Tumoral calcinosis associated with pyrexia and systemic inflammatory response in a haemodialysis patient: successful treatment using intravenous pamidronate

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Introduction

Tumoral calcinosis is a recognized complication of end-stage renal failure [1]. We report a case of tumoral calcinosis associated with systemic inflammatory response that was successfully treated with bisphosphonates.

Case

A 25-year-old patient with end-stage renal failure secondary to reflux nephropathy on maintenance haemodialysis for 8 years was admitted with pyrexia of 3 months duration. A live related renal transplantation from his mother was cancelled on two occasions because of fever of >37.5°C which was noticed on several occasions. His only other complaint was pain and limitation of movements of left shoulder and there were no other systemic symptoms.

Clinical examination revealed a swollen, tender left shoulder joint with limitation of movements in all directions. Systemic examination was otherwise normal. The investigations were as follows: haemoglobin 10.8 g/dl; white cell count 10.55 x 10⁹/l; neutrophils 7.1 x 10⁹/l; ESR 84 mm/h; serum C reactive protein (CRP) 169 mg/l; liver function tests normal; serum aluminium 0.4 μg/l (normal <5 μg/l). Other biochemical investigations were consistent with secondary hyperparathyroidism: serum calcium 2.56 mmol/l, serum phosphate 2.82 mmol/l, total alkaline phosphatase 108 IU/l, and parathyroid hormone (PTH) 38.2 pmol/l (normal, 0.9–5.4 pmol/l). Control of serum phosphate levels had been difficult because of poor compliance with diet and phosphate binders. He was adequately dialysed with a Kt/V of 1.4 and urea reduction ratio of 70%. He was investigated extensively for the cause of fever. Repeated blood and urine cultures were sterile. Serological investigations for Epstein–Barr virus, cytomegalovirus, mycoplasma, and legionella were negative. Autoantibody screens including antinuclear antibodies, rheumatoid factor and anti-neutrophil cytoplasmic antibodies were negative. Chest X-ray, ultrasound scan of the abdomen, and CT scan of the thorax and abdomen were normal. Plain radiograph of the left shoulder revealed extensive peri-articular soft-tissue calcification consistent with tumoral calcinosis.

Technetium isotope bone scan showed intense abnormal uptake in the left shoulder, corresponding to the area of periarticular calcification seen on the plain film. A radiolabelled white-cell scan showed a mild increase of uptake over the left shoulder but was otherwise normal. Transthoracic and transoesophageal echocardiograms were normal. Ultrasound of the shoulder showed no evidence of joint effusion but multiple cystic areas were identified within the calcific mass. Aspiration of one of these cysts yielded a small amount of milky fluid. Gram and acid-fast stains were negative and cultures were sterile. Polarized microscopy failed to identify any crystals. Over a period of 1 month of hospitalization the recurrent pyrexia and shoulder discomfort persisted and the CRP remained >100 mg/l. As investigations had failed to identify an infective cause of the fever and raised CRP, we postulated that the tumoral calcinosis at the shoulder joint might be responsible for the systemic inflammatory response and pyrexia through local activity of osteoclasts and associated release of proinflammatory cytokines.

Treatment with daily intravenous pamidronate (30 mg) was given for 3 consecutive days to inhibit osteoclastic activity. No adverse effects were observed. The fever disappeared within 48 h after completion of
treatment and the CRP returned to normal (<5 mg/l) within 14 days (Figure 1). Treatment with phosphate binders (calcium carbonate) was continued in order to maintain serum phosphate levels at <2 mmol/l and 1-alfacalcidol to suppress PTH production. The patient was also maintained on a phosphate-restricted diet. He was dialysed using a low-calcium dialysate (1.25 mmol/l instead of 1.75 mmol/l) from the time that the diagnosis of tumoral calcinosis was made (for about 4 weeks prior to the administration of pamidronate) and he was maintained on regular dialysis using low-calcium dialysate. All other dialysis parameters including the dialysis time (4-h dialysis sessions three times per week), dialysis membrane (Dicea high-performance cellulose diacetate hollow-fibre dialyser, Baxter), dialysate bicarbonate concentration and control of acidosis remained the same.

Over the next 3 months he remained afebrile with normal CRP levels. His shoulder pain resolved and there was a significant improvement in the range of movement of the left shoulder. Repeat X-ray of the patient’s shoulder joint 4–6 weeks after the bisphosphonate therapy showed some reduction in the calcific deposits. He underwent a successful renal transplant and remains well with good graft function and normal bone chemistry. X-ray of the shoulder joint 6 months after transplantation showed complete disappearance of calcific deposits.

**Discussion**

Tumoral calcinosis in end-stage renal failure patients is a complication associated with high serum calcium and phosphate product and these patients often have secondary or tertiary hyperparathyroidism. Persistently elevated calcium × phosphate product is the major contributing factor in the development of tumoral calcinosis [1,2]. The most common sites for uraemic tumoral calcinosis are the elbow, hip, shoulder, hand, and wrist. Reduced joint mobility and arthralgia may be the associated features and compression of the adjoining structures may give rise to neurovascular symptoms [3]. There are reports of tumoral calcinosis presenting with signs of systemic inflammation leading to fever and other constitutional symptoms [4]. Such a presentation may mimic infection [5] and this can cause management problems as in this case where renal transplantation was cancelled twice because of the possibility of occult infection.

Recognition of the fact that the tumoral calcinosis could be driving the inflammatory response along with an excellent response to bisphosphonates enabled us to proceed with renal transplantation, which remains the definitive therapy to correct the altered calcium–phosphate homeostasis of end-stage renal failure. We feel that the initial response with normalization of temperature and CRP could be attributed to bisphosphonate therapy due to the suppression of osteoclastic activity and release of proinflammatory cytokines. However, use of low-calcium dialysate and better control of serum phosphate would have contributed significantly to slow down the progression of tumoral calcinosis in addition to the bisphosphonate therapy. There was mild reduction in serum calcium levels (2–2.2 mmol/l from 2.5–2.6 mmol/l) following pamidronate therapy and this reached pre-treatment levels within 2 weeks. There was a sustained fall in serum phosphate levels, but this is likely to be due to combination of better compliance with phosphate binders and low-phosphate diet in addition to the bisphosphonate therapy.

The primary mechanism of action of bisphosphonates involves the inhibition of osteoclastic bone resorption [6]. Microscopic and immunohistochemical studies have shown the mechanism involved in the
Pamidronate for treatment of tumoral calcinosis in a HD patient

Pathogenesis of tumoral calcinosis to involve histiocytes and osteoclast-like giant cells of histiocytic origin [7]. The cytokines released from these cells might mediate the associated inflammatory response and pyrexia. The levels of interleukin 1 and tumour necrosis factor can be transiently elevated with aminobisphosphonate therapy in tandem with pyrexia and influenza-like symptoms, but subsequent administrations are associated with a fall in proinflammatory cytokine levels demonstrating anti-inflammatory properties of this group of drugs [8]. Previous reports regarding the use of bisphosphonates in the treatment of ectopic calcification have shown either no therapeutic effect or inconsistent results [9] and we could find one report showing complete regression of soft-tissue calcifications using diphosphonate therapy in five patients on maintenance haemodialysis [10]. The property of bisphosphonates to inhibit osteoclastic activity and hence the metastatic calcification together with the evidence that they reduce the levels of proinflammatory cytokines in blood were the basis of our decision to use pamidronate in this case.

Management of tumoral calcinosis is often difficult and usually involves dietary phosphate restriction, phosphate binders, intensification of dialysis treatment, dialysis using a low-calcium dialysate, parathyroidectomy in those patients with high PTH levels [9], and surgical excision of the calcific mass. The tumoral calcinosis often resolves after successful renal transplantation [11], which is the definitive therapy for this condition, but clearly patients with pyrexia of unknown origin will not undergo transplantation until the cause of pyrexia has been determined. The case described above suggests that tumoral calcinosis can mediate a systemic inflammatory response which can be specifically targeted using bisphosphonates. The clinical response to bisphosphonates may therefore be used to help make important therapeutic decisions as in our case. To our knowledge, use of bisphosphonates in the management of tumoral calcinosis associated with fever in a haemodialysis patient has not previously been reported, and this case illustrates that tumoral calcinosis can elicit a local and systemic inflammatory response which can be suppressed by bisphosphonates.

References


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