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Case Report

Decrement in bone mineral density after parathyroidectomy in a pediatric patient with primary hyperparathyroidism

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Abstract. Primary hyperparathyroidism (PHT) causes increased bone turnover, leading to reduction in bone mineral density (BMD). Parathyroidectomy is a definitive therapy and improves BMD in adult patients with PHT. However, there are no reports regarding alterations of BMD in pediatric or adolescent patients with PHT. Here, we report a case of a 13-yr-old boy with PHT who was referred to our institution for evaluation of hypercalcemia and hyperparathyroidism. Radiological investigation revealed an ectopic parathyroid adenoma below the right thyroid lobe. A minimally invasive radio-guided parathyroidectomy was successfully performed. We followed up the patient's BMD for three years both before and after parathyroidectomy. Over the course of three years, his BMD was steadily decreased, with z-scores of +0.506 at 13 yr and 9 mo, +0.162 at 14 yr and 9 mo, and –0.411 at 15 yr and 9 mo. BMD usually increases during peak height velocity in an adolescent and improves after parathyroidectomy in adult patients with PHT. However, our patient showed decreased BMD z-scores following parathyroidectomy. Therefore, the patient had an increased risk of fracture after parathyroidectomy and was followed up closely. Both height and BMD should be carefully evaluated after parathyroidectomy in pediatric and adolescent patients with PHT.

Key words: ectopic parathyroid gland, hyperparathyroidism, bone mineral density, short stature

Introduction

Primary hyperparathyroidism (PHT) affects 0.3% of the adult population worldwide, especially women. The diagnosis of PHT is based on characteristic biochemical abnormalities, such as persistent increases in serum calcium levels accompanied by elevated or abnormal intact parathyroid hormone (PTH) levels. PHT causes increased bone turnover, leading to reduction in bone mineral density (BMD). Parathyroidectomy is a definitive treatment for PHT, and BMD usually (although not always) improves in adult patients with PHT after parathyroidectomy. PHT is a rare condition in the pediatric population. An increase in BMD during an adolescent's PHV is important to ensure a peak bone mass, which is a critical risk factor for fracture. Here

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we report a case of a 13-yr-old boy with PHT, whose BMD was evaluated three years after parathyroidectomy during his PHV.

Case Report

A 13-yr-old boy complaining of abdominal pain was referred to a doctor for evaluation. Laboratory tests revealed hypercalcemia (11.9 mg/dL) and hypophosphatemia (3.1 mg/dL); however, no further examinations were performed at that time. Three weeks later, the patient experienced a second episode of abdominal pain and visited the same hospital, where tests revealed persistent hypercalcemia (12.4 mg/dL) and high serum intact-PTH levels (102 pg/mL). Ultrasonography of his abdomen revealed hydronephrosis and nephrocalcinosis on the right side. Consequently, the patient was referred to our institution for hyperparathyroidism evaluation.

The patient had no family history of endocrine disorders, including hypercalcemia and endocrine neoplasia. On examination, the patient's blood pressure was 108/58 mmHg, his pulse was 54 beats per min (bpm), and his respiratory rate was 18 breaths per minute; other vital signs were normal. The patient's height was 147.4 cm (−1.9 SD), weight was 32.8 kg (−1.8 SD), and body mass index (BMI) was 15.1 kg/m^2 (Fig. 1). A physical examination revealed no palpable masses on his neck. His penile length was 6 cm and his testes (volume: 5 ml) were in the scrotum. The Tanner stage of pubic hair was III. No other abnormal findings were observed.

Laboratory tests revealed persistent hypercalcemia (12.8 mg/dL), high serum intact-PTH levels (124 pg/mL), and hyperphosphatemia (1259 U/L) (Table 1). A bone X-ray scan showed no skeletal abnormalities, and Tanner-Whitehouse 2 (TW2)-20-bone analysis revealed a bone age of 12 years and 5 months. The lumbar (L2–L4) BMD at 13 yr and 9 mo was 0.628 g/cm^2 (z-score: +0.506). The patient underwent radiological investigations including contrast-enhanced

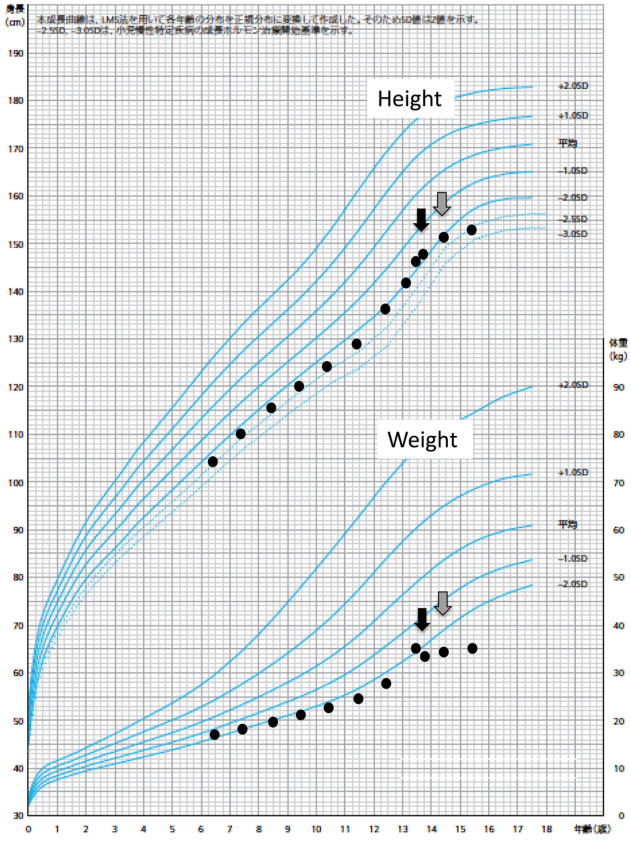

Fig. 1. Growth chart (representative of Japanese boys aged 0–18 yr). The patient's growth curve was just below the −2 SD line before the onset of PHT. Although pubertal development started normally, his growth spurt ceased early. The black and gray arrows show the time of disease onset and surgery, respectively.

computed tomography (CT), technetium-99m sestamibi (99mTc-MIBI), and single photon emission CT (SPECT) (Fig. 2A–D), which clearly revealed an ectopic parathyroid adenoma below the right thyroid lobe. Administration of cinacalcet was thus initiated to reduce calcium levels, and the dose was progressively increased to normalize the serum intact-PTH levels. The medication maintained patient's calcium levels below 11 mg/dL until surgery, although he developed side effects from cinacalcet treatment, such as nausea and diarrhea.

A minimally invasive, radio-guided parathyroidectomy was performed following

Table 1 Laboratory examinations

WBC	5500	/μl	Ca	12.8	mg/dL
Hb	15.3	g/dl	IP	3.8	mg/dL
Plt	40.7×10^4	/μl	T-cho	136	mg/dL
			CK	72	U/L
LDH	212	U/L	CRP	0.01	mg/dL
AST	29	U/L	LH	2.09	mIU/ml
ALT	13	U/L	FSH	1.77	mIU/ml
ALP	1259	U/L	TSH	2.842	μIU/mL
TP	7.7	g/dL	FT3	3.42	pg/mL
Alb	4.9	g/dL	FT4	1.12	ng/dL
BUN	12.5	mg/dL			
Cre	0.55	mg/dL	intact PTH	124	pg/mL
Na	139	mmol/L	HS-PTH	900	pg/mL
K	4.9	mmol/L	1,25(OH)VitD	196	pg/mL
Cl	102	mmol/L			

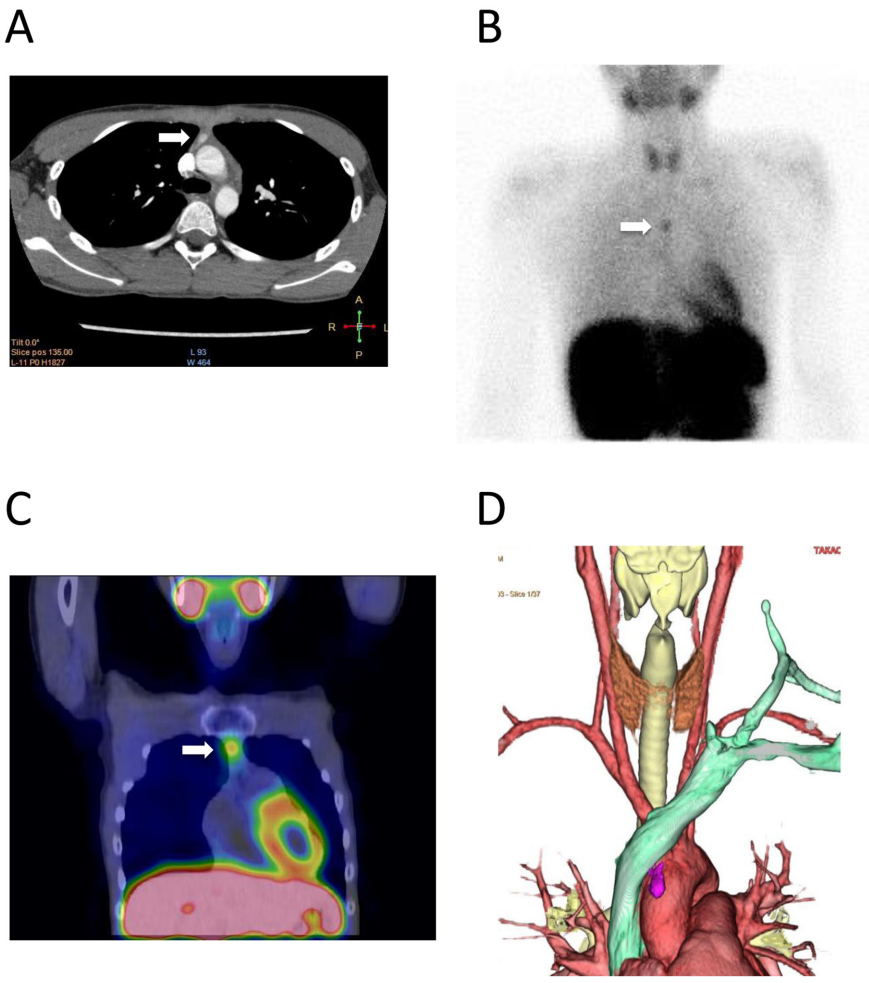

Fig. 2. Radiological findings. Contrast-enhanced computed tomography (CT) (A), technetium-99m sestamibi (B), single photon emission CT (C), and three-dimensional CT (D) scans demonstrate an ectopic parathyroid adenoma below the right thyroid lobe.

identification of the dissection area using a handheld γ-detection probe, and the adenoma was resected while PTH levels were intraoperatively monitored without additional dissection. His serum calcium levels decreased to 8.5 mg/dL 2 d after operation, but rapidly increased to > 9 mg/dL with intravenous calcium supplementation. The final pathology findings were compatible with parathyroid adenoma of the thymus. Two years after the surgery, the patient's calcium levels remained within the normal range. However, his growth spurt ceased earlier than expected, and he currently has a short stature (< −2.5 SD). His BMD at 14 yr and 9 mo and at 15 yr and 9 mo was 0.591 g/cm^3 (z-score: +0.162) and 0.640 g/cm^2 (z-score: –0.411), respectively. The 25(OH)D blood test that measures vitamin D levels yielded a value of 19 ng/mL, which indicates vitamin D deficiency.

Discussion

PHT is a rare condition in the pediatric population with an incidence of only 2–5 patients in 100,000 children, compared with an incidence of approximately 1 per 1,000 adults (1). Parathyroid adenomas are benign tumors and the most common cause of PHT. Multiple endocrine neoplasia 1 (MEN1) is the most common cause of parathyroid adenoma (2), and mutations in *MEN1* have been reported to cause multiple endocrine neoplasia, such as insulinoma and pituitary adenoma. Although we did not check for mutations in *MEN1* in the present case, we will conduct genetic evaluation of this gene if the patient presents with another endocrine neoplasia.

As pediatric PHT is a rare condition that often presents with nonspecific symptoms, such as fatigue, depression, and headache, diagnosis is frequently delayed, leading to end-organ damage. Some studies have reported that all symptomatic patients have end-organ damage (1). Nephrolithiasis has been frequently observed in pediatric patients with parathyroid adenoma (3). Although our patient had high calcium levels during the first episode of abdominal pain, his PHT levels were not evaluated. Hydronephrosis as a result of nephrolithiasis was found during the second episode of abdominal pain, leading to the diagnosis of PHT. Therefore, PHT should be considered when patients with nonspecific symptoms have high calcium levels, despite the rarity of this condition in the pediatric population.

In addition, ectopic parathyroid adenomas are extremely rare in the pediatric population, accounting for only 16% of the etiologies in adults with PHT (4). Precise localization is important for the successful treatment of ectopic parathyroid adenomas, as parathyroidectomy is a definitive treatment. Precise localization using modern radiological modalities, such as MIBI and SPECT scans, is necessary for minimally invasive parathyroidectomy procedures. Parathyroid adenomas have high metabolic rates relative to their size and a high affinity for labeled MIBI. Research has shown that parathyroid adenomas with higher serum PTH levels uptake significantly higher levels of 99mTc-MIBI (5). Notably, our patient had both high PTH levels and a high uptake of 99mTc-MIBI. Intraoperative procedures, such as PTH monitoring and γ-probe techniques, are also important during minimally invasive parathyroidectomy. The use of a multidisciplinary approach for performing parathyroidectomy is critical for improvement in patient outcomes.

Postoperatively, patients with PHT should be followed-up to determine the reestablishment of normal calcium levels, hypocalcemia, or hypercalcemia. Especially, pediatric PHT cases showed a significant risk of postoperative hungry bone syndrome (2). A patient is considered completely cured when normal calcium homeostasis is reestablished for more than 6 months after parathyroidectomy (6). In the present case, the patient's serum calcium levels transiently decreased below normal, but were normalized after intravenous calcium supplementation. The patient

maintained normal calcium levels and serum intact-PTH levels for more than 6 mo after parathyroidectomy. However, his growth spurt ceased earlier than expected, and his final height is < −2.5 SD. As the patient already had a short stature before parathyroidectomy, PHT is not likely to be the cause of his short stature. The patient experienced weight loss at the onset of the disease, which has not been restored postoperatively, although his condition was stable and his laboratory results were normal. He entered puberty at approximately 12 yr of age and his height was approximately 130 cm, suggesting that he entered puberty early. The timing of pubertal initiation and weight loss may have led to his short stature.

PHT causes increased bone turnover, which leads to reduction in BMD. Increased PTH in patients with PHT stimulates osteoclastic activity, resulting in conditions characterized by decreased BMD, such as osteoporosis and osteopenia. The patient's current BMD is similar to that measured before the procedure. Dual-energy x-ray absorptiometry (DXA) is an established method for assessing BMD. However, the results of DXA are influenced by bone size, and therefore, adjustments should be made for body size, especially in children (7). The current patient's BMD z-score was preoperatively normal. However, his BMD z-score was decreasing each year after parathyroidectomy. In contrast, many studies have reported an improvement in BMD after parathyroidectomy. The patient experienced his PHV during this follow-up period. Normally, there is a 25% increase in the peak bone mass during an adolescent's PH (8). PHT may have caused the lack of BMD gain in the patient, probably due to vitamin D deficiency, which is typically present in patients with PHT (9). The finding of a low 25(OH) vitamin D level in our patient (19 ng/mL) is consistent with vitamin D deficiency (10). Although cinacalcet was administered to decrease serum intact-PTH levels, vitamin D supplementation, to achieve the same outcome, should have been administered prior to cinacalcet. As the peak bone mass is a major determinant of fracture risk (11), vitamin D supplementation, periodic BMD measurements, and careful follow-ups for fracture are especially important for pediatric patients with PHT. The limitation of our study is that the evaluation of BMD in pediatric population is challenging. We used height adjustment equations for the evaluation of BMD (7). However, additional factors, such as the timing of puberty (sex hormones), should be considered for the evaluation of BMD.

Conclusion

We report a rare case of a 13-yr-old boy with ectopic parathyroid adenoma, which was successfully managed with a multidisciplinary approach combining input from pediatric endocrinologists, radiologists, and endocrine surgeons. Currently, only a few studies have investigated the changes in height and BMD in pediatric and adolescent patients with PHT after parathyroidectomy; therefore, future research in this area is required.

Conflict of Interest: The authors declare no conflicts of interest.

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