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Case Report

Denosumab as a bridge to surgery in patients with primary hyperparathyroidism, severe hypercalcemia and renal impairment

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ABSTRACT

Severe hypercalcemia caused by primary hyperparathyroidism mandates prompt parathyroidectomy but increases intra-operative risk, and consequently serum calcium levels should be lowered before surgery. We report two patients with severe hypercalcemia and moderate renal impairment treated with the monoclonal antibody denosumab as a bridge to surgery, although the drug had never been used so far for this purpose. The antiresorptive drug denosumab interferes with the RANKL/RANK (Receptor Activator of Nuclear Factor κ B-ligand/Receptor Activator of Nuclear Factor κ B) signaling, thus inhibiting bone resorption, allowing the quick attainment of adequate serum calcium levels. Our cases suggest the possible use of denosumab in the pre-surgical management of severe hypercalcemia, resulting from both benign and malignant parathyroid disease. Such a "bridge" therapy could be suitable for allowing a prompt and safer parathyroidectomy even in patients with impaired renal function.

KEYWORDS: primary hyperparathyroidism, severe hypercalcemia, denosumab, renal failure

ABBREVIATIONS

iCa, serum ionized calcium; PTH, Parathyroid Hormone; eGFR, estimated glomerular filtration rate; βCTX, carboxy-terminal collagen crosslinks; r.v, reference values; i.v, intra venous.

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INTRODUCTION

In patients with primary hyperparathyroidism presenting with marked increase of serum calcium levels, prompt parathyroidectomy is required. However, severe hypercalcemia may significantly increase intra-operative risk, and hence serum calcium levels should be rapidly lowered before surgery. We report two patients with primary hyperparathyroidism and severe hypercalcemia associated with renal impairment. The latter condition hardly challenges the utilization of usual therapeutic tools such as forced hydration and parenteral bisphosphonates. In the reported patients we utilized the monoclonal antibody denosumab as a bridge to surgery.

CASE REPORTS

Case 1

A 58-yr-old man presented with severe hypercalcemia; he was alert but profoundly asthenic. Our tests allowed for the diagnosis of primary hyperparathyroidism. The main biochemical parameters were: serum ionized calcium (iCa) 2.25 mmol/L (r.v. 1.12-1.31), PTH 1286 pg/mL (r.v. 11-65 pg/mL), phosphate 2.1 mg/dL, creatinine 2.52 mg/dL (corresponding to an eGFR of 27.0 mL/min/1.73 m^2), 24 h-urinary calcium 1470 mg, and serum beta-crosslaps (βCTX) 4.3 ng/mL (male r.v. < 0.704).

A forced hydration was immediately started, overall averaging 8-10 liters per day (4 L i.v. and 4-6 by mouth). However, after six days serum calcium and creatinine remained above the desirable values. A single subcutaneous dose of 60 mg of denosumab was administered to reduce bone resorption. Serum iCa started to drop soon, reaching 1.44 mmol/L after 3 days, whereas βCTX decreased to 0.21 ng/mL, and creatinine to 1.32 mg/dL (Figure 1).

After 5 days the patient underwent surgery, and three hyperplastic parathyroid glands were removed. The post-operative course was regular, without significant hypocalcemia. At the time of discharge, five days after surgery, the parameters were: serum iCa 1.17 mmol/L, 24 h-urinary calcium 152 mg, PTH 109 pg/mL and βCTX 0.11 ng/mL. Calcitriol and calcium carbonate therapy was also prescribed.

Case 2

A 55-yr-old woman presented with hypercalcemic coma, caused by primary hyperparathyroidism. Her serum iCa was 2.35 mmol/L, PTH 873 pg/mL, phosphate 2.2 mg/dL, 24 h-urinary calcium 762 mg, and βCTX 2.23 ng/mL (female r.v. < 1.008). Also this patient had impaired renal function, with serum creatinine of 1.70 mg/dL (eGFR of 38.6 mL/min/1.73 m^2). After three days of i.v. hydration with 4 L/d regular saline, we did not obtain a significant decrease in serum iCa levels, and we chose to administer 60 mg of denosumab subcutaneously. After three days the level of serum iCa was 1.48 mmol/L and that of serum creatinine was 1.24 mg/dL, whereas βCTX decreased to 0.20 ng/mL. The patient awakened from coma, but developed delirium, which persisted for several days. Seven days after denosumab administration, the patient developed hypocalcemia, with serum iCa of 0.96 mmol/L, thus necessitating the administration of i.v. calcium gluconate together with oral calcitrol (Figure 2). Twelve days after admission the patient underwent surgery. The histological diagnosis was parathyroid carcinoma. Some days after surgery, delirium progressively disappeared. Oral calcium carbonate and calcitriol treatment was maintained after discharge.

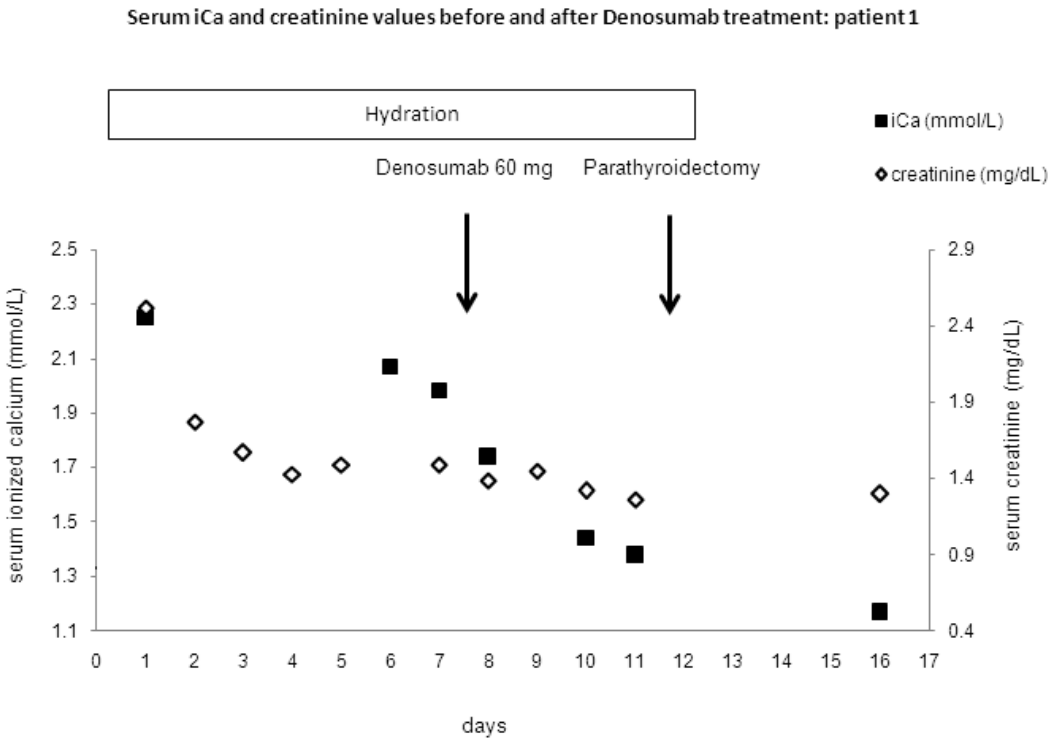

Figure 1. Serum iCa and creatinine values before and after denosumab administration (patient 1).

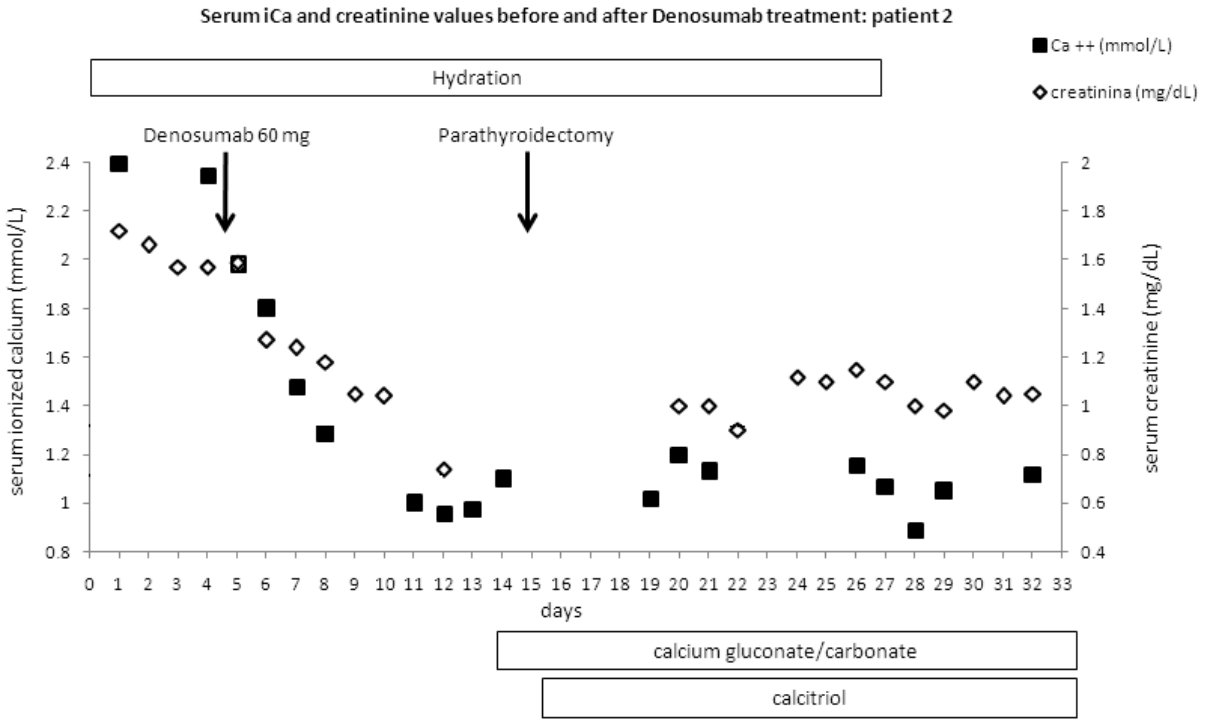

Figure 2. Serum iCa and creatinine values before and after denosumab administration (patient 2).

DISCUSSION

Severe hypercalcemia is a life-threatening condition occurring when serum iCa reaches levels beyond 2.00 mmol/L. It causes deterioration of central nervous system, cardiac, gastrointestinal, and renal functions, and if untreated, leads to death [1]. When caused by primary hyperparathyroidism, surgery is the only definitive cure. However, since severe hypercalcemia results in high intra-operative risk, serum calcium levels around 12 mg/dl (iCa 1.50 mmol/L) should be attained before surgery [2].

Forced hydration is the cornerstone of medical treatment for hypercalcemia. However, simple hydration has often moderate to low efficacy, and the adjunct of antiresorptive therapy is mandatory. Intravenous bisphosphonates are the most utilized treatment [2] as a bridge to surgery, in line with their use in hypercalcemia of malignancy. However, they have a rather delayed onset of action and should be used with caution in patients with renal failure [3].

The antiresorptive drug denosumab interferes with the RANKL/RANK signaling, thus inhibiting bone resorption [4]. Since denosumab is mainly cleared by the reticulo-endothelial system, its use appears relatively safe in patients with renal impairment. High dose (120 mg) of denosumab proved to be effective in refractory hypercalcemia induced by parathyroid carcinoma [5].

We administered denosumab to our patients with severe hypercalcemia and altered renal function, as a bridge to parathyroidectomy, although the drug had never been used so far for this purpose. At the relatively low dose of 60 mg, denosumab markedly inhibited bone resorption (as reflected by βCTx values), allowing the quick attainment of adequate serum calcium levels, and even hypocalcemia in the second case. Denosumab did not affect renal function (Figures 1-2) and the patients underwent surgery without complications.

Besides its demonstrated efficacy in the long-term treatment of refractory hypercalcemia due to parathyroid carcinoma [5], our cases suggest the possible use of denosumab in the pre-surgical management of severe hypercalcemia, caused by both benign and malignant parathyroid disease. Such a “bridge” therapy could be appropriate for

allowing a prompt and safer parathyroidectomy even in patients with impaired renal function.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

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