum calcium × phosphate (Ca × P) product. The TC resulted in occlusion of the right subclavian vein and also contributed to hypercalcaemia, which regressed only after initiation of calcium-free haemodialysis (HD) therapy.

Case. A 50-year-old Chinese woman with ESRD had received HD therapy at a local HD centre since 1995. During the first 3 years of HD, a dialysate calcium of 3.5 meq/l thrice weekly was prescribed. During this time period, poor dietary control, poor compliance with medications, and frequent missing of HD sessions were noted. Persistent pre-HD hyperphosphataemia (6.3–11.1 mg/dl), normal serum calcium (9.0–10.4 mg/dl), high serum Ca × P product (58–110 mg/dl²), and low serum iPTH levels (between 24 and 40 pg/ml) were also found. Progressive enlargement of the tumoural masses complicated by local swelling and tenderness over the two shoulders, elbows, wrists, right sternoclavicular joint, and right gluteal area starting in June 1997. X-ray examination of these lesions showed multiple multilocular peri-articular calcifications, which was compatible with the diagnosis of TC. Meanwhile, intermittent aspirations of milky fluid from TC lesions were necessary to relieve her discomfort. Low phosphate diet with adequate dialysis were prescribed and followed more strictly. Although serum phosphate control (4.2–6.0 mg/dl) improved, hypercalcaemia (11.2–13.9 mg/dl) developed since May 1998. Therefore, HD with low-calcium dialysate (1.75 meq/l) was prescribed since January 1999, but hypercalcaemia persisted. Progressive swelling of the right hand was noted since March 1999. Under the suspicion of right subclavian vein stenosis, she was referred to our hospital for further management in April 1999. Neither calcium salts nor derivatives of vitamin D had been prescribed for the previous year; and no previous subclavian cannulation had ever been performed. Physical examination showed marked engorgement of the bilateral jugular veins and abundant collateral vessels over the right shoulder and neck but good function of the arteriovenous fistula on the left forearm. One large, soft, elastic, and fixed mass (7 × 8 cm²) over the right sternoclavicular joint was palpated, and similar masses existed over the shoulders, elbows, wrists, and the right gluteal area. Pre-HD laboratory data showed albumin 2.7 g/dl, globulin 3.1 g/dl, BUN 46 mg/dl, creatinine 9.1 mg/dl, calcium 12.2 mg/dl, phosphate 4.6 mg/dl; aluminum 29 ug/l; iPTH 30 pg/ml; WBC 13 400/mm³, haemoglobin 9.3 g/dl, and platelet 354 000/mm³.
Bone marrow examination did not show any evidence of malignancy or granulomatous disorders. There was no evidence for tuberculosis. Parathyroid ultrasonography and Gallium scintiscan were negative. Bone scan showed intense isotope uptake over multiple peri-articular soft tissue areas. Chest CT scan revealed one large, multilocular calcification over the right steroclavicular joint with encasement of adjacent tissue (Figure 1). Right subclavian vein occlusion was confirmed by angiography of the right upper extremity (Figure 2). Intravenous pamidronate 60 mg, oral prednisolone 25 mg daily, and low-calcium dialysate (1.75 meq/l) were prescribed for her hypercalcemic condition. But, hypercalcemia did not improve after 2 weeks of treatment, she received calcium-free dialysis thrice weekly. Two weeks later, her hypercalcemia resolved, the right arm swelling gradually improved, and some regression of her TC lesions was also noted. However, she suffered from sepsis due to a perianal abscess and refused surgical drainage in May 1999. She died of septic shock.

Comment. TC is a multilocular calcified lesion with cavities filled with a viscous milky fluid of calcium crystals of hydroxyapatite [2]. Smack et al. [3] reviewed 122 TC cases, and distinct subtypes were pathogenetically classified into: (i) primary normophosphataemic TC (51 cases), usually presenting with a history of antecedent trauma, solitary lesion, and rare recurrence after surgical removal; (ii) primary hyperphosphataemic TC (34 cases), presenting with strong family history, multiple lesions, and a high recurrence rate (>80%) after surgical removal; and (iii) secondary TC (37 cases) with concurrent disorders (e.g. chronic renal failure), presenting with multiple lesions, a high recurrence rate after surgical excision, and high incidence of hyperphosphataemia (73%), like our case.

The pathogenesis of TC remains obscure. Numerous factors are thought to result in TC, including hyperparathyroidism, disturbances of phosphate, calcium and calcitriol metabolism, aluminum intoxication, repetitive local trauma, and genetic predisposition [1–4]. TC develops only rarely in ESRD patients with high serum Ca × P product. However, its incidence appears to be increasing over the past 20 years, possibly due to recent changes in the therapeutic modalities of ESRD, such as more use of calcitriol, calcium-based phosphate binders, high calcium content in the dialysate, and failure to lower serum phosphate [4]. In our case, persistent hyperphosphataemia together with high serum Ca × P product was noted during the first 3 years of HD therapy. However, the patient did not take any vitamin D derivatives or calcium salts, and denied a previous history of joint injury. Serum iPTH and aluminum levels were also low. All of above findings suggested that hyperphosphataemia and high serum Ca × P product played an important pathogenic role in her TC.

Another interesting feature in this case is the presence of hypercalcemia. A precise cause of hypercalcemia could not be identified. Wald et al. [5] demonstrated that calcium resorption from soft tissue calcification was the cause of hypercalcemia in an experimental rat model with normal or abnormal renal function. Therefore, we postulate that the hypercalcemia in our case was a consequence of TC. This hypothesis is supported by the following evidence.

(i) The patient had no hypercalcemia before the development of marked TC.
(ii) Hyperphosphataemia was noted in the early years of HD, and TC appeared subsequently.
(iii) The hypercalcemia was noted only once marked TC had developed and normophosphatemia was achieved.
(iv) The strong isotope uptake over soft tissues at bone scan study suggested increased calcium turnover in her TC.
(v) Persistently low serum iPTH levels implicated an underlying low-turnover bone disease.

The latter two findings suggest to us that both the increased release of calcium from TC and the inability of low turnover bone to incorporate excess calcium might be the pathogenic mechanisms for hypercalcemia in our patient. A similar observation was reported by Fernandez et al. [6], who successfully treated TC in one ESRD patient by daily HD with low-calcium dialysate. Transient hypercalcemia from mineral mobilization in TC was noted during their therapeutic intervention. A similar phenomenon has also been noted by Eisenberg et al. [7].

The usual course of TC is progressive enlargement of calcified masses over periarticular areas. This may result in pain, disfigurement, functional impairment, secondary ulceration, and infection. In our case, TC was severe with widespread involvement of the majority of the large joints. The right subclavian vein was encased by the steroclavicular TC, which resulted in severe swelling of the right arm. To
our knowledge, this is the first reported case of TC-related vascular compression. Due to widespread lesions and deep infiltration of TC, operative intervention is generally not recommended. The treatment of TC is still controversial. Since hyperphosphataemia with high serum Ca×P product appears to be the major culprit of its formation, reduction of phosphate intake, administration of phosphate-binders, and adequate dialysis may decrease its occurrence or delay its progression. Other medical interventions such as steroid, calcitriol, bisphosphonates, and radiation have proved to be unsuccessful [1,3]. Recently, negative calcium balance from low-calcium dialysis has successfully reversed the ESRD-related TC [6,8], and this may be the most promising treatment modality. In our case, thrice-weekly calcium-free dialysis reversed refractory hypercalcaemia. The massive TC and swelling of the right arm improved gradually, although the patient died too soon to observe any further response.

In conclusion, evidence is accumulating to support the contention that prolonged hyperphosphataemia and high serum Ca×P product are the most important risk factors for TC formation in patients with ESRD. Therefore, preventive control of hyperphosphataemia is indicated in every case of ESRD. Once TC has occurred, treatment is usually extremely difficult. Intensive dialysis with low-calcium dialysate or calcium-free dialysis may be beneficial, especially in patients with hypercalcaemia.

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