Supported by an educational grant from Fresenius Medical Care

Remembrance of things past: tumoural calcifications in a haemodialysis patient

Gunter Wolf and Rolf A. K. Stahl

Department of Medicine, Division of Nephrology and Osteology, University of Hamburg, Hamburg, Germany

Keywords: tumoural calcifications; haemodialysis

Case

A 58-year-old dialysis patient was seen by the nephrology consultant on the orthopaedic ward. He was admitted for exploratory surgery of a slowly growing tumour of the left knee. The patient could not remember any previous trauma or injury to this region. The tumour had grown over the previous year, was painful, and the patient was concerned about suffering from cancer. The tumour was localized in the left knee region. It was approximately 9 × 7 × 5 cm in size. Magnetic resonance imaging revealed an inhomogeneous tumour with infiltration of the lateral ligament reaching into the subcutis. The contrasting of selected tumour regions increased after administration of gadolinium. Since the nature of the tumour remained unclear, exploratory surgery was strongly recommended.

The patient had been undergoing maintenance haemodialysis since 1993, three times a week (4 h per session). The dialysate calcium concentration was 1.75 mmol/l. The underlying renal disease was autosomal dominant polycystic kidney disease. Bilateral nephrectomy was performed in 1995 because of increasing pain and discomfort caused by massive renal cysts. In February 2000, the diagnosis of prostate cancer was made. There was no evidence of bony metastases. Medication consisted of aluminium hydroxide and calcium carbonate as phosphate binders, the i.v. administration of 2 µg 1α(OH)-cholecalciferol twice a week, 10 000 IU erythropoietin intravenously per week, and an α-adrenoreceptor antagonist to control blood pressure.

On physical examination, the patient’s general condition was reduced, and he had difficulties walking on his left leg. Another tumour-like swelling was noted on the left shoulder. Blood pressure was 160/80 mmHg. Physical examination of heart and lungs was within normal limits. Peripheral pulses of both legs were not palpable. Laboratory values showed serum creatinine 5.8 mg/dl, BUN 23 mg/dl, albumin 23 g/l, sodium 139, potassium 4.1, calcium 2.43, and phosphorus 2.88 (all mmol/l). Serum total alkaline phosphatases were 414 U/l (normal range 70–170 U/l). Venous blood gas analysis revealed metabolic acidosis (pH 7.36, P CO2: 30.6 mmHg, HCO3−: 17.1 mmol/l). Serum intact parathyroid hormone (PTH) was 1632 ng/l (normal range 10–65). Serum aluminium was 31.5 µg/l (normal <10). Bone radiographs of the left knee and left shoulder are shown in Figure 1. Severe bone erosions, as a radiographic feature of osteitis fibrosa, are seen particularly in the humerus besides extraskeletal calcifications (Figure 1B).

A diagnosis of severe secondary hyperparathyroidism with extraskeletal tumoural calcification was made. Aluminium hydroxide and 1α(OH)-cholecalciferol was stopped, and exploratory surgery of the knee was cancelled. Instead, a total parathyroidectomy with autotransplantation of parathyroid tissues into the right forearm was performed. The postoperative PTH level was 48 ng/l. Calcium carbonate substitution was increased, and a treatment with 0.5 µg oral calcitriol per day was initiated. The patient was seen 2 months later. The knee tumour had almost completely disappeared. Similarly, the calcification of the shoulder...
had regressed (Figure 2). At this time, serum PTH was 66 ng/l, and the patient was still hypocalcaemic (1.83 mmol/l) without symptoms.

Comments

This dialysis patient suffered from extensive soft tissue calcifications due to severe secondary hyperparathyroidism. The periarticular calcification in the knee region was initially mistaken as a tumour of unclear origin and exploratory surgery with tumour removal was recommended. In fact, surgical removal is not indicated in soft tissue calcifications, and even a biopsy should be avoided because of the risk of infection. Why was the correct diagnosis not made earlier?

Extraskeletal calcifications in chronic dialysis patients were common in the past [1] but they are less frequently seen today. The first description of metastatic calcifications dates back to Rudolf Virchow [2] who clearly linked this phenomenon to chronic nephritis in six cases, suggesting severe secondary or tertiary hyperparathyroidism. Tumour-like calcifications are well-known to older nephrologists, and a total prevalence as high as 80% with severe lesions in 35% was described in chronic dialysis patients in the 1970s [3,4]. However, the frequency of severe calcifications in dialysis patients has markedly decreased in recent years [5], probably due to a more effective control of hyperphosphataemia and secondary hyperparathyroidism. Thus, younger physicians taking care of dialysis patients may not have seen such severe cases of tumoural calcifications.

Although the pathogenesis appears straightforward, the detailed mechanisms of tissue calcifications are not, in fact, completely understood [5,6]. An increase in serum calcium phosphate product greater than 70 mg²/dl², mainly due to hyperphosphataemia, has been proposed. Indeed, our patient exhibited such a high product (86.7 mg²/dl²). However, other authors failed to find a correlation between the calcium phosphate product and the presence of periarticular

Fig. 1. Radiography of the left knee (A) and shoulder (B) on admission. (A) Extraskeletal calcifications are visible on the left lateral knee reaching into the subcutis. (B) A large calcified mass encases the shoulder joint and humeral head. In addition, erosive lesions indicating increased bone resorption being typical of hyperparathyroidism are visible.
calcifications [5,6]. Other important factors are: overt secondary hyperparathyroidism, high dialysate calcium, the presence of metabolic alkalosis, vitamin K and D overload, as well as local tissue injury [5]. Interestingly, aluminium intoxication can contribute to the development of such tumour-like calcifications [7,8]. Zins et al. [7] described a series of dialysis patients with tumoural calcifications who had evidence of aluminium intoxication. Parathyroidectomy had no effect on tissue calcifications in these patients. Furthermore, extraskeletal calcifications in patients with aluminium intoxication may decrease by desferrioxamine therapy, despite worsening of hyperparathyroidism [8]. Aluminium may initiate tissue precipitation of calcium and can also induce crosslinks of collagen fibres fostering deposition of calcium phosphate [9]. At present, most tumour-like calcifications are observed in association with low-normal PTH levels in chronic haemodialysis patients [5,7].

Although our patient was treated with aluminium hydroxide for some time and had a slightly increased serum aluminium level, the almost complete disappearance of the extraskeletal calcifications 2 months after parathyroidectomy suggests that severe hyperparathyroidism played a major role in these soft tissue calcifications. The patient did not remember any trauma to the knee and shoulder, and there was no evidence of other predisposing factors, but it could not be excluded that the 1α(OH)-cholecalciferol therapy in the presence of a minor aluminium overload have contributed to the tumoural calcifications. Parathyroidectomy has been proposed as major therapy in cases with extraskeletal calcifications and high circulating PTH levels [10,11].

**Teaching points**

(i) Marcel Proust (1871–1922) wrote in his masterpiece, *Remembrance of Things Past*, of disease: ‘If it is capable of deceiving the doctor, how should it fail to deceive the patient?’ These tumour-like calcifications deceived both patient and doctor. Although dialysis patients have an increased incidence of cancer, not every tumour is a malignant disease. It is sometimes important to remember diseases of the past that may play at first sight a minor role today.

(ii) From a practical point of view, it is important to determine serum calcium, phosphorus, the calcium × phosphorus product, PTH, and other parameters reflecting a disturbed calcium metabolism in uraemic patients with tumour-like calcifications.

(iii) Although, at present, tumour-like calcifications are observed most frequently in association with
a low or normal serum PTH and adynamic bone disease, the possibility of its association with severe osteitis fibrosa should not be forgotten.

References

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