Primary Hyperparathyroidism From Ectopic Parathyroid Adenoma in a 12-Year-Old With Slipped Capital Femoral Epiphysis

Rebecca J. Vitale,1,2,10 Hester F. Shieh,3 Biren P. Modi,3 and Rebecca J. Gordon1,6

1Division of Endocrinology, Department of Pediatrics, Boston Children’s Hospital, Boston, MA 02115, USA
2Division of Endocrinology, Department of Medicine, Brigham and Women’s Hospital, Boston, MA 02115, USA
3Department of Surgery, Boston Children’s Hospital, Boston, MA 02115, USA

Abstract

Primary hyperparathyroidism has been reported in pediatric patients presenting with slipped capital femoral epiphysis (SCFE), but never in patients with ectopic parathyroid adenoma. A 12-year-old boy with obesity and autism spectrum disorder presented with a limp and was found to have bilateral SCFE. Calcium was elevated to 12.3 mg/dL with parathyroid hormone (PTH) of 1191 pg/mL. Neck ultrasound revealed no parathyroid adenoma. He was discharged following bilateral surgical pinning with plans for outpatient workup. Repeat labs 5 days later demonstrated calcium had risen to 16.7 mg/dL. Technetium-99m sestamibi scintigraphy and a computed tomography scan revealed a 2.7 × 1.6 × 1.9 cm intrathyroid mediastinal lesion. He underwent a thoracoscopic resection of the mass, and intraoperative PTH levels fell appropriately. Pathology revealed a parathyroid adenoma. Postoperatively, the patient developed hungry bone syndrome followed by normocalcemic secondary hyperparathyroidism which resolved with high-dose vitamin D supplementation. Primary hyperparathyroidism presenting as SCFE in a pediatric patient has been reported in 13 previous cases. This is the first reported case of bilateral SCFE arising from an ectopic parathyroid adenoma.

Thoracoscopic resection is a relatively new approach in pediatrics. Primary hyperparathyroidism can be associated with SCFE, especially bilateral, and should be considered in patients with traditional risk factors for SCFE. Pediatric patients with primary hyperparathyroidism and negative neck imaging should be further evaluated for ectopic parathyroid adenomas with nuclear medicine or cross-sectional imaging that includes the head, neck, and mediastinum. Thoracoscopic resection can be considered in pediatric patients with mediastinal ectopic parathyroid adenoma.

Key Words: hypercalcemia, primary hyperparathyroidism, ectopic parathyroid adenoma, slipped capital femoral epiphysis

Abbreviations: PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; SCFE, slipped capital femoral epiphysis.

Primary hyperparathyroidism (PHPT) is a rare cause of hypercalcemia in pediatric patients with an incidence of 2 to 5 cases per 100,000 children and often the presentation is more indolent than in adults [1, 2]. As the presenting symptoms can be quite nonspecific, many patients are not diagnosed until relatively late in the disease course when they may have significant end-organ damage [3]. There are also pathophysiologic reasons for pediatric disease to have a more fulminant presentation, including increased bone turnover and the role of the growth hormone axis [4]. Slipped capital femoral epiphysis (SCFE) is an unusual presentation for PHPT which has been reported in the literature previously [5, 6], but never secondary to an ectopic parathyroid adenoma.

In this case, a 12-year-old patient presented with bilateral SCFE and was found to have hypercalcemia with a workup consistent with PHPT caused by an ectopic parathyroid adenoma. Surgical management was performed thoracoscopically with resolution of hypercalcemia. The postoperative course was marked by persistent hyperparathyroidism secondary to vitamin D deficiency which resolved with adequate supplementation. We additionally performed a literature review of pediatric hyperparathyroidism focusing on the relationship to SCFE, ectopic parathyroid adenomas, and optimal surgical approaches to such lesions.

Case Presentation

Initial Presentation of SCFE

A 12-year-old boy with obesity (body mass index 99th percentile) and autism spectrum disorder (not on any medication) presented with a limp and was found to have bilateral SCFE (Fig. 1). His pubertal development was Tanner stage 4 and his growth velocity had accelerated from 6.84 cm/year 2 years prior to 8.41 cm/year in the year immediately prior to presentation, suggesting he was near the time of maximal pubertal growth velocity. Calcium was elevated to 12.3 mg/dL with elevated alkaline phosphatase and low 25OH vitamin D (Table 1 and Fig. 2). He had significant neuropsychiatric agitation but denied constipation, polyuria, and other symptoms of hypercalcemia. His exercise history was notable for minimal physical activity. In terms of family history, his mother reported a personal history of secondary hyperparathyroidism which had been attributed to vitamin D deficiency...
and resolved with vitamin D supplementation. There was no other known family history of hypercalcemia or hyperparathyroidism.

His SCFE was managed surgically with bilateral in situ pinning. He was hyperhydrated with normal saline 200 mL/hour for management of his hypercalcemia, but calcium improved to only 12.0 mg/dL. Hyperhydration was discontinued and calcium rose to 12.4 mg/dL. Given concern for primary hyperparathyroidism (though parathyroid hormone [PTH] level was still pending) neck ultrasound was obtained but was unable to localize a parathyroid adenoma. Renal ultrasound revealed no evidence of nephrocalcinosis or nephrolithiasis.

His hospital course was characterized by poor coping with hospitalization, frequent angry outbursts, and refusal of blood draws. As this was thought to be a subacute to chronic hypercalcemia and he was minimally symptomatic, he was discharged with plans for outpatient technetium-99m sestamibi scintigraphy the following week. For his vitamin D deficiency and recognizing his recent orthopedic surgery, he was prescribed low-dose cholecalciferol 1000 IU daily daily to optimize bone healing. The family was instructed to ensure at least 3 L of fluid intake daily after discharge.

### Second Hospitalization for Hypercalcemia

After discharge, the PTH level was 1191 pg/mL (Table 1 and Fig. 2). Follow-up labs were challenging to obtain as the patient weighed 82 kg, was non-weight bearing for 2 weeks, and lived in a third-floor walk-up apartment. He developed significant nausea and was not able to meet the oral hydration goal of 3 L/day and he tolerated only 1 L of oral intake of fluid. Repeat labs were not obtained until 5 days later and demonstrated calcium had risen to 16.7 mg/dL with phosphorus 2.2 mg/dL. Calcium was elevated to 13.9 mg/dL.

He was admitted to the hospital for management of symptomatic severe hypercalcemia. Hyperhydration with normal saline 200 mL/hour was initiated. Calcium improved transiently to less than 12 mg/dL with intranasal calcitonin therapy and he required 12 doses of calcium over the following 5 days to keep the calcium level in an acceptable range (Fig. 2). He was discharged to home on calcium carbonate 100 mg daily and calcium citrate 600 mg daily.

Calcium improved to 12.4 mg/dL with intranasal calcitonin therapy and he required 4 doses of calcitonin over the following 5 days to keep the calcium level in an acceptable range. Calcium carbonate 100 mg daily was prescribed and calcium citrate 600 mg daily was continued. Calcium improved to 12.0 mg/dL with calcitonin therapy and he was discharged to home on calcium carbonate 100 mg daily and calcium citrate 600 mg daily.

### Table 1. Bone Metabolism Labs Throughout the Clinical Course

| Lab                  | Presentation | Discharge #1 | Rehospitalization | After surgery | Discharge #2 | 6 months after surgery | 9 months after surgery (1500 IU cholecalciferol) | 1 year after surgery (5000 IU cholecalciferol) |
|----------------------|--------------|--------------|-------------------|---------------|--------------|------------------------|-----------------------------------------------|-----------------------------------------------|
| Calcium              | 8.0-10.5 mg/dL | 12.3         | 12.4              | 16.7          | 10.0         | 8.9                    | 9.9                                           | 9.6                                           |
| Phosphorus           | 2.7-4.9 mg/dL | 3.2          | 3.8               | 2.2           | 2.7          | 3.4                    | 5.9                                           | 5.8                                           |
| Alkaline phosphatase | 70-390 unit/L | 775          |                   |               | 297          |                        | 263                                           |                                               |
| Parathyroid Hormone  | 10-65 pg/mL   | 1191         | 1339              | 76            | 160          | 123                    | 42                                           |                                               |
| 25-OH Vitamin D      | 30-80 ng/mL   | 12.1         |                   | 8.6           | 16.7         |                        | 19.5                                         | 30.5                                         |
| 1,25-OH Vitamin D    | 19.9-79.3 pg/mL | 246.6    |                   |               | 236.7        | >200                   |                                               | 97.8                                         |
A 2.7 × 1.6 × 1.9 cm mass in the right anterosuperior mediastinum along the right aspect of the thymus nestled between the superior vena cava, left brachiocephalic vein, right internal mammary vessels, aortic arch, and innominate artery (Fig. 3B).

Based on preoperative localization studies and proximity to the great vessels, a right thoracoscopic transthoracic approach was performed. On hospital day 5, he underwent resection of the mass, which was found to be intrathymic. It was anterior and medial to the superior vena cava, phrenic nerve, and left brachiocephalic vein, and posterior to the internal mammary vessels. Inferiorly, there was visualization and preservation of the aortic arch and superiorly the innominate artery (Fig. 4). PTH levels fell from 1613 pg/mL preoperatively to 115 pg/mL 10 minutes postexcision to 76 pg/mL 30 minutes postexcision, suggesting a single adenoma and precluding further neck exploration. Postoperatively, as anticipated, the patient developed hungry bone syndrome with a calcium nadir of 7.6 mg/dL and phosphorus nadir of 1.6 mg/dL, which required oral calcium and calcitriol for 10 days (Fig. 2). With normalization of his calcium, his neuropsychiatric symptoms substantially improved. Pathologic evaluation revealed a “well-circumscribed hypercellular proliferation of parathyroid tissue abutting the thymus. Although quite large, this mass consistent with ectopic parathyroid adenoma shows no features of malignancy.” No molecular analyses were performed. He was discharged without calcium and calcitriol supplements. Just prior to discharge, his PTH was 122 pg/mL. Plans were made to continue to follow his PTH as an outpatient after reinitiation of his cholecalciferol supplementation.

Postdischarge Course: Ongoing Secondary Hyperparathyroidism

Due to his history of autism and difficulty tolerating lab draws, repeat labs could not be drawn for 6 months despite multiple attempts by the family. His PTH at this time had risen to 160 pg/mL, with normal calcium of 9.9 mg/dL and low 25OH vitamin D of 16.7 ng/mL, consistent with secondary hyperparathyroidism due to vitamin D deficiency (Table 1). The patient had a very restrictive diet and resultant inadequate dairy intake and was nonadherent to cholecalciferol and calcium supplementation. He was restarted on cholecalciferol 1500 IU/37.5 µg daily and 1000 mg of elemental calcium daily; the importance of adherence was reinforced.

Three months later, despite reported adherence, his 25-OH vitamin D level had risen to only 19.5 ng/mL with calcium 9.6 mg/dL and PTH 123 pg/mL. His cholecalciferol dose was increased to 5000 IU/125 µg daily and his 25-OH vitamin D level finally improved to 30.5 ng/mL. With this increase in 25OH-vitamin D, PTH normalized to 42 pg/mL. Calcium remained normal at 9.7 mg/dL. A limited workup was sent to
evaluate for malabsorptive disease to explain his high vitamin D requirement, but it was unremarkable and no cause was determined. A PHPT genetic panel was offered to the family, but they declined it. A dual-energy x-ray absorptiometry scan was not performed as he had required sedation for his prior parathyroid imaging studies and this would not change his management.

Discussion

PHPT classically presents with symptoms of hypercalcemia, but these can be very nonspecific and difficult to elicit in children and in people with developmental disabilities. This patient has a history of autism which may have limited his reporting of these nonspecific symptoms. Indeed, when he presented to his pediatrician with a limp, this was based on his mother’s observation of a change in gait rather than the patient reporting any pain or difficulty walking. While the diagnosis of hypercalcemia in pediatrics is often delayed due to nonspecific symptoms [3], it may have been further delayed due to this patient’s autism spectrum disorder.

SCFE is a subacute growth plate fracture with specific risk factors that this patient had, including his adolescent age, obesity, male gender, and African American ethnicity. The calcium level was evaluated as part of the standard preoperative evaluation for SCFE without any clinical suspicion for any abnormalities, as this patient had several classic risk factors for SCFE. To our knowledge, there are 13 reported cases of PHPT presenting with SCFE [5, 6], all but 1 of the patients had bilateral disease. Given this, at presentation with bilateral SCFE, even in a patient with classic risk factors, it should prompt a biochemical evaluation and at a minimum a serum calcium level should be obtained.

PHPT is common in adults (incidence of 1 in 1000) and often presents with mild hypercalcemia, but in children it often has a more severe phenotype [2]. In a retrospective case series of 52 patients <19 years with PHPT, 44% of them had evidence of end-organ damage such as nephrolithiasis, nephrocalcinosis, acute pancreatitis, fracture, or other radiographic evidence of bone involvement at presentation [1]. Our patient’s SCFE would put him in this category of having end-organ damage. While some of the increased severity may be related to delays in presentation due to the nonspecific symptoms and less frequent screening labs in the pediatric population [3], there may be physiological reasons for the response to PHPT to be more pronounced in children. Children have higher rates of bone turnover at baseline because they are growing. This may explain the higher rate of bony manifestations in pediatric patients when combined with increased bone turnover from PHPT [1, 4]. It is also hypothesized that the growth hormone axis may play a role in the severity of PHPT in children. The association between PTH and the growth hormone axis is not well understood, but it is thought that higher growth hormone and insulin-like growth factor 1 levels in children may alter the responsiveness of bone to PTH with even higher bone turnover and trabecular remodeling [4]. More research is needed to better elucidate the role of other hormonal axes on the severity of PHPT in children.

The difficulties in localizing our patient’s lesion led to a delay in definitive surgical treatment. Thanseer et al conducted a prospective cohort study of 54 adults with PHPT to determine the relative sensitivity of ultrasonography, technetium-99m sestamibi, and 18F-fluorocholine positron emission tomography/computed tomography in localizing lesions in PHPT. Neck ultrasound had a sensitivity of 69.3% and a positive predictive value of 87.1% in localizing such lesions [7], and the sensitivity is operator dependent. Pediatric ultrasound technicians often have less experience in localizing parathyroid adenomas and this sensitivity may be lower in the pediatric hospital setting. This patient’s lesion was discovered on technetium-99m sestamibi scintigraphy, which had a sensitivity of 80.7% and a positive predictive value of 97.6% among all patients in the Thanseer et al study. The highest sensitivity and positive predictive values (100% and 96.3%, respectively) were seen with 18F-fluorocholine positron emission tomography/computed tomography.

Parathyroid glands are frequently ectopic due to the complex migration of the parathyroid glands during embryological development. The third pharyngeal pouch gives rise to the inferior parathyroid glands and the fourth pharyngeal pouch gives rise to the superior parathyroid glands. After being formed in the pouches, the glands migrate to their final location; inferior glands are more likely to be ectopic because they have a longer distance to travel to their final location [8]. As the parafollicular cells of the thyroid and the thymus are also formed in the third and fourth pharyngeal pouches, respectively, ectopic glands are frequently found in the thymus, thyroid, and mediastinum in addition to the paracervical region [9].

Neck ultrasound will be ineffective in localizing ectopic parathyroid adenomas. The reported frequency of ectopic adenomas among adults with PHPT ranges from 6% to 22% [10] and in children has been reported to be as high as 25% [11]. In adults with ectopic parathyroid adenomas, technetium-99m sestamibi scintigraphy has a sensitivity that is similar to eutopic adenomas (66-81% for ectopic vs 81-82% for eutopic) [7, 8, 12]. Technetium-99m sestamibi scintigraphy is not nearly as sensitive in children; a recent retrospective cohort study of 86 patients ≥21 years of age (cases collected from 1997 to 2017) showed a sensitivity of only 10% in localizing ectopic lesions [11].
The patient’s ectopic mediastinal parathyroid adenoma was resected using a thoracoscopic approach. This has been a common approach in adult patients for decades [13], but has been reported in just a handful of recent pediatric cases [14, 15]. Preoperative localization studies and cross-sectional imaging are essential for operative planning. In this case, due to the proximity of the mass to the great vessels, a right thoracoscopic approach was assessed to be the safest option for visualization. This was further validated by the low likelihood (and low morbidity) of needing additional neck dissection if there had been persistent intraoperative PTH elevation. With proper patient selection, including appropriate and adequate preoperative imaging and adenoma localization, successful surgical management of PHPT secondary to an ectopic mediastinal parathyroid adenoma can be utilized with a thoracoscopic parathyroidectomy.

Following his resection, the patient continued to have an elevated PTH level, which was attributed to his profoundly low 25-OH vitamin D level. His calcium remained normal after the “hungry bone” phase had resolved, so there was low suspicion for recurrent PHPT. Unfortunately, due to his autism, it was very difficult to obtain labs after discharge, but with the assistance of the Child Life team, labs were able to be obtained 6 months later which revealed persistent secondary hyperparathyroidism with low 25-OH vitamin D. High doses of cholecalciferol were needed to normalize his 25-OH vitamin D level, which was achieved 1 year after his initial presentation.

In all pediatric patients with PHPT, it is advisable to offer genetic testing. Recent case series have revealed that up to 50% of pediatric PHPT cases are associated with genetic syndromes, including in the calcium sensing receptor signaling pathway in infants and in parathyroid cell proliferation pathways in older children and adolescents [16]. We had recommended genetic testing for the patient, but the family has declined further evaluation. We will continue to recommend this in follow-up given the monitoring for other associated problems that is necessary in some of these syndromes. This patient did not have a family history of PHPT or other endocrine tumors, but given the frequency of genetic syndromes underlying PHPT in this age group, genetic testing is still indicated.

To our knowledge, this is the first reported case of PHPT secondary to ectopic parathyroid adenoma presenting with bilateral SCFE. The thoracoscopic approach to ectopic parathyroid adenoma resection has also been reported only a few times in the literature [14, 15]. This patient’s presentation underscores the severity with which PHPT can present in pediatric patients and the rapidity with which the hypercalcemia can progress. In children presenting with bilateral SCFE, even those with classic risk factors, biochemical evaluation should be considered to evaluate for PHPT as an underlying etiology. Pediatric patients with PHPT and negative neck imaging should be further evaluated for ectopic parathyroid adenomas with nuclear medicine or cross-sectional imaging that includes the head, neck, and mediastinum. Lastly, thoracoscopic resection should be considered in pediatric patients with mediastinal ectopic parathyroid adenoma.

Financial Support
R.J.V.’s work was supported in part by NIH training grant no. T32DK007529.

Disclosures
The authors have no conflicts of interest to disclose.

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

References
1. Kollars J, Zarroug AE, van Heerden J, et al. Primary hyperparathyroidism in pediatric patients. Pediatrics. 2005;115(4):974-980.
2. Roizen J, Levine MA. A meta-analysis comparing the biochemistry of primary hyperparathyroidism in youths to the biochemistry of primary hyperparathyroidism in adults. J Clin Endocrinol Metab. 2014;99(12):4555-4564.
3. Li CC, Yang C, Wang S, Zhang J, Kong XR, Ouyang J. A 10-year retrospective study of primary hyperparathyroidism in children. Exp Clin Endocrinol Diabetes. 2012;120(04):229-233.
4. McKenna K, Dunbar NS, Parham K. Why is primary hyperparathyroidism more severe in children? Med Hypotheses. 2021;147:110482.
5. George GS, Raizada N, Jabbar PK, Chellamma J, Nair A. Slipped capital femoral epiphysis in primary hyperparathyroidism – case report with literature review. Indian J Endocrinol Metab 2019;23(4):491-494.
6. Roztoczyńska D, Wójcik M, Konturek A, Nogię A, Hubalewska-Dydejczyk A, Starzyk J. Bilateral slipped capital femoral epiphysis as first manifestation of primary hyperparathyroidism in a 15-year-old boy. Pediatr Endocrinol Diabetes Metab 2020;26(4):220-224.
7. Thanpeer NTK, Bhadada SK, Sood A, et al. Comparative effectiveness of ultrasonography, 99mTc-sestamibi, and 18F-fluorocholine PET/CT in detecting parathyroid adenomas in patients with primary hyperparathyroidism. Clin Nucl Med. 2017;42(12):e491.
8. Phityakorn R, McHenry CR. Incidence and location of ectopic abnormal parathyroid glands. Am J Surg. 2006;191(3):418-423.
9. Shen W, Duren M, Morita E, et al. Reoperation for persistent or recurrent primary hyperparathyroidism. Arch Surg. 1996;131(8):861-7; discussion 867.
10. Roy M, Mazeh H, Chen H, Sippel RS. Incidence and localization of ectopic parathyroid adenomas in previously unexplored patients. World J Surg. 2013;37(1):102-106.
11. Ramm RD, Mancilla EE, Adnick NS, et al. Single gland, ectopic location: adenomas are common causes of primary hyperparathyroidism in children and adolescents. World J Surg. 2020;44(5):1518-1525.
12. Castellani M, Reschini E, Longari V, et al. Role of Tc-99m sestamibi scintigraphy in the diagnosis and surgical decision-making process in primary hyperparathyroid disease. Clin Nucl Med. 2001;26(2):139-144.
13. Prinz RA, Lonchyna V, Carnaille B, Wurtz A, Proye C. Thoracoscopic excision of enlarged mediastinal parathyroid glands. Surgery. 1994;116(6):999-1004; discussion 1004; discussion 1004-1005.
14. Seo Y, Song K, Choi HS, et al. A case of primary hyperparathyroidism due to an intrathyroidic ectopic parathyroid adenoma in a 15-year-old boy. Ann Pediatr Endocrinol Metab. 2020;23(3):187-191.
15. Flokas ME, Ganieva G, Grieco A, Agdere L. Ectopic parathyroid adenoma in an 11-year-old girl: case report and literature review. AACE Clin Case Rep. 2021;7(1):51-56.
16. Allali YE, Hermetet C, Bacchetta J, et al. Presenting features and molecular genetics of primary hyperparathyroidism in the paediatric population. Eur J Endocrinol. 2021;184(2):347-355.