CLINICAL VIGNETTE

Acute Hypercalcemia Following Hip Fracture Surgery

Maristela B. Garcia, MD and Grace I. Chen, MD

Division of Geriatrics, Department of Medicine, David Geffen School of Medicine at UCLA

An 86-year-old woman with recurrent left hip dislocation and periprosthetic fracture presented with new onset hypercalcemia 4 days after a complex revision of her left total hip arthroplasty and open reduction internal fixation of left periprosthetic hip fracture, with placement of antibiotic-impregnated calcium sulfate beads. Her medical history consists of mild dementia, osteoarthritis, hypothyroidism, and glaucoma. Her medications include levothyroxine, pantoprazole, docusate, and latanoprost eyedrops. Her labs upon admission showed a white blood cell count of 9.6 x 10^3/uL, hemoglobin of 11.1 g/dL, platelet count of 296 x 10^3/uL,sodium of 140 mmol/L, potassium of 4.5 mmol/L, blood urea nitrogen of 13 mg/dL, serum creatinine of 0.7 mg/dL, glucose of 97 mg/dL, calcium of 8.1 mg/dL, and albumin of 3.8 g/dL.

The patient underwent surgery with an uncomplicated intraoperative course. Post-operatively, she had a drop in her hemoglobin to 7.4 g/dL, which appropriately responded to transfusion of one unit of packed red blood cells. She developed mild delirium and transient urinary retention. Postoperative pain control was achieved with around the clock acetaminophen and low dose oxycodone on an as needed basis. She participated in brief sessions with physical therapy, while awaiting transfer to a skilled nursing facility for rehabilitation. On the 4th postoperative day, the patient became increasingly delirious, with episodes of combativeness requiring a low dose of psychotropic. Her vital signs remained within normal limits and her neurologic examination did not suggest focal deficits. Review of her medications did not suggest a cause for the acute worsening of her mental status. Head computerized tomography scan did not reveal any acute findings. Her chest x-ray was unremarkable, as was her electrocardiogram. Infectious work-up was also negative. A notable finding in her serum chemistries was an acute increase of serum calcium to 10.7 mg/dL (ionized calcium was 1.63 mmol/L) from a normal level at admission. She also had a slight increase of serum creatinine to 0.9. Given the clinical suspicion that her newly elevated serum calcium was related to the implanted calcium sulfate antibiotic beads during surgery, no additional work-up for hypercalcemia was warranted, and supportive measures with aggressive intravenous fluid therapy and management of her delirium were instituted. Her serum calcium peaked at 11.6 mg/dL (ionized calcium 1.69 mmol/L) on the 12th postoperative day. She was transferred to the skilled nursing facility where she continued to receive intermittent intravenous fluids until her serum calcium finally normalized to 9.4 mg/dL on the 16th postoperative day. Her delirium gradually cleared a few weeks after her surgery.

Discussion

Joint periprosthetic infections are among the most dreaded complications of orthopedic surgeries. Their impact in the morbidity, function, and quality of life of older adults is devastating. The economic toll on health care resources has grown substantially in the past decade. In 2020, the annual cost for infected joint revisions in the US is estimated at $1.62 billion, an increase from $566 million in 2009.[1,2] Various strategies have been employed to prevent and treat this serious complication to optimize functional outcomes and minimize morbidity.

In the past decade, the use of antibiotic-impregnated calcium sulfate beads has gained increasing popularity over the traditional polymethylmethacrylate (PMMA) void filler. These calcium sulfate beads (CSB) act dually as a joint space filler and as a mechanism to deliver antibiotics locally around the revision components and joint space. Interestingly, the first described use of calcium sulfate as a filler of bone defects dates back to 1892, and the compound gained more attention in 1959 when it was discovered that as a filler of joint space during orthopedic surgery, calcium sulfate did not generate any foreign body reaction.[3] Subsequently, some evidence emerged that calcium sulfate stimulates new bone formation in the presence of periosteum or bone[3] and can act as a scaffold for bone repair.[4] In contrast to PMMA which requires a second surgery for removal, a practical advantage of calcium sulfate as a joint space filler is its ability to gradually be resorbed completely by the body over a period of several weeks.[5,6] Because of its highly efficient drug eluting characteristics,[7] calcium sulfate is also an ideal vehicle to deliver sustained, high amounts of antibiotics to the surrounding tissue over a period of 30 to 60 days,[8] while generally avoiding toxic systemic levels of the drug.[4] Antibiotics usually mixed with the calcium sulfate beads include vancomycin, tobramycin, and gentamicin. In certain cases, other antimicrobials such as cefazolin or amphotericin B may also be incorporated in the mixture.[6]

The highly favorable properties of antibiotic impregnated CSB described have made these an attractive off-label adjunct, not

only in the treatment of joint prosthetic infections, but also in the prevention of infection in complex joint revision surgeries.[3,5] To date, there is insufficient evidence available in the literature to demonstrate that as an adjuvant, it is more effective than usual care in the treatment of joint prosthetic infections involving hip and joint replacement surgeries.[6] Nonetheless, the observed benefit has led to increased application of CSB in orthopedic practice and to a growing body of medical literature which has enhanced our understanding of its complications.

Complications reported in literature include hypercalcemia,[7] antibiotic-related acute kidney injury,[7] wound drainage, and heterotopic calcification.[3,9] The case series reported by Kallala and Haddad in 2015 involving 15 patients (mean age of 64.8 years) who underwent revision arthroplasties for joint prosthetic infection utilizing antibiotic impregnated CSB, documented 3 patients who developed transient hypercalcemia. Of the three, one required treatment and observation in intensive care after he developed severe hypercalcemia 48 hours after surgery. His serum calcium peaked at 14.2 mg/dL and was associated with acute confusion and lethargy.[9] A much larger prospective, observational study reported by Kallala et al in 2018 involving 755 patients (mean follow-up of 35 months) reported hypercalcemia in 5.4% of patients (mean level was 11.7 mg/dl; range 10.8 mg/dL - 14.9 mg/dL), with only 2 patients reported as symptomatic. Wound drainage and heterotopic ossification were reported in 4.2% and 1.7% of patients, respectively.[3,6] In this report, the serum calcium levels returned to normal at a maximum of 5 days postoperatively. The risk of hypercalcemia appeared to be associated with the use of a higher volume of calcium sulfate beads.[3,6] Other factors suggested to explain the cause of hypercalcemia include premature breakdown of the calcium sulfate beads, bead placement near vasculature, and more rapid absorption of calcium. However, the pathophysiology remains incompletely understood.[8] Management of the transient hypercalcemia uniformly consisted of aggressive intravenous hydration, with or without furosemide and with or without intravenous bisphosphonate or calcitonin.

This illustrative case demonstrates the importance of recognizing hypercalcemia as a complication of orthopedic surgeries involving the implantation of calcium sulfate beads. In elderly patients, acute hypercalcemia, though mild, may lead to a sudden worsening of postoperative delirium. Successful management of transient elevation of serum calcium is achieved by aggressive intravenous fluid therapy, with or without furosemide. Furosemide may be necessary in physiologically frail patients with inability to tolerate rapid volume expansion due to reduced ejection fraction heart failure or unrecognized diastolic dysfunction. Hypercalcemia is expected to resolve after several days, as is the associated delirium in the absence of other contributing factors that may prolong it. Other complications of the locally implanted antibiotic-impregnated calcium beads reported in literature include wound drainage, the rare occurrence of heterotopic ossification, and the much rarer antibiotic-related acute kidney injury resulting from systemic absorption of a nephrotoxic antibiotic.[7] Manufacturer-listed contraindications to the use of impregnated calcium sulfate beads include renal dysfunction, hypercalcemia, severe vascular or neurological disease, uncontrolled diabetes, pregnancy, and severe degenerative bone disease.[8]

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