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CASE REPORT

Severe Hypercalcemia Following Hip Joint Implantation of Calcium Sulfate Antibiotic Beads: Case Series and Review of Literature

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Abstract

Purpose: **The diagnosis and management of hypercalcemia in hospitalized patients can be challenging. Hypercalcemia is often associated with significant morbidity and end-organ damage which may delay a patient's recovery.**

Methods: **We report a case series of three patients who underwent orthopedic procedures with intraoperative placement of vancomycin-loaded calcium sulfate beads. Patients had no known history of malignancy or excess intake of calcium, vitamin A or vitamin D. Laboratory workup showed low parathyroid (PTH) levels and normal PTH-related peptide levels. The temporal nature of the non-PTH mediated hypercalcemia in relation to implantation of the antibiotic beads suggests causality of exogenous calcium sulfate with the patients' subsequent hypercalcemia.**

Results: **Patients were treated with aggressive intravenous saline and zoledronic acid resulting in resolution of hypercalcemia in all cases. The antibiotic impregnated beads did not require explantation.**

Conclusion: **Hypercalcemia following calcium sulfate antibiotic bead implantation may contribute to patient morbidity and increased length-of-stay. We recommend serum calcium and creatinine be closely monitored during the early post-operative period in patients who receive calcium sulfate antibiotic beads.**

Keywords: Hypercalcemia, Calcium sulfate, Antibiotic beads, Joint infection, Vancomycin-loaded calcium sulfate

1. Introduction

The diagnosis and management of hypercalcemia in hospitalized patients can be challenging.[1] Hypercalcemia is often associated with significant morbidity and end-organ damage, which may delay a patient's recovery. When calcium levels rise above 12 mg/dL, patients can develop weakness, lethargy, anorexia, nausea, vomiting, constipation, neuropsychiatric effects and confusion.

Prevention and treatment of bone infection are key priorities in orthopedic surgery. Continued-release calcium sulfate antibiotic beads have been used to deliver antibiotics to sites of infected bone.[2–5] The adverse events associated with this type of therapy have not been completely characterized.

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1.1. Case 1

A 79-year-old male presented for evaluation of left knee pain and was found to have a periprosthetic joint infection of a total knee arthroplasty (TKA). His past medical history was significant for coronary artery disease, hypertension, and prediabetes. He had no known history of malignancy or excess intake of calcium, vitamin A or vitamin D. The patient's initial serum calcium was 9.6 mg/dL (range, 8.4–10.5 mg/dL), serum creatinine was 0.8 mg/dL (range, 0.6–1.3 mg/dL), hemoglobin was 11.5 g/dl (range, 13.9–16.3 g/dl), total protein was 8.0 g/dl (range, 6.0–8.2 g/dl), and albumin was 4.2 g/dl (range, 3.5–5.0 g/dl). He underwent debridement and revision of the TKA with implantation of 20 mL of vancomycin-loaded calcium sulfate beads (STIMULAN® Rapid Cure, Biocomposites Inc., Wilmington, NC). On postoperative day (POD) 2, the patient's serum calcium level rose to 11.2 mg/dL despite being on continuous intravenous (IV) fluids, with a peak of 12.4 mg/dL on POD 5. Further laboratory workup showed serum creatinine 1.0 mg/dL, intact parathyroid hormone (PTH) 3 pg/mL (range, 15–65 pg/mL), PTH-related peptide (PTHrP) 11 pg/mL (range, 14–27 pg/mL), and Vitamin D25(OH) 50 ng/mL (range, 30–100 ng/mL) (Fig. 1).

On POD 5, the patient reported fatigue and showed signs of lethargy, and was given 4 mg of zoledronic acid and was continued on IV fluids. On POD 6, serum calcium level decreased from 12.4 mg/dL to 10.2 mg/dL. Subsequent outpatient labs performed on POD 12 revealed normalized serum calcium at 9.4 mg/dL.

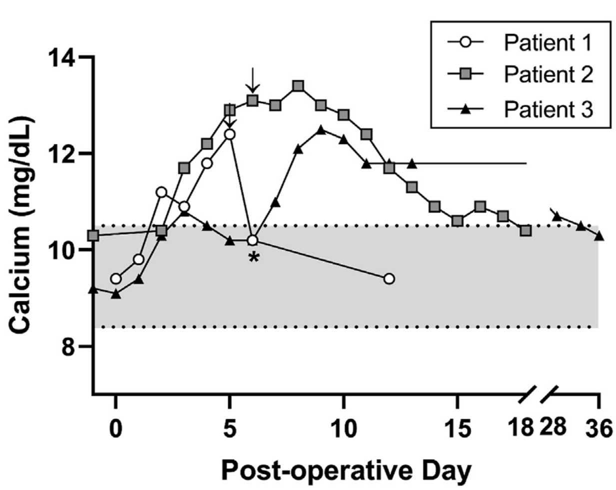

*Fig. 1. **Serum calcium levels during hospitalization and follow-up.** All calcium values were corrected for hypoalbuminemia, as necessary, using the equation: Corrected Calcium = 0.8 * (4.0 − Albumin) + Serum Calcium. Dotted horizontal lines: upper and lower limits of normal serum calcium (8.4 and 10.5 mg/dL, respectively); down arrows: zoledronic acid IV infusion; *: date of second operation and second calcium bead implantation for Patient 3.*

1.2. Case 2

A 78-year-old female with a history of type 2 diabetes, hypothyroidism, scleroderma, and left intertrochanteric hip fracture necessitating open reduction and internal fixation two years earlier, presented with left hip pain. She was found to have abnormal migration of the intramedullary lag screw and nonunion of the left intertrochanteric fracture.

Initial corrected serum calcium was 10.3 mg/dL, hemoglobin was 8.8 g/dl (range, 12.0–16.0 g/dl), total protein was 4.6 g/dl (range, 6.0–8.2 g/dl), and albumin was 2.3 g/dl (range, 3.5–5.0 g/dl). She underwent total hip arthroplasty and two doses of 20 mL vancomycin-loaded STIMULAN® Rapid Cure calcium sulfate beads were implanted. On POD 2, serum calcium was 10.4 mg/dL, but the following day (POD 3), the calcium increased to 11.5 mg/dL.

Laboratory workup for the etiology of the hypercalcemia was unrevealing. Intact PTH was suppressed at 6 pg/mL and PTHrP was low at 9 pg/mL. Vitamin D25(OH) was 44 ng/mL and Vitamin D was 1,25(OH) 9 pg/mL (range, 18–72 pg/mL).

Despite starting IV fluids, the calcium continued to rise, and the patient developed worsening lethargy, anorexia and altered mental status, and was given zoledronic acid 4 mg infusion on POD 6. The calcium peaked at 13.4 mg/dL on POD 8, and one dose of calcitonin (Miacalcin) intramuscularly was given. The calcium level decreased to 10.6 mg/dL by POD 15 (Fig. 1).

1.3. Case 3

A 72-year-old female with a history of hypothyroidism and recent bilateral TKA presented to the hospital after sustaining a fall. She was found to have bilateral periprosthetic femoral fractures and was admitted for staged revision surgery.

Initial corrected calcium was 9.2 mg/dL, creatinine 1.3 mg/dL, eGFR 41 ml/min/1.73m2, hemoglobin was 7.2 g/dl (range, 12.0–16.0 g/dl), total protein was 4.8 g/dl (range, 6.0–8.2 g/dl), and albumin was 2.8 g/dl (range, 3.5–5.0 g/dl). On HD 1, the patient underwent revision of the left TKA with implantation of two doses of 20 mL STIMULAN® Rapid Cure beads. Serum calcium peaked to 10.8 mg/dL on POD 3 before trending down.

The right TKA revision took place on HD 7, and two additional doses of 20 mL STIMULAN® Rapid Cure beads were implanted. On the morning of the surgery, creatinine was 0.9 mg/dL, eGFR 64 ml/min/1.73m2, and calcium 10.2 mg/dL. Postoperatively, the calcium rose again, peaking to 12.5 mg/dL on POD 3. IV normal saline was initiated, and calcium trended down to 11.8 mg/dL by POD 5. Hypercalcemia workup was unrevealing: intact PTH 8 pg/mL, PTHrP 14 pg/mL, Vitamin D25OH 19 ng/mL, Vitamin D1,25 (OH) < 8 pg/mL, TSH 4.9 uIU/mL, free T4 1.1 ng/dL, cortisol 18.3 ug/dL (ruling out adrenal insufficiency), SPEP negative for monoclonal gammopathy. Serum calcium remained elevated at 10.7 mg/dL 26 days after the first revision surgery, but normalized by POD 33 to 10.3 mg/dL.

2. Discussion

The differential of non-PTH-mediated hypercalcemia is broad, and the diagnosis not always clear in patients with complex medical histories. In general, malignancy, granulomatous disease, excess vitamin D intake, or other medications (e.g. thiazide diuretics) should be considered in hypercalcemic patients with concurrent PTH suppression. Here, the patients' history and laboratory data were not consistent with these conditions. Instead, the temporal nature of hypercalcemia following implantation of antibiotic-impregnated calcium sulfate beads suggests causality.

Antibiotic-impregnated beads have become widely utilized in the treatment of chronic osteomyelitis and periprosthetic joint infections to deliver and maintain high doses of antibiotics locally while avoiding systemic circulation.[2] The two most common types of beads are: 1) poly(methyl) methacrylate beads, and 2) mineral-based formulations like calcium sulfate.[6] Both types of carrier beads have favorable diffusion kinetics to maintain a prolonged minimum inhibitory concentration within the implanted environment, though they differ with respect to biodegradability. Poly(methyl) methacrylate beads are non-resorbing and require retrieval in a subsequent operation to avoid becoming a nidus for future infections. Conversely, calcium sulfate beads do not require explantation, and thus have become an increasingly popular choice for orthopedic surgeons. However, the use of antibiotic-loaded calcium sulfate beads has been associated with several complications, including wound discharge, heterotrophic ossification and hypercalcemia.[2]

Kallala et al. published several case studies describing hypercalcemia following implantation of antibiotic-impregnated calcium sulfate beads.[7,8] In the first of these prospective cohort studies, a total of 15 patients underwent revision for infected arthroplasty of the hip or knee with implantation of antibiotic-impregnated calcium sulfate beads. In their study, 20 % of patients developed hypercalcemia, one of whom became severely symptomatic requiring admission to the intensive care unit for intravenous crystalloids and bisphosphonates. A much larger prospective cohort study enrolled 755 patients undergoing revision of hip or knee arthroplasty; the indication in 51 % of these revisions was for prosthetic joint infection.[8] Following surgery, only 5.4 % developed hypercalcemia, and only two of these patients developed symptoms requiring intravenous crystalloids and bisphosphate administration. However, other reports are mostly limited to single case reports[9] with only one other case series including three or more patients.[10] Given that these surgical patients will likely come under the care of hospitalists and endocrinologists, it is of vital importance that there be increased awareness, anticipation and screening for this complication.

The exact mechanism or risk factors for the development of hypercalcemia in patients receiving calcium sulfate beads during surgery is not entirely clear. It has been shown that the volume of the calcium sulfate beads correlates with the degree of hypercalcemia; consequently it is currently recommended to use 40 mL or less of the compound.[9] The simplest explanation for the induction of hypercalcemia is the 'dumping' of highly concentrated calcium ions from the calcium sulfate beads and subsequent absorption by the local capillary network.[10] This mechanism is attractive, as it would explain why hypercalcemia is delayed, typically developing within 3–7 days after implantation. The mean amount of elemental calcium used in patients who developed hypercalcemia in the Kallala et al. study[10] was 32.3 mL (64.6 g) of calcium sulfate hemihydrate, which is approximately 17.8 g of elemental calcium. Assuming a normal baseline serum calcium level of 10 mg/dl and an average blood volume of 5 L, the total calcium load from these beads is equivalent to 35.6 times the total body serum calcium.[11] Other considerations that could potentially explain severity and likelihood of toxicity include host factors (renal function, immobility, underlying parathyroid dysfunction), location of bead placement, and operator-specific variability (e.g. amount of saline used to mix the calcium sulfate power, the antibiotic used, and the amount of time left to cure prior to implantation).

Importantly, our cases illustrate that the calcium rise is not instantaneous and may be delayed by several days. As such, checking serum calcium 3–7 days postoperatively should be considered in patients who have received calcium suflate bead therapy.

Unfortunately, limited data exist with respect to the management of non-PTH mediated hypercalcemia following calcium sulfate antibiotic bead implantation. In the cases presented here, IV fluids were used in all cases, and when symptoms of hypercalcemia were present, IV bisphosphonates were initiated. Management of these cases should include consideration of patient characteristics like pre-existing renal dysfunction, mobility and frailty, the rate of rise of serum calcium, and presence of signs or symptoms of hypercalcemia. In cases of mild hypercalcemia (10.5–11.9 mg/dl), clinicians may choose observation and serial serum chemistries in lieu of active medical management. However, until the pathophysiology and risk factors of hypercalcemia following calcium sulfate bead implantation are better elucidated, the best treatment strategy remains to be determined.

3. Conclusions

Hypercalcemia in the setting of calcium sulfate antibiotic bead implantation may contribute to patient morbidity and increase hospital length-of-stay. Serum calcium and creatinine should be closely monitored during the early postoperative period and potentially following discharge in patients who receive calcium sulfate antibiotic beads. Risk factors for the development of hypercalcemia require additional study, though patients with pre-existing renal insufficiency, decreased mobility and/or underlying parathyroid dysfuction may not be good candidates for this modality of antibiotic administration.

Disclaimers

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Regulatory approval or research subject protection requirements

Not applicable.

Conflicts of interest

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