Case Report

EXTREME HYPERCALCEMIA OF MALIGNANCY IN A PEDIATRIC PATIENT: THERAPEUTIC CONSIDERATIONS

Marisa M. Fisher, MD[1]; Jason M. Misurac, MD[2]; Jeffrey D. Leiser, MD, PhD[2]; Emily C. Walvoord, MD[1]

ABSTRACT

Objective: Hypercalcemia of malignancy is rarely seen in children, and therefore few cases are available to illustrate the potential severity of presentation and clinical course. The objective of this report is to present the case of a pediatric patient with extreme hypercalcemia of malignancy and his successful management.

Methods: We describe the therapeutic course of a pediatric patient with one of the highest calcium levels (21.4 mg/dL) reported in the literature and provide a review of what is published on pediatric hypercalcemia of malignancy, focusing on aspects of management.

Results: Our patient's severe hypercalcemia rapidly responded to aggressive normal saline hydration, calcitonin, and zoledronic acid but was followed by hypocalcemia and hypophosphatemia, which were treated with oral supplementation.

Conclusion: This case and review of the literature illustrate the potential severity of hypercalcemia of malignancy and important therapeutic considerations for practitioners. **(AACE Clinical Case Rep. 2015;1:e12-e15)**

Abbreviation:
PTH = parathyroid hormone

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From the [1]Department of Pediatrics, Division of Pediatric Endocrinology, Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, Indiana, and [2]Department of Pediatrics, Division of Pediatric Nephrology, Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, Indiana.
Address correspondence to Dr. Marisa M. Fisher; Department of Pediatric Endocrinology, Riley Hospital for Children, 705 Riley Hospital Drive, Room 5960, Indianapolis, IN, 46202. E-mail: mamfishe@iu.edu.
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INTRODUCTION

Hypercalcemia of malignancy occurs frequently in adult oncology patients (10 to 40%) but is rare (0.4 to 0.7%) in children (1). Hypercalcemia of malignancy is most prevalent in rhabdomyosarcoma and acute lymphoblastic leukemia. When associated with rhabdomyosarcoma, hypercalcemia tends to present later, with more therapy resistance (2,3). Mechanisms of hypercalcemia of malignancy include parathyroid hormone–related peptide (PTHrP) secretion, local calcium release from bone secondary to tumor invasion, and unregulated extrarenal production of 1,25-dihydroxyvitamin D (4,5). Nausea, weakness, polyuria, and constipation arise at calcium levels above 12 mg/dL. Confusion or coma typically develop at levels above 15 mg/dL (1-3). We describe the clinical and biochemical course of a patient who presented with a serum calcium level of 21.4 mg/dL (normal, 8.5 to 10.5 mg/dL), one of the highest reported levels in a child (6).

CASE REPORT

The patient was a previously healthy 15-year-old male who presented with 3 months of increasing back pain, fatigue, urinary retention, and constipation. He was found to have a large pelvic alveolar rhabdomyosarcoma with diffuse vertebral and pelvic bony metastases. Therapy included chemotherapy, bracing for fractures, and steroids for nerve compression. Initial chemotherapy was complicated by bladder obstruction with acute kidney injury (creatinine, 4.0 mg/dL [normal, 0.3 to 1.2 mg/dL]), tumor lysis syndrome, and hypercalcemia (calcium, 14 mg/dL). Bladder obstruction relief normalized his renal function and calcium level.

Three days after discharge from initial hospitalization, the patient presented with extreme fatigue, weakness, polydipsia, anorexia, emesis, conjunctivitis, hallucinations, as well as abdominal, leg, tooth, and "hair" pain. Evaluation revealed a calcium level of 21.4 mg/dL, phosphorus level of 5 mg/dL (normal, 2.6 to 5.2 mg/dL), 25-hydroxyvitamin

D level of 23.5 ng/mL (normal, 25 to 80 ng/mL), uric acid level of 11.9 mg/dL (normal, 3 to 8 mg/dL), blood urea nitrogen level of 29 mg/dL (normal, 5 to 20 mg/dL), and creatinine level of 1.13 mg/dL. An electrocardiogram was normal. Normal saline and furosemide were initiated, and on arrival to our hospital 6 hours later, his calcium was 18.6 mg/dL and phosphorus 4.4 mg/dL. Multiple therapies were initiated simultaneously due to extreme hypercalcemia. Management details are outlined in Table 1. In particular, he received 1 dose of zoledronic acid (adult dosing) and scheduled calcitonin (7). Over the next 6 hours, his serum calcium decreased to 13.4 mg/dL and his creatinine to 0.97 mg/dL. His mental status improved, but nausea, fatigue, and abdominal and leg pain continued and his conjunctivitis worsened. Based on a normal PTHrP level of 0.5 pmol/L (normal, <2 pmol/L) and an unmeasurable 1,25-dihydroxyvitamin D level of <8 pg/mL (normal, 24 to 86 pg/mL), the etiology of his hypercalcemia was believed to be massive bony calcium release due to extensive metastases. Thirty-six hours after therapy initiation, his calcium had fallen to 10.1 mg/dL and his mental status returned to baseline. All of his other symptoms improved except for the "hair" pain and fatigue, which continued for 5 more days.

Subsequently, the patient developed mild asymptomatic hypophosphatemia (24 hours after therapy initiation) and hypocalcemia (72 hours after therapy initiation) (Fig. 1). These are known side effects of zoledronic acid, with up to 74% of patients experiencing hypocalcemia and 82% hypophosphatemia (8). He began oral phosphorus and calcium citrate administered separately to avoid enteral binding (Table 1). Additionally, magnesium was replaced as necessary to maintain normal levels. Due to his persistent hypocalcemia with normal parathyroid hormone (PTH) level of 18 pg/mL (normal, 10 to 65 pg/mL), judged to be inappropriate in the face of hypocalcemia, he eventually was started on 1,25-dihydroxyvitamin D (calcitriol) (Table 1). The patient was discharged after 10 days, with complete symptom resolution. All supplements were weaned and discontinued over several weeks (Table 1).

DISCUSSION

Our patient's quick increase in calcium demonstrates the potentially rapid onset of hypercalcemia of malignancy and the need for careful vigilance and aggressive treatment. The differential for hypercalcemia can be divided into PTH and non-PTH-mediated causes. PTH is the main modulator of calcium homeostasis, acting through increasing the vitamin D to 1,25-dihydroxyvitamin D conversion, decreasing renal calcium excretion, and increasing osteoclast-mediated bony calcium release (9). This case illustrates a non-PTH-mediated cause of hypercalcemia.

Therapy

There are multiple evidence-based guidelines for the treatment of adults with hypercalcemia of malignancy. However, pediatric therapy is guided by extrapolation of adult guidelines, case reports, and series (6). Therefore, this discussion focuses on describing therapeutic options and complications of management. The goals of therapy are correcting volume depletion, limiting bony calcium release, and achieving long-term control by tumor-directed

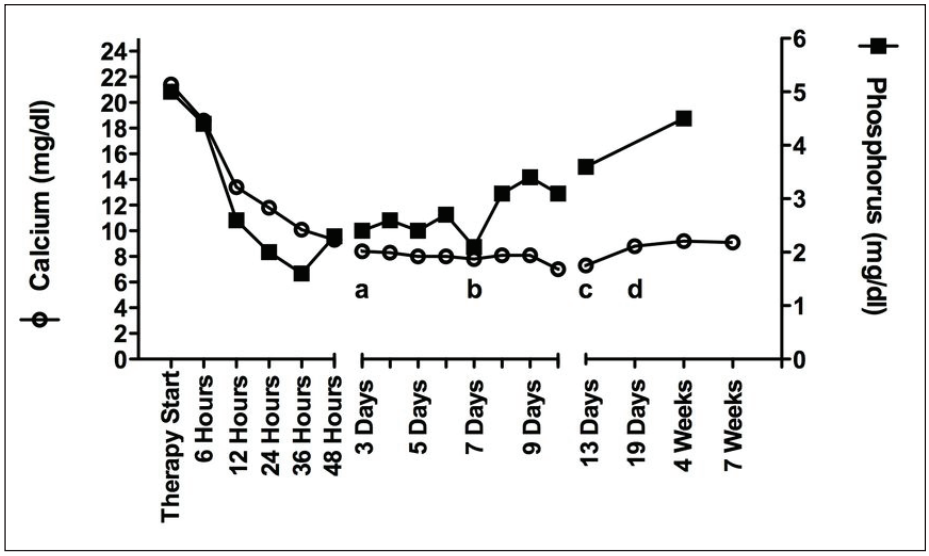

Fig. 1. Longitudinal laboratory values. Longitudinal serum levels of calcium and phosphorus are shown for our patient starting at therapy initiation. Start and stop times are shown for calcium carbonate and calcitriol and are denoted as follows: a, calcium carbonate started; b, calcitriol started; c, calcitriol stopped; d, calcium carbonate stopped. *X-axis is not to scale.

Table 1
Outline of Therapeutic Interventions

Therapy	Start of Therapy (time from presentation)	Starting Dose	Duration of Therapy
Normal Saline	At presentation	2 L bolus then 300 mL/hour titrated to keep urine output 200-300 mL/hour	3 days
Furosemide	At presentation	1 mg/kg (60 mg) intravenously every 6 hours	24 hours
Zoledronic Acid	6 hours	4 mg intravenously once	Single dose
Calcitonin	6 hours	240 units subcutaneously every 12 hours	42 hours
Phosphorus	24 hours	16 mmol orally 3 times daily	12 days
Calcium Citrate	3 days	2375 mg orally 3 times daily	16 days
Calcitriol	7 days	0.5 μcg orally daily	6 days

therapy (9). Modalities include aggressive normal saline hydration, loop diuretics, calcitonin, bisphosphonates, and if necessary, renal replacement therapy (4,5).

Fluids

Hypercalcemia decreases urine concentrating capacity, causing a forced diuresis. The underlying mechanism is incompletely understood but may function to prevent nephrolithiasis (10). In severe hypercalcemia, this often causes significant dehydration and decreased renal function. Thus, normal saline hydration is an essential first step in management, first as boluses and then at 1.5- to 2-times maintenance or higher, depending on urine output. Hydration accomplishes 2 goals: (*1*) renal blood flow restoration, and (*2*) dilution of urine, minimizing crystalline precipitates. The sodium load in normal saline may augment urinary calcium excretion in hypercalcemia, as sodium intake correlates with urinary calcium excretion in other contexts (11).

Whether loop diuretics play a useful role in the treatment of hypercalcemia beyond the management of fluid overload is controversial. Although widely recommended for severe hypercalcemia in texts, there is a paucity of evidence (12). Loop diuretics augment urinary calcium excretion in other conditions due to upregulation of distal convoluted tubule calcium channels (13). Loop diuretics should not be used before rehydration in severe hypercalcemia; dehydration and worsened electrolyte abnormalities are important risks of their use (14). We felt the potential benefits outweighed the risks, given the severity of the patient's hypercalcemia and the close monitoring he would receive.

Calcitonin

Calcitonin treats hypercalcemia by decreasing renal calcium reabsorption and diminishing osteoclast maturation (15). Its rapid onset of action is valuable but its effect is short-lived since tachyphylaxis develops after 48 hours (15). Calcitonin typically lowers serum calcium by 1 to 2 mg/dL and may be more helpful in children than adults due to their higher bone turnover (16). Side effects may include nausea/vomiting, diarrhea, and rarely, anaphylaxis.

Bisphosphonates

Bisphosphonates act by decreasing osteoclast resorption of bone. They act slower than calcitonin and fluids, with initial calcium decreases in 2 to 4 days and nadir levels in 4 to 7 days (5,9). Thus, bisphosphonates can be used with fluids and calcitonin to provide bridge therapy while bisphosphonates take effect. Bisphosphonates are the most effective and studied therapy for the treatment of hypercalcemia of malignancy. Pamidronate and zoledronic acid are currently U.S. Food and Drug Administration–approved for this indication in adults only (5). Multiple reports have documented the efficacy of pamidronate in children, yet zoledronic acid is more effective than pamidronate in adults (3,6,17,18). Two multicenter, randomized, double-blind trials compared the effectiveness of pamidronate to zoledronic acid in a total of 287 adult patients with hypercalcemia of malignancy (17,18). Zoledronic acid was superior to pamidronate, with over 86% of patients treated with zoledronic acid versus only 70% of patients treated with pamidronate achieving a normal calcium level within 10 days (17). Additionally, pamidronate-treated patients experienced earlier hypercalcemia recurrences than those treated with zoledronic acid (17). Zoledronic acid is the bisphosphonate of choice for hypercalcemia of malignancy in adults. However, definitive studies in children are lacking.

Hypocalcemia and hypophosphatemia often follow bisphosphonate use and should be anticipated. Our patient experienced both. Patients who have vitamin D deficiency,

hypoparathyroidism, or renal impairment or who receive a more potent bisphosphonate (e.g., zoledronic acid) are at higher risk (19). Calcium and perhaps calcitriol supplementation may therefore be needed once calcium levels normalize (19). Usually, a PTH rise reduces the risk of hypocalcemia. The absence of a PTH rise in our patient was presumably due to a slow parathyroid response, from mild hypomagnesemia and profound suppression due to his astonishing hypercalcemia (20). Thus, his hypocalcemia and hypophosphatemia were not surprising. Other side effects of bisphosphonates include acute-phase reactions, nephrotoxicity, and anterior uveitis. Uveitis was a concern, as our patient had worsening of his conjunctivitis. Fortunately, an ophthalmologic examination ruled out uveitis, and his conjunctivitis spontaneously resolved.

Renal Replacement Therapy

When hypercalcemia is severe or renal function is seriously compromised, renal replacement therapy may be required. Hemodialysis using a low-calcium dialysate is the most widely used treatment among adults. In children, equally efficacious calcium removal may be possible using newer continuous renal replacement equipment and calcium-free dialysate and/or replacement fluids.

Serum calcium levels over 18 mg/dL or renal failure are typical criteria for dialysis. However, hemodialysis requires hemodynamic stability and carries significant risks (e.g., other electrolyte imbalances, bleeding from heparinization, and line infections). Fortunately, our patient did not require dialysis because his calcium rapidly responded to initial therapy and he maintained good renal function.

CONCLUSION

In conclusion, we report the successful management of a child with one of the highest serum calcium levels reported in the medical literature (6). His case highlights the need for heightened vigilance for the rapid development of severe hypercalcemia in children with malignancies (particularly rhabdomyosarcoma) and careful monitoring for hypocalcemia and hypophosphatemia following bisphosphonate therapy. Once identified, severe hypercalcemia in children can be rapidly and effectively treated with a combination of highly effective therapies, including high-volume saline, furosemide, calcitonin, and zoledronic acid.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

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