Refractory hypercalcemia after Denosumab treatment in pediatric age: a case report

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INTRODUCTION

Denosumab is a new class of antiresorptive medication and a fully human monoclonal antibody of the IgG2 immunoglobulin isotype to RANKL. In fact, it binds with high affinity and specificity to RANKL, mimicking the inhibitory effects of Osteoprotegerin, resulting in rapid suppression of bone resorption. Denosumab is commonly used also in pediatric age for treatment of osteoporosis, malignancies, and other benign bone lesions, such as fibrous dysplasia, central giant cell granuloma and aneurysmal bone cyst (ABC). ABC is a rare benign skeletal tumor characterized by multilocular, expansile and osteolytic lesions. Treatment options are en bloc resection, intralesional curettage followed by bone grafting, sclerotherapy, radionuclide ablation, embolization, and radiotherapy. Since these approaches may be associated with severe and long- lasting morbidity especially in cases with spinal and large pelvic lesions denosumab has been advocated and used as alternative therapy. Nevertheless, studies focused on the pharmacokinetics and pharmacodynamics in children are limited and after treatment a phenomenon of bone turnover rebound associated ort not with hypercalcemia has been described in adults and aneddotically reported in pediatric patients.

OBJECTIVE

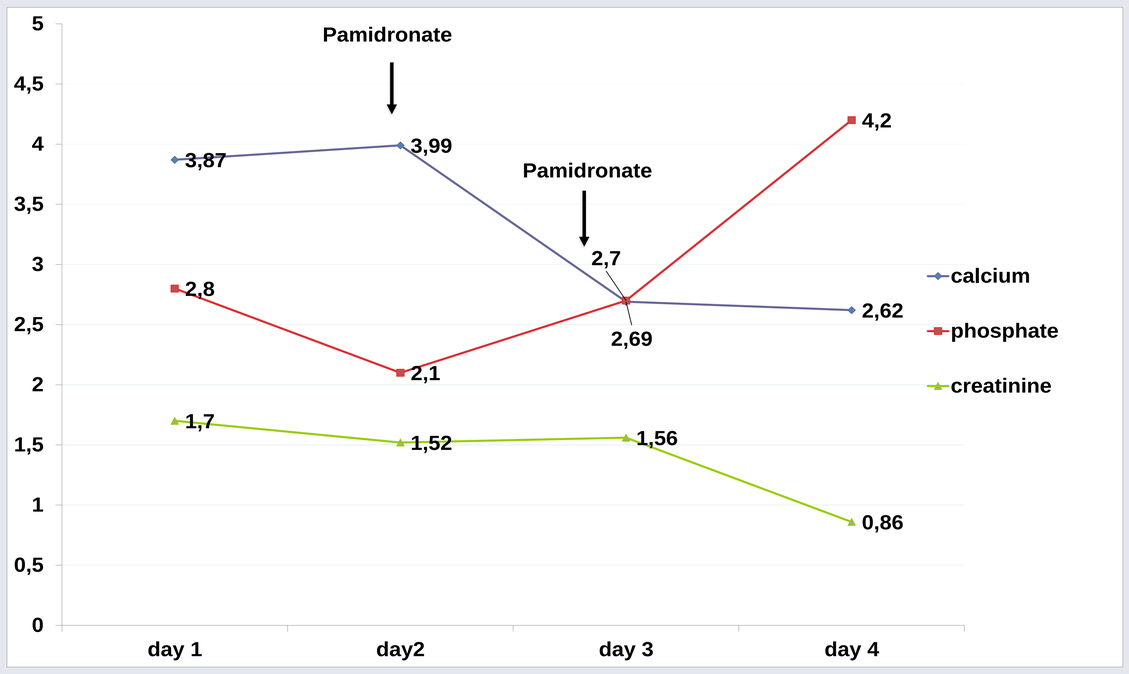
To describe serious adverse effects after high-dose denosumab therapy in ABC patients

CASE REPORT

A 10 years old male with pelvic ACB diagnosis underwent high dose of denosumab (120 mg s.c for every month for 10 months).

4 months after stopping denosumab, the patient presented with a 2-week history of nausea and vomiting. Investigations identified raised serum calcium (3.87 mmol/L) with high ionized calcium level (1.64 mmol/L) and creatinine, indicating acute kidney injury (1.7 mg/dl) and U.S. showed nephrocalynosis. Serum phosphate and alkaline phosphatase were normal, 25-hydroxy vitamin D was low, and parathyroid hormone appropriately suppressed, with normal thyroid function. Total body CT scan and body X-ray excluded local or metastatic disease. Initially, hypercalcemia was treated with rehydration associated with intravenous furosemide (1 mg/Kg i.v.) with very poor response. For recurrent increase in serum calcium level 3 doses of Bisphosphonates i.v. (pamidronate 1 mg/Kg i.v.) in one week and than followed by 5 doses every 15 days (0.5 mg/kg i.v.) were administered, with improvement of clinical and biochemical parameters. Last calcium was 2.47 mmol/L and renal function was totally normalized (creatinine 0.6 mg/dl) (.

FACS analysis of osteoclast precursors on PBMC showed a significant increase of osteoclastogenesis pathway compared to controls matched for age and sex (Fig.1). Furthermore, PBMC cultured in the presence of M-CSF and RANKL documented multinucleated giant cells (osteoclasts) at 7 day compared to helathy controls (Fig.2)



Graphs with serum calcium (mmol/L), phosphate (mmol/L) and creatinine level (mg/dl) and pamidronate i.v. treatment is indicated by vertical arrows.

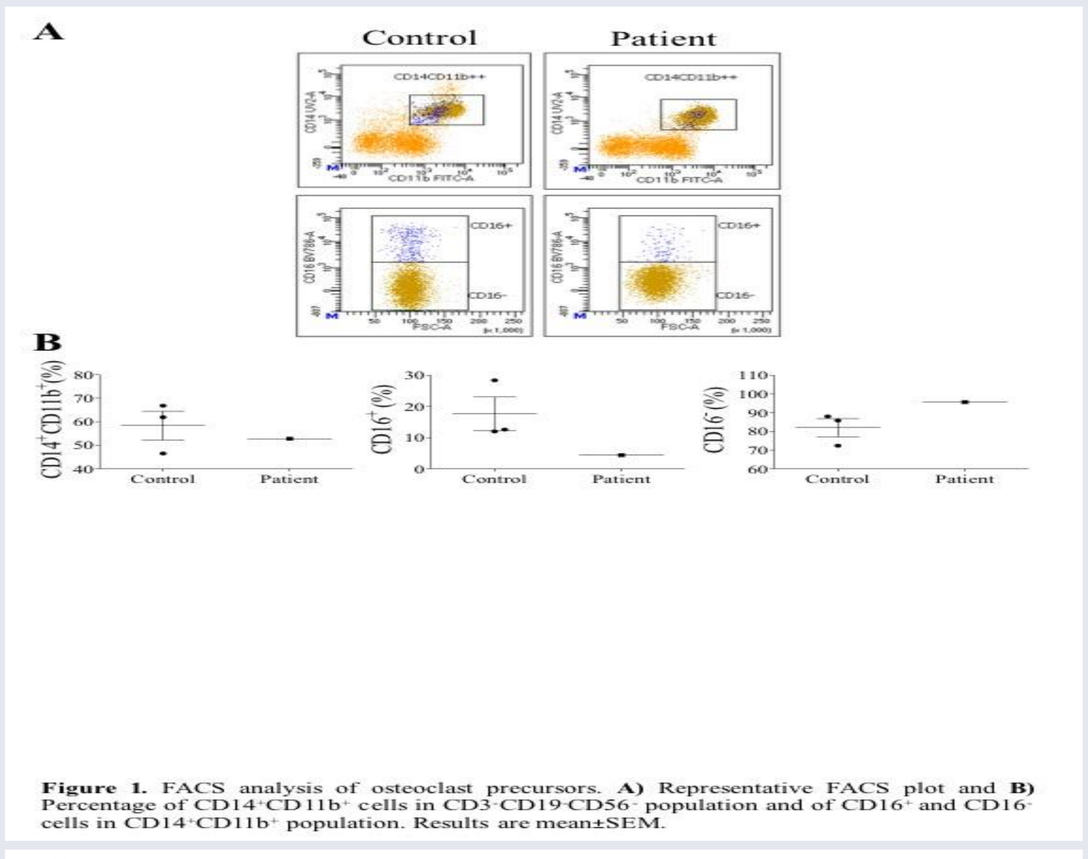


Figure 1. FACS analysis of osteoclast precursors. **A)** Representative FACS plot and **B)** Percentage of $CD14^+CD11b^+$ cells in $CD3^-CD19^-CD56^-$ population and of $CD16^+$ and $CD16^-$ cells in $CD14^+CD11b^+$ population. Results are mean±SEM.

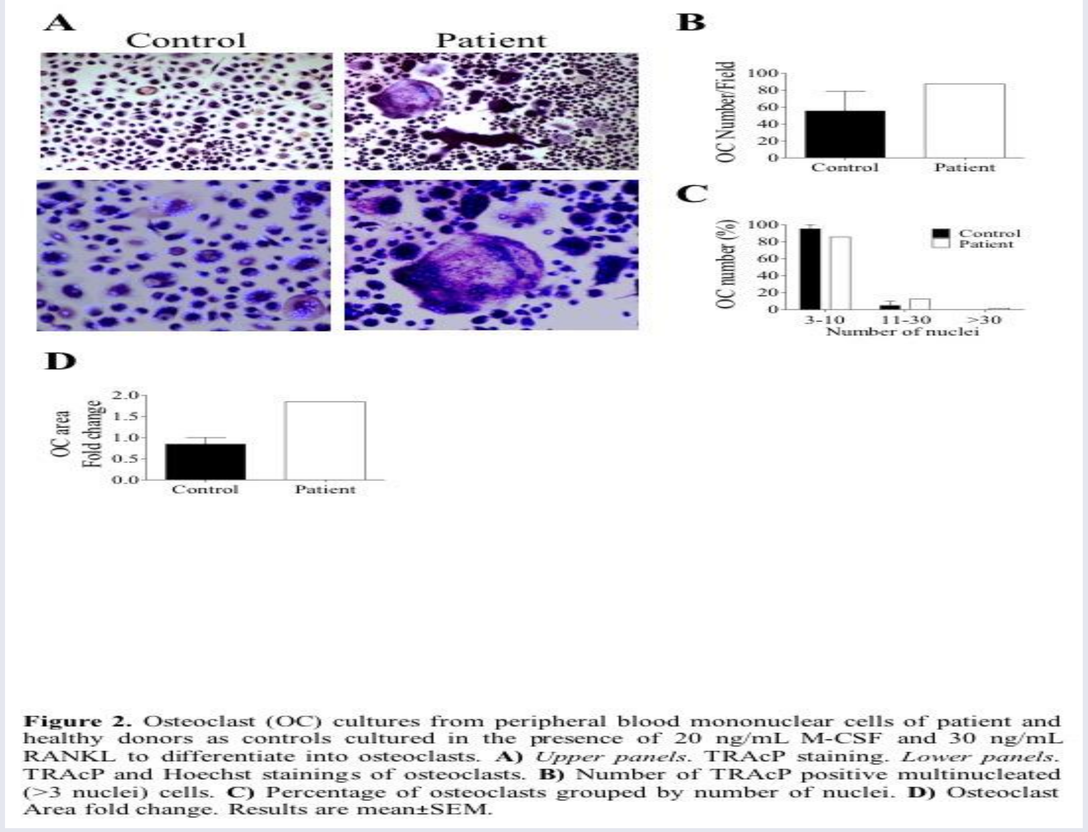


Figure 2. Osteoclast (OC) cultures from peripheral blood mononuclear cells of patient and healthy donors as controls cultured in the presence of 20 ng/mL M-CSF and 30 ng/mL RANKL to differentiate into osteoclasts. **A)** *Upper panels.* TRAcP staining. *Lower panels.* TRAcP and Hoechst stainings of osteoclasts. **B)** Number of TRAcP positive multinucleated (>3 nuclei) cells. **C)** Percentage of osteoclasts grouped by number of nuclei. **D)** Osteoclast Area fold change. Results are mean±SEM.

CONCLUSIONS

Our case report showed a severe symptomatic hypercalcemia in paediatric patient after discontinuation of treatment with denosumab in ACB.
The increasing use of denosumab needs urgent surveillance and increased awareness among clinicians and patients.

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