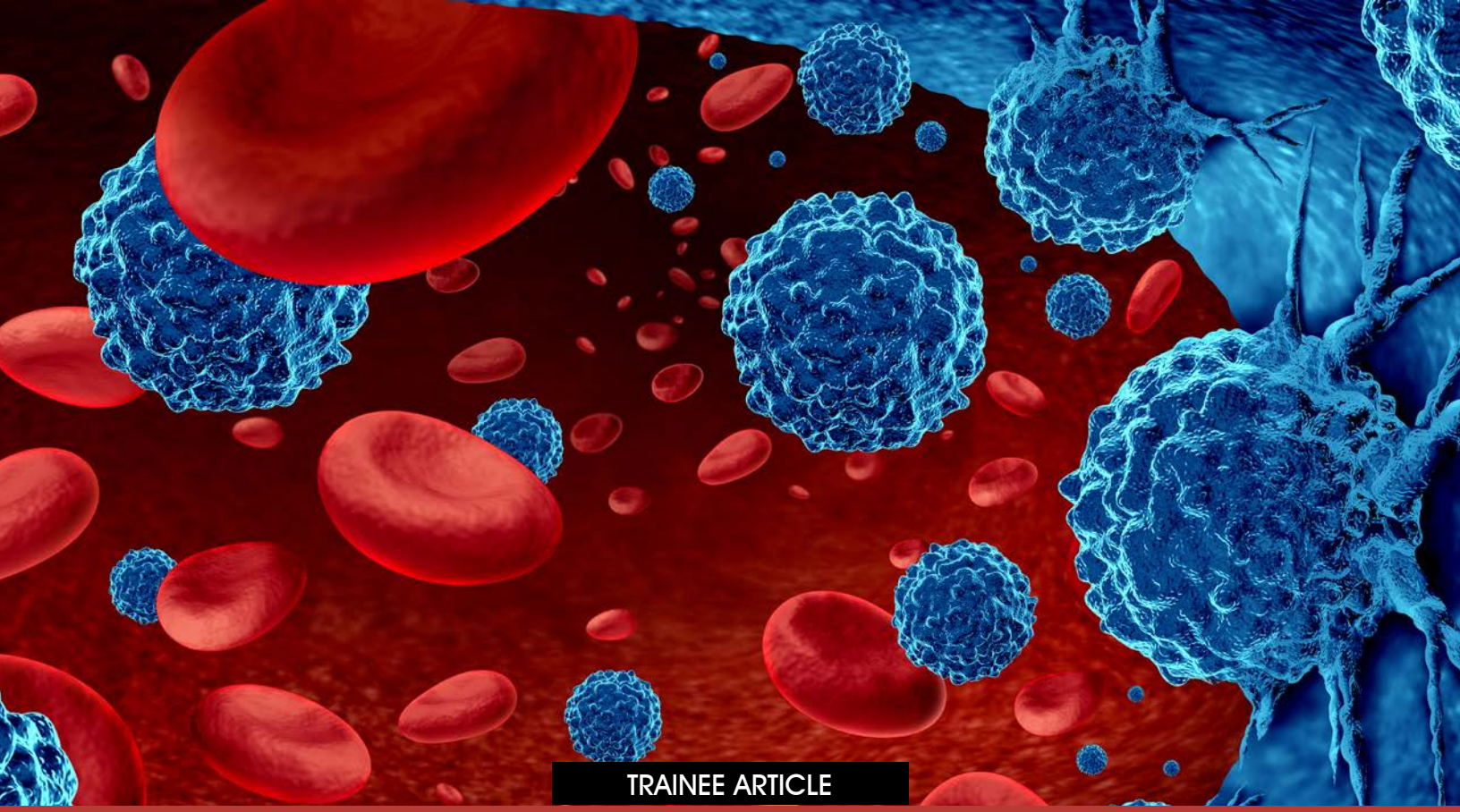

TRAINEE ARTICLE

Symptomatic Hypercalcemia as a Rare Presentation of Leukemia in an Adolescent Male

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ABSTRACT

We present a case of symptomatic hypercalcemia as the presentation of leukemia in a teenage male. He presented with a serum calcium level of 13.9 mg/dL associated with nausea, vomiting, constipation, abdominal pain, and leg pain. He had no abnormality in his WBC count or presence of peripheral blast cells. After an extensive evaluation he was ultimately diagnosed with B-cell ALL based on bone marrow biopsy. Chemotherapy was initiated, and his hypercalcemia was managed with IV fluids, bumetanide, calcitonin, and pamidronate. Hypercalcemia of malignancy is well described in adults, but its prevalence in pediatric cancer patients is only about 0.5-1.5%. While hypercalcemia among pediatric patients is rare, it is important for the general pediatrician to recognize the symptoms and guide their work-up based on a broad differential diagnosis, considering malignancy as an important potential cause.

INTRODUCTION

Calcium plays an essential role in many biologic processes and organ systems including cardiac muscle contraction, nerve conduction, and strengthening bones and teeth to name a few. Calcium homeostasis is maintained by a delicate interplay between the parathyroid gland, the kidney, and skeletal factors.[1-3] The pathophysiology of hypercalcemia is often related to a disturbance in one of these three systems. "Hypercalcemia is defined as a serum calcium concentration that is greater than two standard deviations above the mean", which can vary based on age specific normal values.[2] Additionally, serum calcium levels need to be interpreted in the context of age, as well as the albumin concentration and acid-base status, all of which can alter calcium binding.[2] The clinical presentation of hypercalcemia is a spectrum ranging from an asymptomatic incidental finding to abdominal pain, constipation, lethargy, seizures, psychiatric symptoms, and in severe cases, acute renal failure or pancreatitis.[2]

Hypercalcemia can pose a diagnostic challenge to practicing pediatricians as it is not commonly encountered, and symptoms may be non-specific. Primary hyperparathyroidism and malignancy are the most common causes of hypercalcemia in adults (>90% of cases), but as a cause for hypercalcemia in children only accounts for <5%.[2] Hypercalcemia in children is more likely to be PTH-independent and can be due to a variety of genetic and acquired causes.[1,2] Thus, the differential diagnosis can be quite broad and a systematic approach to diagnosis is required. We present a unique case of an adolescent male who presented with symptomatic hypercalcemia secondary to acute lymphoblastic leukemia (ALL).

PATIENT PRESENTATION

The patient is a previously healthy 13-year-old male who presented to the emergency department (ED) with 5 days of abdominal pain, nausea, vomiting, constipation, and decreased oral intake. The patient's mother reported that he had significant fatigue and lost about 10 pounds over a 2-month period. For the past 6 weeks he also had multiple bone and joint pains lasting for several days at a time and then self-resolving. At the time of presentation, he complained of right ankle pain for one week.

His vital signs were normal for age. He appeared as a thin male with a BMI of 16 (10th percentile for age). His cardiorespiratory, HEENT, and neurological exams were normal. His abdomen was full but non-tender with good bowel sounds and without hepatosplenomegaly. He had no palpable lymphadenopathy. Pain with active and passive range of motion of the right ankle was demonstrated, but with no swelling, redness, or warmth. There was no bony tenderness elsewhere.

He was found to have a serum calcium of 13.9 mg/dL at his pediatrician's office, which precipitated the ED evaluation, where a repeat calcium was 12.6 mg/dL with an ionized calcium of 1.74 mmol/L. He was admitted to the hospitalist service with initial consultations to nephrology and endocrinology. A broad differential diagnosis was considered, divided into parathyroid and non-parathyroid mediated causes (Table 1). Additional work-up is summarized in Table 2. In summary, he was found to have hypercalcemia with suppressed parathyroid hormone (PTH), hypercalciuria, mild acute kidney injury, and mild anemia and thrombocytopenia.

PARATHYROID MEDIATED	NON-PARATHYROID MEDIATED
Primary hyperparathyroidism • Hyperplasia • Adenoma/Carcinoma • MEN type 1 and 2A	Hypervitaminosis D • Excessive intake • Granulomatous Diseases (e.g., Sarcoidosis, Tuberculosis, Cat Scratch Disease)
Familial hypocalciuric hypercalcemia	Medications • Thiazide diuretics • Lithium • Theophylline • Excessive vitamin A
Tertiary Hyperparathyroidism of Renal Failure	Hypercalcemia of Malignancy • Paraneoplastic PTHrp secretion • Bone Tumors • Osteolytic bone metastases • Leukemia • Other malignancies associated with release of inflammatory mediators
	Endocrinopathies • Hyperthyroidism • Pheochromocytoma • Adrenal insufficiency
	Milk-alkali syndrome (excess calcium ingestion, e,g., Tums)
	Immobilization
	Liver Disease
	Inborn Errors of Metabolism
	Chronic Inflammation

Table 1: Differential Diagnosis for Hypercalcemia in Children and Adolescents

LABORATORY TEST	PATIENT'S VALUE	REFERENCE RANGE
WBC count	5.21 x103/μL	4-10.5x103/μL
Differential		
% lymphocytes	48.1%	
% monocytes	3.2%	
% neutrophils	45.9%	
% eosinophils	2.2%	
% basophils	0.6%	
% blasts	0	
Hemoglobin	11.4g/dL	12.5-16.1g/dL
Hematocrit	32.4%	36-47%
Platelets	123 x103/μL	150-450 x103/μL
MCV	83.1 fL	78-95 fL
Total Serum Calcium	12.6 mg/dL	8.8-10.6 mg/dL
Ionized Calcium	1.74 mmol/L	1.15-1.35 mmol/L
Serum Creatinine	1.11 mg/dL	0.42-0.81 mg/dL
BUN	15 mg/dL	7-17 mg/dL
Urine calcium excretion	25.6 mg/dL	
Urine calcium to creatinine ratio	0.39	
Parathyroid Hormone (PTH)	2	11-74
PTHrp	0.6	<2
Vitamin D,25-OH	29 ng/mL	30-100 ng/mL
Vitamin D 1,25-OH	<8 pg/mL	30-83 pg/mL
Vitamin A	47 mcg/dL	26-72 mcg/dL
TSH	3.1 UIU/mL	0.5-4.5 UIU/mL
AM Cortisol	13.1 μg/dL	4.5-22.7 μg/dL
ESR	17 mm/hr	0-15 mm/hr
CRP	<0.5 mg/dL	<1 mg/dL
LDH	437	470-750IU/L
Uric Acid	7.4	2.7-6.7mg/dL

Table 2: Laboratory Evaluation – Abnormal Values are highlighted

The etiology of his hypercalcemia, however, remained unclear and given the persistent right ankle pain with mild cytopenias hematology/oncology was consulted about 3 days into the admission. An x-ray of the right ankle revealed an abnormal lucency of the metaphysis of the distal tibia and fibula with subtle periosteal reaction. An MRI of the lower extremities was then obtained to further investigate this finding and revealed a marrow replacement process of the tibia and fibula (Figure 1). He underwent bone marrow biopsy which showed B-cell ALL with 64% blasts.

He was started on chemotherapy and his hypercalcemia was managed with IV fluids, loop diuretics (bumetanide), calcitonin, and pamidronate. His calcium trended down nicely after initiation of treatment (Figure 2). He is currently in remission and doing well without the need for additional medications aside from his maintenance chemotherapy.

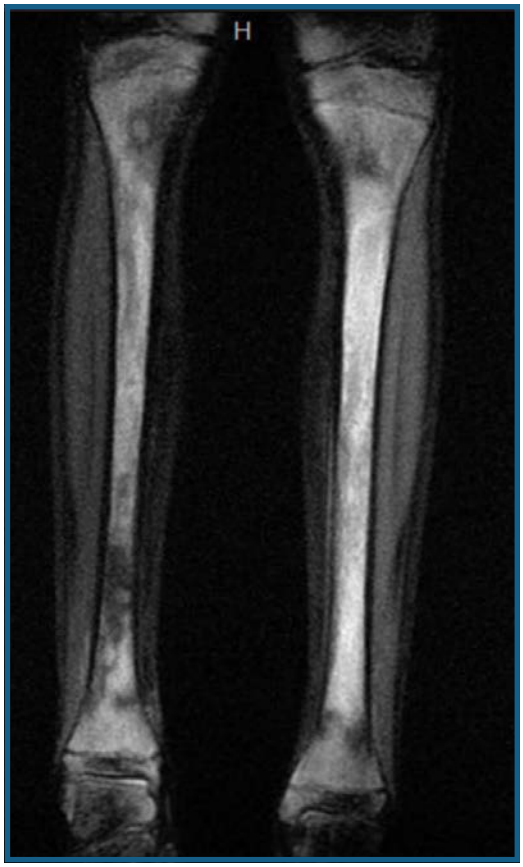

Figure 1: MRI bilateral lower extremities
Marrow replacement process involving the tibias and fibulas

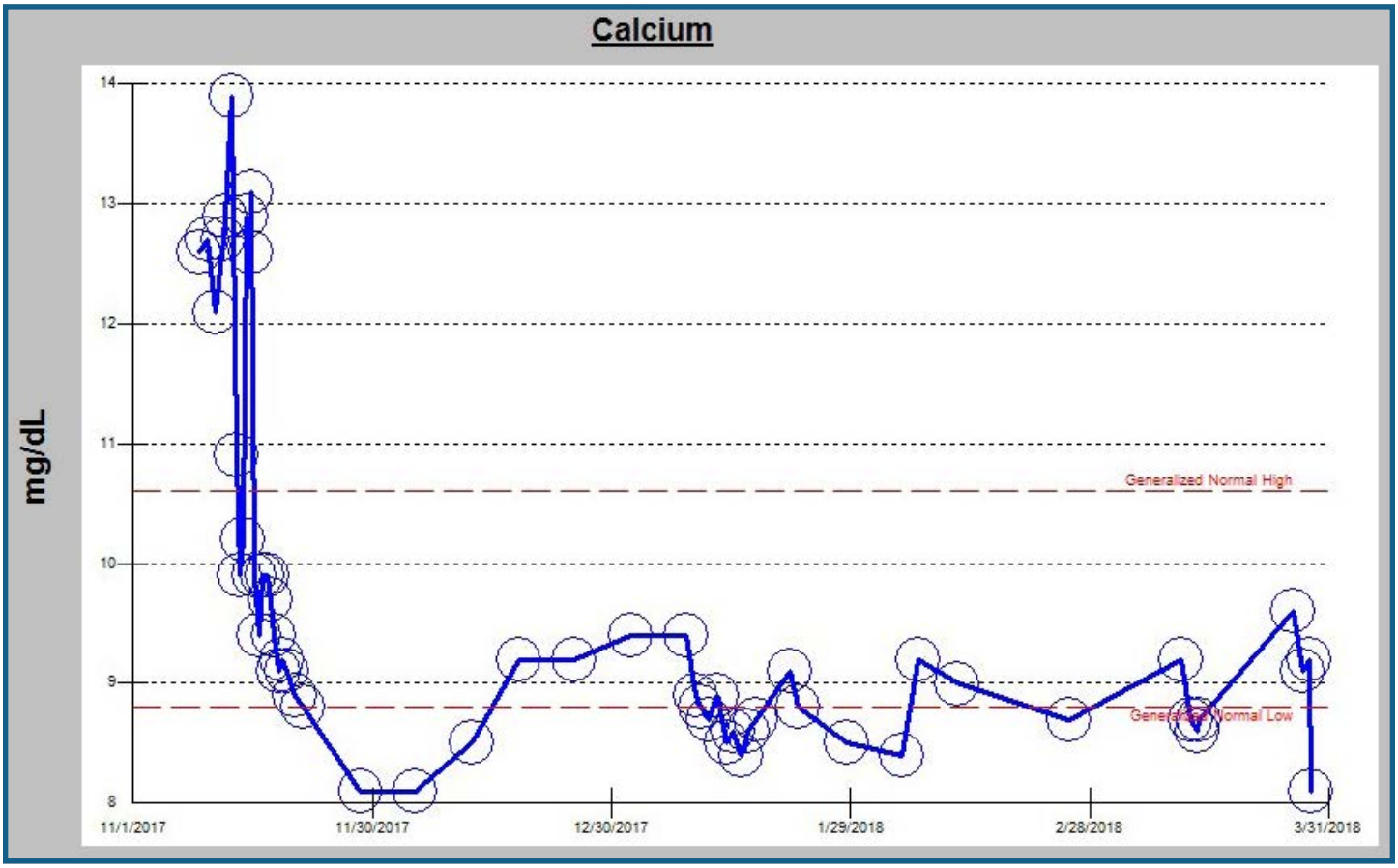

Figure 2: Calcium trend

DISCUSSION

Hypercalcemia is a rare presentation of pediatric malignancies with an overall estimated prevalence of 0.5-1.5%.[4] It has been reported in a variety of malignancies including leukemia, lymphoma, neuroblastoma, and rhabdomyosarcoma, among others.[1] The pathogenesis is hypothesized to be related to PTHrp secretion from tumor cells, altered osteoclastic activity by inflammatory mediators (including TNF-alpha, TNF-beta, IL-6, and TGF-B), osteolytic metastases, and increased activated vitamin D.[1,3,5] In our patient, since the PTHrp was negative, the hypercalcemia was suspected to be secondary to increased osteoclast activity mediated by inflammatory cytokines.

The literature on management of hypercalcemia in pediatric malignancies is limited to case reports and case series. In general, the main principles for treatment of acute hypercalcemia include hydration, prevention of bone resorption, and ultimately treating the underlying cause, the malignancy in this case.[3] Since the cancer is driving the hypercalcemia initiation of chemotherapy is effective, although with delayed response. In addition to aggressive rehydration, several pharmacologic agents have been utilized including loop diuretics (ex. furosemide), which increase calcium excretion, bisphosphates and calcitonin, which inhibit osteoclastic activity.[2] Bisphosphate use has shown promising results to manage acute symptomatic hypercalcemia in this population.[6-9] One case series of 8 children treated with an IV infusion of the bisphosphonate pamidronate showed a rapid decline in serum calcium level within 48 hours.[6] Additionally, Inukai et al, reported in their case series of 22 children with leukemia associated hypercalcemia that children who received bisphosphonate therapy experienced a more rapid normalization of serum calcium level and renal function compared to those that did not receive bisphosphonate therapy.[10]

For patients who require a more rapid decrease in their serum calcium level bisphosphonate therapy may not suffice. Calcitonin can be utilized to drop the calcium level more quickly, with a peak response of 12-24 hours.[3] While the initial response is rapid, repeated administration is not effective due to downregulation of calcitonin receptors and resultant tachyphylaxis.[3] In case reports of pediatric ALL with symptomatic hypercalcemia a combination of bisphosphonates and calcitonin was effective and safe for treatment of hypercalcemia.[11,12]

Malignancy associated hypercalcemia by itself has not been shown to impact overall prognosis in leukemia patients.[10] Although it may not impact overall prognosis, it is important to recognize as it can be associated with significant symptomatology or co-morbidities. Further studies are needed to better understand this rare complication and optimize its treatment. While hypercalcemia among pediatric patients is rare, it is important for the general pediatrician to recognize the symptoms and guide their etiologic evaluation based on a broad differential diagnosis, considering malignancy as an important potential cause.

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