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Case Report

Severe Hypercalcemia due to Hypervitaminosis D in a Breastfed Infant

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Abstract

Vitamin D is one of the most commonly recommended dietary supplements and is often the first medication ever prescribed in infancy. However, with the variety of concentrations available, including many over-the-counter formulations, dosing errors can easily occur. We present a case of a breastfed infant with a calcium level greater than 23 mg/dL (5.75 mmol/L), whose severe hypercalcemia was due to hypervitaminosis D from accidentally overdosed vitamin D supplementation. We consider the differential diagnosis for her presentation and review the interventions required for treatment of her hypercalcemia. Notably, we reinforce the importance of carefully reviewing dosing of vitamin D supplementation with families. We also discuss the management of hypercalcemia, including the role of fluids, diuretics, and glucocorticoids, as well as the long-term sequalae of severe hypercalcemia.

Key Words: hypervitaminosis D, hypercalcemia, pediatric

Abbreviations: ED, Emergency Department; PTH, parathyroid hormone.

Introduction

Vitamin D is important for bone and mineral metabolism and to maximally absorb calcium. The American Academy of Pediatrics (AAP) recommends 10 mcg (400 International Units or IU) of vitamin D supplementation daily for breastfeeding infants [1]. Because of the variety of vitamin D supplements available, dosing errors can easily occur.

We present a case of severe hypercalcemia due to hypervitaminosis D in a 6-month-old breastfed infant. Our patient presented with an initial calcium level of 23.8 mg/dL (5.95 mmol/L), which is among the highest pediatric calcium values recorded in the literature. Her case highlights the nonspecific symptoms that can result from hypercalcemia, and the risk for vitamin D dosing errors. Management of severe hypercalcemia is also reviewed.

Case Presentation

A previously healthy, exclusively breastfed, 6-month old female, born at 40 weeks 6 days, presented to her 6-month well child visit with 2 weeks of fussiness, constipation, poor feeding, non-bloody, non-bilious emesis, and lethargy. She had adequate wet diapers, but had worsening constipation, with only 3 bowel movements over the prior 2 weeks. She had been at the 33rd percentile for weight at birth, increased to the 79th percentile at 4 months, then dropped to the 7th percentile by 6 months (Fig. 1). She was in the 76th percentile weight for length at birth but dropped to the 3rd percentile weight for length by 6 months. She had met all growth and developmental milestones at prior visits, but at 6 months, she was noted to have head lag and growth deceleration. There was no known family history of genetic or metabolic disorders.

Her pediatrician referred her to the Emergency Department (ED) for further evaluation of failure to thrive. In the ED, her temperature was 36.1 °C, heart rate 124 beats per minute, respiratory rate 32 breaths per minute, blood pressure 95/76 mmHg, and oxygen saturation 100%. Her exam was notable for hypotonia with head lag and signs consistent with dehydration.

Diagnostic Assessment

Initial laboratory evaluation (Table 1) demonstrated an elevated calcium level of 23.8 mg/dL (5.95 mmol/L), with a confirmatory repeat level of 23.2 mg/dL (5.80 mmol/L) (normal, 8–10.5 mg/dL or 2.00–2.63 mmol/L), and a normal albumin level 4.8 g/dL (48 g/L) (normal, 3.5–5.0 g/dL or 35–50 g/L). The ionized calcium was 11.56 mg/dL (2.89 mmol/L) (normal, 4.56–5.16 mg/dL or 1.14–1.29 mmol/L). Additional electrolyte derangements included hyponatremia, hypochloremia, hypophosphatemia, and hypermagnesemia. An initial electrocardiogram showed normal QTc for age (QTc of 396 milliseconds) (normal range, 340–450 milliseconds) [3].

In the ED, she was given a normal saline bolus, and fluids were gradually uptitrated to 2 times maintenance (about 3 L/m^2/day). Endocrine was consulted, and the patient was admitted for frequent laboratory monitoring and telemetry.

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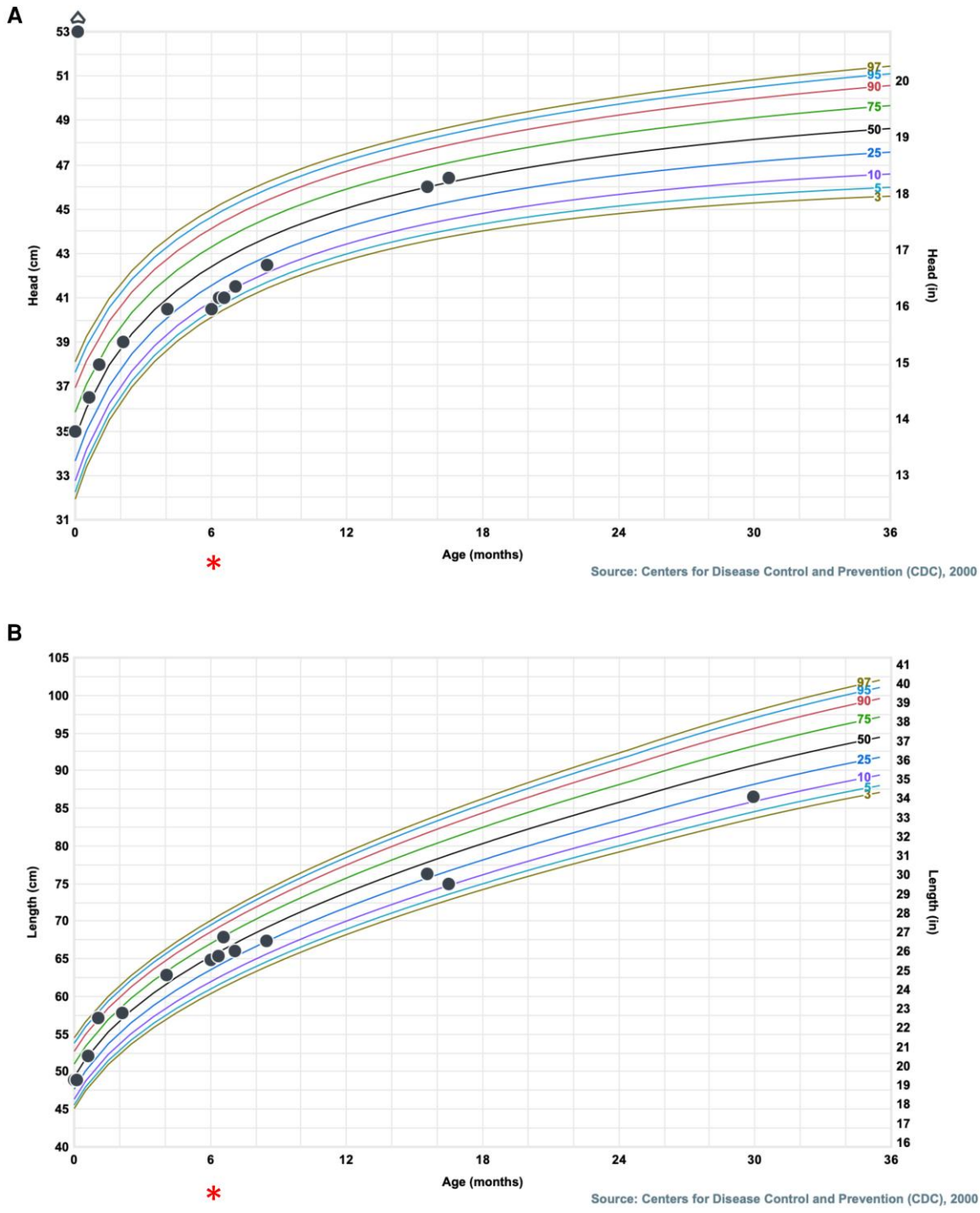

Figure 1. 1A, Head Circumference; 1B, Length; 1C, Weight; 1D, Weight for Length. *Denotes 6-month pediatrician visit from which patient was referred to the Emergency Department.

A renal ultrasound demonstrated bilateral medullary nephrocalcinosis with mildly echogenic renal cortex (Fig. 2), which indicated that her hypercalcemia was likely chronic. Further laboratory studies revealed an appropriately suppressed parathyroid hormone (PTH), suggesting that her hypercalcemia was a PTH-independent mediated process.

Additional history revealed that the patient's mother had inadvertently been giving 225 to 250 mcg (5000–10 000 IU) of cholecalciferol (vitamin D3) daily to the patient instead of 10 mcg (400 IU) per day for about 4 months. Rather than giving 1 mL per day of 10 mcg/mL (400 IU/mL) cholecalciferol, her mother had purchased vitamin D online, with a concentration of 125 mcg/mL (5000 IU/mL), and she was giving 1 to 2 mL daily. The patient's mother was taking a prenatal vitamin daily, which included 400 IU of cholecalciferol and 200 mg of calcium. The patient's 1-25-dihydroxy vitamin D level was 534.0 pg/mL (1281.6 pmol/L) (normal range, 19.9–79.3 pg/mL or 47.76–190.32 pmol/L) and her 25-OH vitamin D level was 397.0 ng/mL (990.91 nmol/L) (normal range, 30.0–80.0 ng/mL or 74.88–199.68 nmol/L).

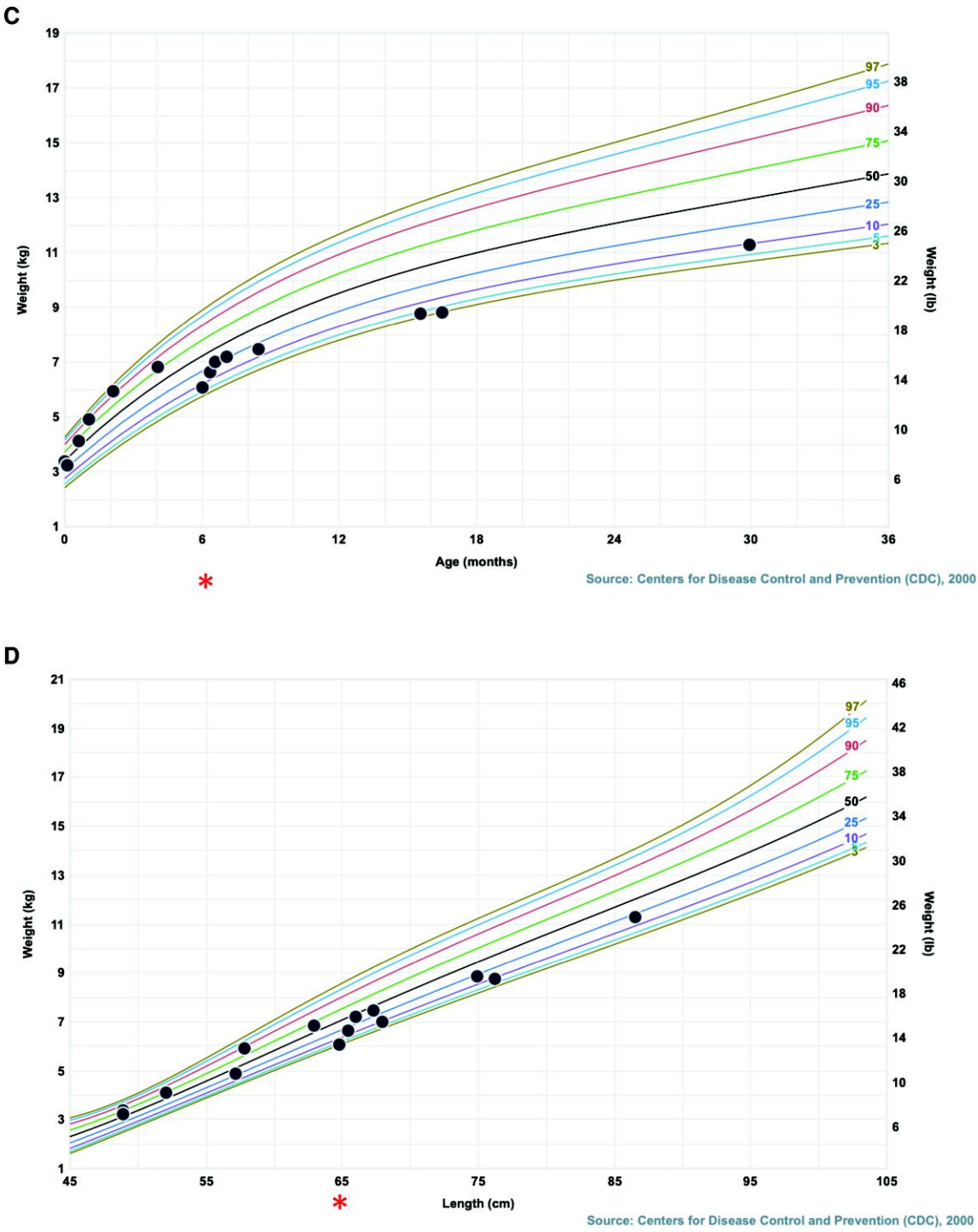

Figure 1. Continued

Treatment

1. **Hyperhydration**, at first with 1.5× maintenance (2.25 L/m^2/day) and then 2× maintenance (3 L/m^2/day), with D5 Normal Saline. Fluids were gradually decreased, with improving calcium.
2. **Diuresis with furosemide** to eliminate calcium via the urine (2 doses in total). This reduced potassium and magnesium levels, which required some intravenous repletion.
3. **Prednisolone** 1.6 mg/kg daily was started on hospital day 2, and continued for 6 weeks, including a gradual taper.
4. Breastmilk was replaced with **low calcium and vitamin D free formula (Calcilo)** in the acute hypercalcemic period. Breastfeeding was reintroduced after a few days, but the

Table 1. Initial laboratory values at presentation

Labs	Value, SI units	Value, conventional units	Reference range (SI units and conventional units)
Sodium	134 mmol/L	134 mEq/L	135 mmol/L – 148 mmol/L (135 mEq/L - 148 mEq/L)
Potassium	3.81 mmol/L	3.81 mEq/L	3.2 mmol/L – 4.5 mmol/L (3.2 mEq/L – 4.5 mEq/L)
Chloride	96 mmol/L	96 mEq/L	99 mmol/L – 111 mmol/L (99 mEq/L - 111 mEq/L)
Bicarbonate	23 mmol/L	23 mEq/L	17 mmol/L – 29 mmol/L (17 mEq/L - 29 mEq/L)
BUN	9.64 mmol/L	27 mg/dL	1.43 mmol/L – 6.78 mmol/L (4 mg/dL – 19 mg/dL)
Creatinine	30.06 µmol/L	0.38 mg/dL	17.68 µmol/L – 35.36 µmol/L (0.2 mg/dL – 0.4 mg/dL)
Calcium	5.95 mmol/L	23.8 mg/dL	2.00 mmol/L – 2.63 mmol/L (8 mg/dL – 10.5 mg/dL)
Phosphorus	1.00 mmol/L	3.1 mg/dL	1.13 mmol/L – 2.13 mmol/L (3.5 mg/dL – 6.6 mg/dL)
Magnesium	1.19 mmol/L	2.9 mg/dL	0.62 mmol/L – 0.91 mmol/L (1.5 mg/dL – 2.2 mg/dL)
ALT	0.52 µkat/L	31 U/L	0.05 µkat/L – 0.90 µkat/L (3 U/L – 54 U/L)
AST	1.29 µkat/L	77 U/L	0.17 µkat/L – 1.09 µkat/L (10 U/L – 65 U/L)
Alkaline phosphatase	1.57 µkat/L	94 U/L	1.84 µkat/L – 6.68 µkat/L (110 U/L – 400 U/L)
Albumin	48 g/L	4.8 g/dL	35 g/L – 50 g/L (3.5 g/dL – 5.0 g/dL)
Calcium, urine	7.15 mmol/L	28.6 mg/dL	
Creatinine, urine	1838.72 mmol/L	20.8 mg/dL	
Calcium/creatinine ratio		1.37	<0.86[a]
PTH	<3 ng/L	< 3 pg/mL	10 ng/L – 65 ng/L (10 pg/mL – 65 pg/mL)
PTHrP	17.2 pmol/L		
25-hydroxy vitamin D	990.91 nmol/L	397 ng/mL	74.88 nmol/L – 199.68 nmol/L (30 ng/mL – 80 ng/mL)
1,25-dihydroxy vitamin D	1281.6 pmol/L	534 pg/mL	47.76 pmol/L – 190.32 pmol/L (19.9 pg/mL – 79.3 pg/mL)
ESR	36 mm/h	36 mm/h	0 mm/hr – 30 mm/hr
CRP	2.00 mg/L	0.20 mg/dL	≤5.00 mg/L (≤0.50 mg/dL)

Units: g/L, grams per liter; µmol/L, micromoles per liter; µkat/L, microkatal per liter; mEq/L, milliequivalents per liter; mg/L, milligrams per liter; mm/h, millimeters per hour; mmol/L, millimoles per liter; ng/L, nanograms per liter; ng/mL, nanograms per milliliter; nm/L, nanomoles per liter; pg/mL, picograms per milliliter; pmol/L, picomoles per liter; pg/mL, picograms per milliliter.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PTH, parathyroid hormone; PTHrP, PTH-related peptide.

[a]Reference [2]

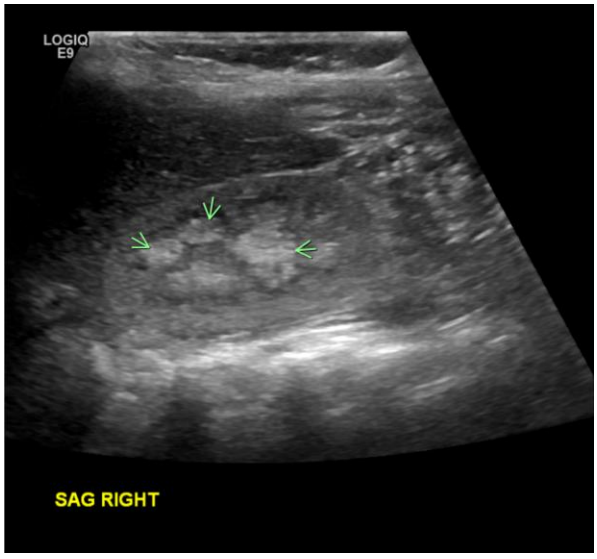

Figure 2. Ultrasound demonstrating medullary nephrocalcinosis. The arrows denote several areas of nephrocalcinosis.

patient was primarily fed Calcilo for 1 month, until breastfeeding was resumed.

Outcome and Follow-up

The patient's calcium levels decreased dramatically over the first few days of admission (Fig. 3), decreasing from 19.4 mg/dL (4.85 mmol/L) to 12.2 mg/dL (3.05 mmol/L) in the first 16 hours after the introduction of prednisolone. Calcium returned to a normal range (10.2 mg/dL or 2.55 mmol/L) by hospital day 6. Of note, her magnesium, phosphorous, alkaline phosphatase, aspartate aminotransferase (AST), and creatinine all quickly normalized without any intervention.

Over the course of her hospitalization, additional services were consulted given the broad differential for her hypercalcemia. Genetics was consulted, and *CYP24A1* testing demonstrated a normal 1,25 hydroxyvitamin D to 24,25 dihydroxyvitamin D ratio (16.75) and normal 24, 25-dihydroxyvitamin D level (3.88 ng/mL or 9.68 nmol/L). Oncologic workup was initiated to rule out hypercalcemia of malignancy. Incidentally, a 1.0 × 1.6 × 1.6 cm right upper posterior mediastinal mass was identified on chest x-ray. Metaiodobenzylguanidine (MIBG) study showed moderate MIBG uptake, suggesting a posterior mediastinal neuroblastoma. However, oncology concurred that her hypercalcemia was not a consequence of malignancy. She has been observed closely as per ANBL1232 protocol for over 2 years, and the presumed neuroblastoma has shown no evidence of progression on serial chest x-rays.

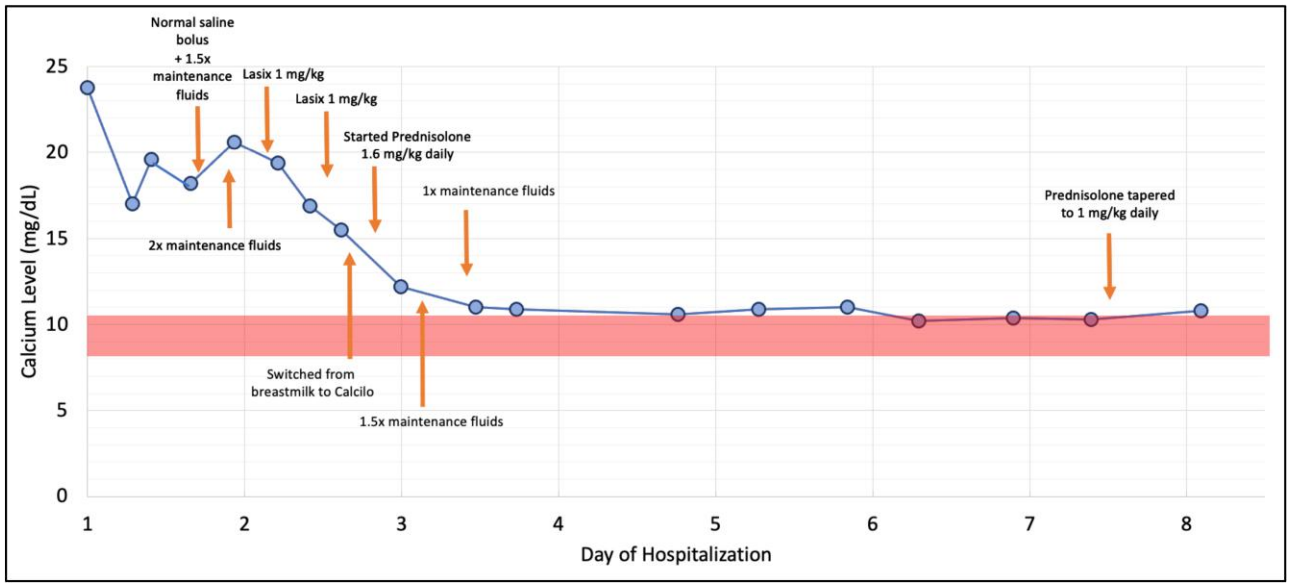

Figure 3. Calcium levels throughout hospitalization. The arrows denote different interventions to lower the patient's calcium level. The pink shading represents the normal reference range for calcium.

At her endocrine follow-up visit 1 month after discharge, she was feeding and growing well, around the 25th percentile for weight and 48th percentile weight for length. Her calcium and 25-hydroxyvitamin D levels were within the normal range, although 1,25-dihydroxyvitamin D remained elevated. The patient's mother had not fully resumed breastfeeding, but subsequently did. Nephrology continued monitoring her persistent nephrocalcinosis with serial laboratory studies and renal ultrasounds. Notably, her kidney function has remained within normal limits, but her nephrocalcinosis has persisted, raising concern for increased risk of chronic kidney disease.

Discussion

Vitamin D supplementation is critical for the exclusively breastfed infant because breast milk has limited vitamin D; the AAP recommends supplementation with 10 mcg (400 IU) cholecalciferol per day. There are numerous formulations and brands of vitamin D that are commercially available. This has led to an increased potential for dosage errors, particularly in the youngest patients. One case of hypervitaminosis D was recently reported in an infant in Europe, who was accidentally administered 1000–1250 mcg (40 000–50 000 IU) cholecalciferol per day after switching to a "natural" dietary supplement [4].

There has also been increasing prevalence of hypervitaminosis D as a result of families intentionally administering additional supplementation (ie, beyond what is recommended by a patient's primary care physician). Recently, some have advocated for a protective effect of vitamin D supplementation against COVID-19, which has also prompted excess vitamin D intake. Our case highlights the importance of counseling families on proper vitamin D supplementation given the potential negative effects of oversupplementation.

Although health literacy was not formally assessed, both parents had received higher education (her father was a graduate student, and her mother had studied mathematics). English was not the family's primary language, and while interpreters were used, it is possible language barriers contributed to the dosing error. The patient's mother was initially advised to obtain vitamin D over the counter and was counseled on dosage but was not given a prescription. This illustrates that it may be beneficial for primary care providers to prescribe cholecalciferol as a prescription to enable parents to reference it and to facilitate the option of discussing it with their local pharmacists when obtaining this supplement.

In this case, given the infant's relatively mild symptoms and nephrocalcinosis, she had chronic rather than acute hypercalcemia. Nephrocalcinosis or nephrolithiasis in infants has a median age of diagnosis at 2.9 months, suggesting that it takes some time for hypercalciuria to cause nephrocalcinosis [5]. However, there are also cases of nephrocalcinosis noted as early as 1 month of age [6]. Beyond nephrocalcinosis, the risks associated with hypervitaminosis D are numerous. Complications of hypercalcemia include neuromuscular effects (weakness, fatigue); abdominal effects (constipation, abdominal pain); renal effects (polydipsia, polyuria, nephrocalcinosis, dehydration); cardiovascular effects (hypertension, vascular calcification, shortened QT, and rarely arrhythmias); and neurologic effects (seizures, reduced consciousness) [7]. This patient's presentation serves as a reminder of the nonspecific findings that can represent an initial presentation of severe hypercalcemia in infants, such as poor growth, constipation, and irritability. A focused and comprehensive history, including all medications and supplements and notably vitamin D supplementation, should be completed in all infants.

Before the vitamin D supplementation error was revealed, the differential for hypercalcemia was broad. This included genetic conditions, including familial hypocalciuric hypercalcemia, Williams syndrome, Janson disease, and Bartter syndrome [8]. Oncologic and infectious etiologies should also remain on the differential.

Hypercalcemia can be managed with multiple interventions. Hydration is almost always first-line treatment, as polyuria with hypercalcemia can lead to dehydration, further exacerbating hypercalcemia. The use of normal saline for hydration is critical since sodium is necessary to excrete calcium. Furosemide can be used to acutely lower calcium levels,

although it is not a sustainable strategy for reducing calcium levels and it increases the risk of nephrocalcinosis. In this case, glucocorticoids were very effective. Glucocorticoids are thought to work by reducing intestinal calcium absorption by decreasing transcellular active transport processes and increasing urinary calcium excretion [9]. Glucocorticoids also inhibit synthesis of 1,25-dihydroxyvitamin D3, the active form of vitamin D, from 25-hydroxyvitamin D [10].

There was initial consideration of using calcitonin or bisphosphonates to treat her hypercalcemia. Calcitonin decreases bone resorption of hydroxyapatite and increases renal excretion of calcium; however, its effectiveness declines quickly due to tachyphylaxis of the osteoclasts [8]. Bisphosphonates inhibit osteoclastic bone resorption, preventing calcium mobilization from its greatest storage depot within the body, the bone. However, since she responded to glucocorticoids and a low calcium formula, these interventions were unnecessary.

Overall, this is an instructive case, as it demonstrates that hypercalcemia, even in severe cases, can present with nonspecific symptoms. A thorough history is essential to making the correct diagnosis. It also illustrates the importance of family education regarding vitamin D supplementation, as improper supplementation can lead to short- and long-term complications.

Learning Points

- Hypercalcemia in an infant can present with nonspecific symptoms such as growth failure, hypotonia, and constipation.
- Vitamin D supplementation comes in numerous formulations; prescribing and reviewing specific dosing instructions with families can reduce the risk of accidental overdose.
- Glucocorticoids are an effective treatment for hypercalcemia secondary to hypervitaminosis D and may need to be used in combination with other treatments in severe hypercalcemia.

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Contributors

J.B., R.K., and R.G. conceptualized this case report, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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