Case Report

Osteoclast-like multi-nucleated giant cells in uraemic tumoral calcinosis

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Abstract

A 46-year-old woman under 6-year haemodialysis was admitted for uncontrollable hip pain. An X-ray film revealed calcified mass around the ‘left femur head’, which was diagnosed as calcium deposition by percutaneous biopsy. Calcinotic tissues were removed surgically, and the resected specimen revealed tumoral calcinosis caused by low bone turnover. A complete resolution of calcinotic lesions around the ‘left knee’ occurred 6 months after treatment modification. Immunohistochemistry showed recruitment of multi-nucleated giant cells positive for CD68, tartrate resistant acidic phosphatase and calcitonin receptor, indicative of osteoclast-like features. We propose the involvement of osteoclast-like cells in active resorption of tumoral calcinosis.

Keywords: calcitonin receptor; multi-nucleated giant cell; osteoclast; tumoral calcinosis

Introduction

Tumoral calcinosis, an ectopic calcification occasionally seen in haemodialysis patients, is characterized by massive periarticular deposition of calcium (Ca) and phosphorus (P), and various factors are involved in its pathogenesis of tumoral calcinosis such as secondary hyperparathyroidism and adynamic bone disease [1]. With regard to the regression of tumoral calcinosis, there have been several case reports of haemodialysis patients who show complete resolution of such calcifications after appropriate treatment [2–4]. However, the precise mechanism of such regression remains unclear.

We present here the case of a haemodialysis patient with tumoral calcinosis whose surgically resected specimen revealed recruitment of multi-nucleated giant cells

Fig. 1. X-ray films of tumoral calcinosis. Tumoral calcinosis around the ‘left femur head’ (A). Tumoral calcinosis around the ‘left knee’ before changing treatment (B). This calcified material was not removed surgically. Note that calcification around the ‘left knee’ almost disappeared 6 months after changing treatment (C) (arrows). with osteoclast-like features. These cells are presumed to play a role in the regression of tumoral calcinosis.

Case report

A 46-year-old female with 6-year history of haemodialysis therapy for chronic glomerulonephritis was admitted to Kyushu University hospital for the management of severe hip pain. The past history included the appearance

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of left hip pain about 3 years prior to admission, which gradually worsened with time. At that stage, plain X-ray films showed calcified masses around the ‘left femur head’ (Figure 1A) and the ‘left knee’ (Figure 1B). Six months prior to admission, she was referred to the orthopedicians at our hospital, and a percutaneous biopsy was performed; histopathology revealed massive Ca deposition. Because of the severe hip pain, the calcified mass around the ‘left femur head’ was removed surgically. After surgery, the patient was transferred to our department for further management of hypercalcaemia. At that time, tumoral calcinosis around the ‘left knee’, which was not removed at surgery, was still evident radiologically.

At the first consultation, 3 days after surgery, the patient had high serum Ca level (12.2 mg/dl) (N; 8.7–10.3), high serum P level (6.4 mg/dl) (N; 2.5–4.7), high Ca–P product (78 mg²/dl²) and low levels of intact-parathyroid hormone (PTH, 19 pg/ml) (N; 10–65) and alkaline phosphatase (ALP, 109 IU/l) (N; 115–359). She had been treated for the last 6 years with alfacalcidol (0.25 μg/day), Ca bicarbonate (1.5 g/day) and high Ca dialysate (3.0 mEq/l). Based on these findings, we concluded that the calcified mass around the ‘left femur head’ and ‘left knee’ was tumoral calcinosis, which was caused by low bone turnover followed by reduced capacity for Ca and P.

The clinical course is shown in Figure 2. We changed the P binders to non-Ca containing ones and discontinued alfacalcidol. We also converted the dialysate Ca concentration to 2.5 mEq/l. Such changes in treatment brought in decrease of Ca, P and Ca–P product, and then resulted in the elevation of intact PTH and ALP and in the improvement of bone turnover. Six months after switching to the new treatment, the calcified lesions around the ‘left knee’ disappeared completely (compare Figure 1C with B). At the last follow-up examination at the outpatient clinic, the patient was free of pain and calcified lesions as confirmed radiologically.

Histopathological examination of the calcified mass around the ‘left femur head’ showed calcification
areas surrounded by many multi-nucleated giant cells and mononuclear cells with fibrous tissues. Immunohistochemical staining showed that the multi-nucleated cells and mononuclear cells were positive for CD68, TRACP (tartrate-resistant acidic phosphatase, calcitonin receptor) and RANK (receptor activator of nuclear kappa beta) (Figure 3A–D).

Discussion

We present here the case of a haemodialysis patient with tumoral calcinosis caused by low bone turnover. Tumoral calcinosis in one site was surgically resected and tumoral calcinosis in another site regressed spontaneously after treatment modification. The surgically resected specimen revealed recruitment of multi-nucleated giant cells positive for CD68 and calcitonin receptor, indicative of osteoclast-like features.

Previous histopathological studies of resected tissues of tumoral calcinosis have already reported the presence of multi-nucleated giant cells and inflammatory cells surrounding the calcified region [5], and several groups have provided some explanation for the regression of ectopic calcification [6–8]. Veress et al. [7] histopathologically evaluated 20 patients with tumoral calcinosis, and proposed the involvement of the multi-nucleated giant cells in the regression process. Using a rat model, Bas et al. [8] found infiltrating CD68-positive mononuclear cells in the walls of calcified artery and reported the reversibility of arterial medial calcification. Although these two reports indicated the association of CD68-positive cells with regression of ectopic calcifications, they did not fully describe all the features of the giant cells.

In our patient, the multi-nucleated giant cells and mononuclear cells around the calcified masses were positive for CD68, TRACP and calcitonin receptor. Thus, these multi-nucleated giant cells are phenotypically similar to osteoclasts since CD68 is a marker of macrophage differentiation and TRACP and calcitonin receptor are markers of osteoclasts. We also found these giant cells positive for RANK, which is essential for osteoclast maturation in the bone into activated osteoclasts that can intercalate with RANK-ligand [9]. Thus, we hypothesized that the mononuclear cells of macrophage lineage are recruited to tumoral calcinosis and eventually become multi-nucleated giant cells with osteoclast-like phenotype by fusion, where they participate in resorption of the calcified material similar to the resorption of bone by osteoclasts.

Regarding the regression process in tumoral calcinosis, we speculate that such process depends on the relative balance between passive accumulation and active resorption of Ca–P products. It is likely that the osteoclast-like multi-nucleated giant cells are involved in removal of calcified material during the active resorption process. This hypothesis is proven by the clinical results that appropriate medical and surgical treatment can occasionally lead to spontaneous regression of tumoral calcinosis [2–4]. In the present case, before changing treatment, passive accumulation was dominant over active resorption. After changing treatment, the bone turnover improved, and active resorption process became relatively dominant. Finally, regression of tumoral calcinosis around the ‘left knee’ was evident radiologically.

The present report has a few limitations. First, the specimen examined was from the ‘left femur head’ and not from the ‘left knee’ where spontaneous regression was noted. Second, whereas recruitment of giant cells was demonstrated, no evidence of activation and phagocytosis by giant cells was presented.

In summary, we described here the case of a haemodialysis patient with tumoral calcinosis whose surgically resected specimen revealed recruitment of multi-nucleated giant cells with osteoclast-like features. We conclude that these cells were involved in the active resorption process of tumoral calcinosis.

Conflict of interest statement. None declared.

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