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CASE REPORT

A case of adolescent giant parathyroid adenoma presenting multiple osteolytic fractures and postoperative hungry bone syndrome

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Key Clinical Message

Primary hyperparathyroidism (PHPT) and postoperative hungry bone syndrome are very rare conditions in adolescents, and may be frequently misdiagnosed as a metastatic bone tumor. However, delay in diagnosis may lead to a fatal preoperative hypercalcemia and postoperative hypocalcemia. PHPT is a differential diagnosis of adolescent hypercalcemia and osteolytic fractures.

Keywords

Brown tumor, hungry bone syndrome, hyperparathyroidism, parathyroid adenoma, parathyroidectomy.

Introduction

Primary hyperparathyroidism (PHPT) is a relatively rare disease in adolescents with an incidence of 2–5 in 100,000 [1, 2], compared to that of adult with 1 in 500–2000 [2]. Brown tumors are rare focal osteolytic lesions that occur as an effect of excessive parathyroid hormone (PTH) on bone tissue in some patients with PHPT, and they appear most commonly as solitary lesions in the ribs, clavicle, pelvic girdle, and mandible [3]. In addition, hungry bone syndrome (HBS), that is profound (serum calcium <8.4 mg/dL) and prolonged (longer than 4th day postoperatively) hypocalcemia, which follows parathyroidectomy of severe PHPT as a result of extensive remineralization of bone tissue [4], is rarely developed (less than 13%) in PHPT patients [5–7].

In this report, we present a rare case of 16-year-old boy's pathological fractures of both proximal femur and right radius that was associated with a prolonged HBS after parathyroidectomy of parathyroid adenoma.

Case History

A 16-year-old boy was admitted after suffering severe both hip and right forearm pain during playing tennis that made him unable to walk. The plain radiographs and CT showed osteolytic fractured lesion in both femoral neck (Fig. 1A) and radial shaft (Fig. 1B). In addition, MRI revealed large T1-low and T2-high intensity changed lesion in his left proximal femur (Fig. 1A). The past medical history of the patient and his family was unremarkable. There was no familial history of primary hyperparathyroidism and no evidence of multiple endocrine neoplasia (MEN).

Laboratory data on admission were as follows (Table 1): hemoglobin: 17.4 g/dL, white blood cell: 10,800/mm^3,

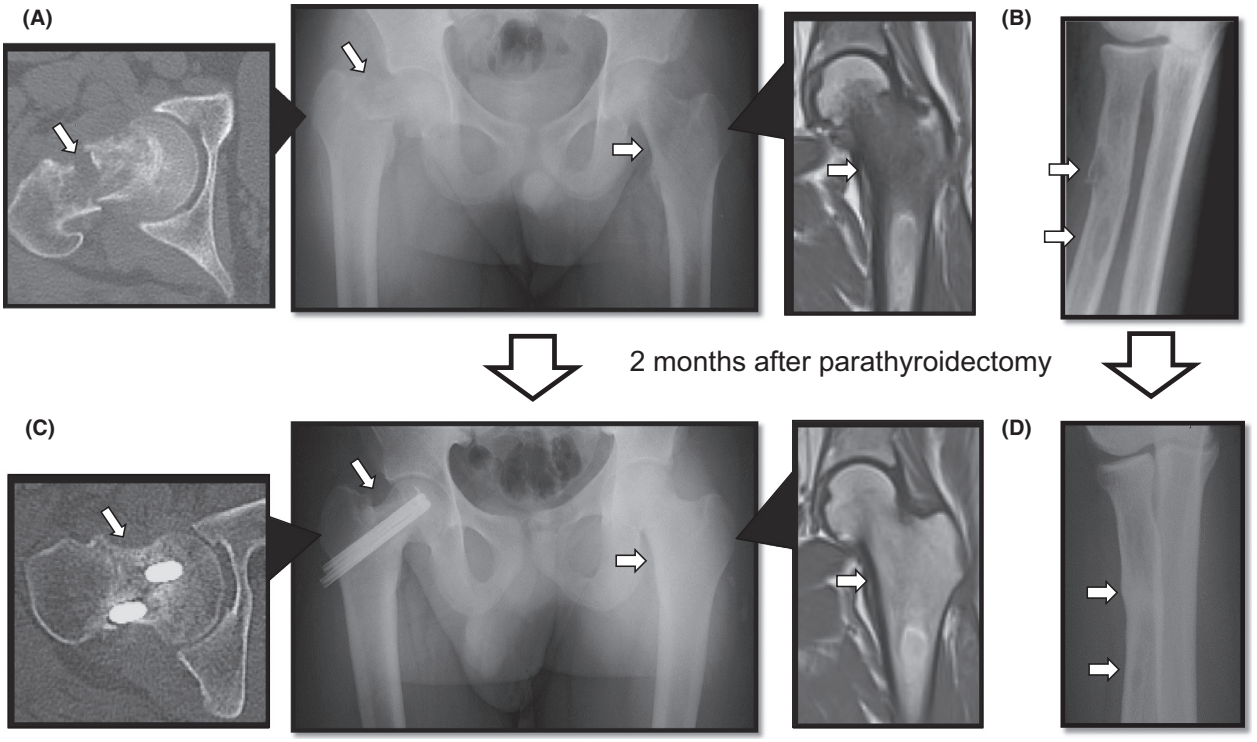

Figure 1. (A) CT, plain radiograph, and MRI of the bilateral hip joints; osteolytic fracture of the right hip, and massive intensity change of MRI associated with insufficient fracture of the left hip. (B) Multiple osteolytic lesions with fracture of the right forearm. (C) Bone union of the right hip and recovery of MRI intensity change of the left hip, and (D) Bone union of the right forearm 2 months after parathyroidectomy.

Table 1. Laboratory data of before and after the parathyroidectomy.

			Postope						
Laboratory findings	Initial	Preope	1 day	4 days	20 days	4 months	8 months	12 months	16 months
Ca (8.5–10.3 mg/dL)	11.4	11.7	8.4	7.3	7.6	9.4	8.8	9.4	8.6
P (2.5–4.5 mg/dL)	3.3	1.9	1.7	2.0	2.4	4.6	4.7	5.9	4.2
Mg (1.5–2.5 mg/dL)	2.4	1.5	1.2	2.4	2.4	2.5	2.5	2.3	2.2
ALP (68–430 U/L)	5890	1929	2214	3582	3056	453	424	411	278
Intact-PTH (−65 pg/mL)	1220	938.1		59.3	70.9	47	86	45	64
Urine Ca/Cr (<0.21)	0.84	0.42		0.09	0.01				0.02
Albumin (3.5–5.0 g/dL)	4.5	4.4			4.0	4.4	4.4	4.6	4.5
$1,25(OH)^2D$ (20.0–70.0 pg/mL)	105	96							
PINP (14.9–68.8 μg/L)	953				588		113		77.5
ucOC (<4.50 ng/mL)	>50				>50		9.49		5.84
TRACP-5b (170–590 mU/dL)	1370				221		321		165
Lumbar spine BMD (g/cm^2)	0.766					1.003	1.048	1.142	1.189
Peak reference (%)	61								
% increase from baseline						31.0	36.8	49.1	55.2
Left femoral neck BMD (g/cm^2)	0.569					0.922	1.026	1.089	1.200
Peak reference (%)	60								
% increase from baseline						62.0	80.3	91.4	110.9
Left total hip BMD (g/cm^2)	0.568					0.789	0.896	0.961	1.032
Peak reference (%)	53								
% increase from baseline					38.9		57.7	69.2	81.7

Ca, calcium; P, phosphorus; Mg, magnesium; ALP, alkaline phosphatase; PTH, parathyroid hormone; Cr, creatinine; $1,25(OH)^2D$, calcitriol; PINP, type I collagen N-terminal propeptide; ucOC, undercarboxylated osteocalcin; TRAP-5b, Isoform 5b of tartrate-resistant acid phosphatase; BMD, bone mineral density.

calcium: 11.4 mg/dL (normal: 8.5–10.3 mg/dL), phosphorus: 3.3 mg/dL (normal: 2.5–4.5 mg/dL), and alkaline phosphatase (ALP): 5890 U/L (normal range of 16-year-old male: 68–430 U/L) [8]. Open reduction internal fixation of right proximal femur was performed on the next day of injury. However, severe bilateral hip and right forearm pain remained, and serum calcium and ALP level increased continuously, which led us to speculate metastatic bone tumor. Nevertheless, tumor-related markers such as serum parathyroid hormone-related protein (PTHrP): 1.0 ρmol/L (normal: 0–1 ρmol/L), soluble interleukin-2 receptor (sIL-2R): 218 U/mL (normal: 145–519 U/mL), carcinoembryonic antigen (CEA): 1.6 ng/mL (normal: 0–5 ng/mL), cancer antigen 19-9 (CA19-9): 3 U/mL (normal: 0–37 U/mL), alpha fetoprotein (AFP): 3 ng/mL (normal: 0–10 ng/mL), squamous cell carcinoma (SCC): <1.0 ng/mL (normal: <2.0 ng/mL), and urinary beta 2-microglobulin: 100 μg/L (normal: 0–230 μg/L) were all within normal range. An open biopsy was performed from his right forearm for diagnosis and the result of biopsy was a fatty degenerated bone marrow without malignancy.

Accordingly, examination for other bone metabolism diseases was done (Table 1). Urinary calcium/creatinine ratio was 16.6 mg/dL/19.7 mg/dL = 0.84 (normal: <0.21); Serum intact parathyroid hormone (PTH): 1220 ρg/mL (normal: 12–87 ρg/mL); isoform 5b of tartrate-resistant acid phosphatase (TRAP-5b): 1370 mU/dL (normal: 170–590 mU/dL); bone alkaline phosphatase (bone ALP): 258 U/L (normal: 9.6–35.4 U/L); N-terminal type I procollagen propeptide (PINP): 953 μg/L (normal: 14.9–68.8 μg/L); undercarboxylated osteocalcin (ucOC): >50 ng/mL (normal: <4.50 ng/mL); calcitriol (1,25(OH)2D): 105 ρg/mL (normal: 20.0–70.0 ρg/mL). Other bone metabolism-related hormones such as free triiodothyronine (T3): 3.0 ρg/mL (normal: 2.0–3.4 ρg/mL); free thyroxine (T4): 1.0 ρg/mL (normal: 0.9–1.6 ρg/mL); thyroid-stimulating hormone (TSH): 0.67 μIU/mL (normal: 0.4–3.8 μIU/mL); cortisol: 9.1 μg/dL (normal: 4.3–20.0 μg/dL); and adrenocorticotropic hormone (ACTH): 8.0 ρg/mL (normal: <60 ρg/mL) (morning value) were all within normal range.

Extremely high urine calcium concentration, high serum intact-PTH levels, and high bone turnover led us to speculate hyperparathyroidism. Parathyroid tumor was confirmed by enhanced-CT and technetium-99 m sestamibi dual-tracer (subtraction) scintigraphy, which showed a hot spot accumulation in the right lower parathyroid gland (Fig. 2A and B). In addition, bilateral renal stone and salt and pepper appearance in the skull were observed by enhanced-CT, both of which are features of hyperparathyroidism. The patient also had a severe and generalized osteoporosis. Regional bone mineral density (BMD) examined by dual-energy X-ray absorptiometry (DEXA) was as follows (L2-4 lumbar spine: BMD 0.766 g/cm^2, peak reference 61%; left femoral neck: BMD 0.569 g/cm^2, peak reference 60%; left total hip: BMD 0.568 g/cm^2, peak reference 53%; and left total forearm: BMD 0.406 g/cm^2, peak reference 59%) (Table 1). The treatment of progressive hypercalcemia was performed simultaneously. The effect of abundant hydration with saline infusion combined with zoledronate and elcatonin administration, remained temporary (Fig. 3). The preoperative diagnosis was multiple brown tumors and secondary osteoporosis associated with PHPT, and parathyroidectomy of right lower parathyroid grand was performed.

Macroscopically, hypervascular soft reddish nodule with capsule (22 × 16 × 15 mm) was found inferior–posterior to the right lobe of the thyroid gland (Fig. 2C and D). Microscopically, the tumor was composed of uniform, follicular cells and was diagnosed as parathyroid adenoma (Fig. 2E). The removal of tumor resulted in severe HBS, which required long-term and large amount of calcium, magnesium, and vitamin D supplementation (Fig. 3). Immediately, after surgery, the patient suffered numbness of face and muscular cramps in the limbs, which were consistent with hypocalcemia, whereas a severe systemic pain rapidly improved from the next day of the parathyroidectomy. Serum calcium level decreased from 11.7 to 7.3 mg/dL, and intact-PTH levels decreased from 938.1 to 59.3 pg/mL on the 4th day of operation compared to just before the surgery. The patient required intravenous calcium (3–5 g/day) and magnesium (2–6 g/day) infusion with oral calcitriol (1–3 μg/day) supplementation until the 28th postoperative day, and then changed to a high dose of oral calcium (1.2 g/day) and calcitriol (3 μg/day) supplementation, which were gradually decreased owing to the serum ALP levels. After the parathyroidectomy, formation of callus was observed after 3 weeks, and bone union with recovery of MRI intensity change was observed after 2 months (Fig. 1C and D). In addition, a rapid improvement in bone mineral density was observed (Table 1, Fig. 4). At 16 months postparathyroidectomy, serum calcium, phosphorus, intact-PTH, and ALP levels decreased to the normal range, and the patient had no pain and limitation on the activities of daily life.

Discussion

Although the incidence is very rare, symptoms of PHPT in children are more common and more severe than in adults [9]. Among patients with PHPT, adolescents presented symptoms in 70–90% of cases, while adults presented symptoms in 20–50% [1, 2, 10, 11]. Moreover, 33% of adolescents with PHPT suffered bone lesions,

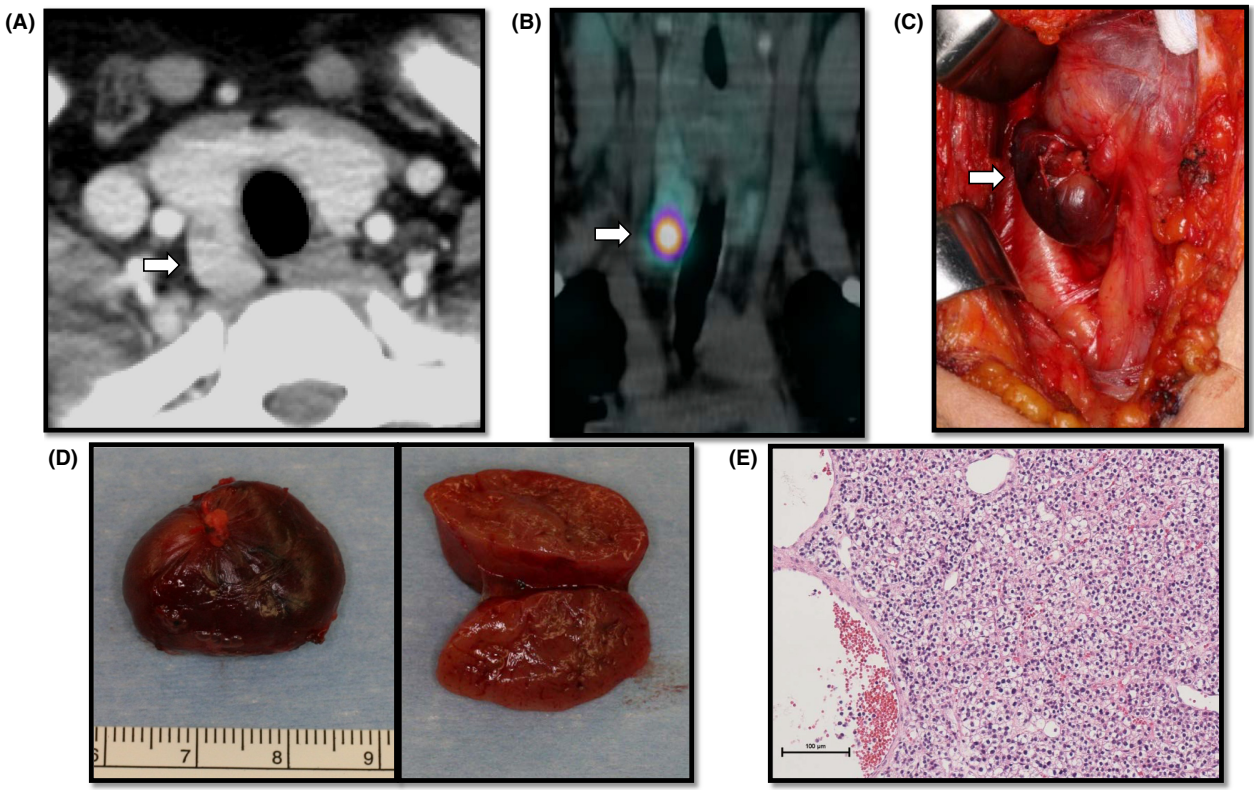

Figure 2. (A) Enhanced CT and (B) 99mTc-MIBI scintigraphy showing enhancement and hot spot accumulation in the right lower parathyroid gland. (C, D) Hyper-vascular soft swollen reddish parathyroid gland (22 × 16 × 15 mm)s observed just behind the right lobe of thyroid gland. (E) Histopathological examination of parathyroid tissue tumor revealed uniform follicular cells and was diagnosed as parathyroid adenoma (hematoxylin and eosin staining, ×200).

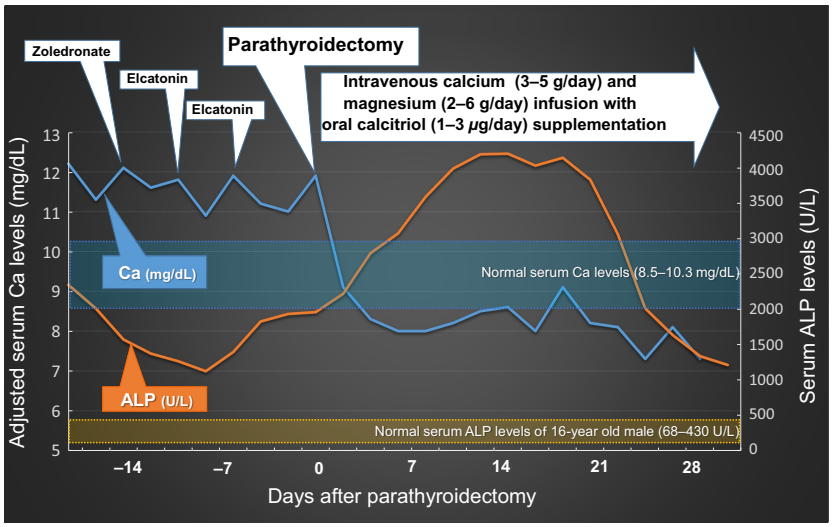

Figure 3. Drastic change in serum Ca and ALP levels (hungry bone syndrome) during the perioperative treatment of primary hyperparathyroidism.

for example, fractures and brown tumors [9], which were relatively high compared to the previous reports in adults (4.5%) [3]. This may be partially due to the fact that skeletal growth during adolescent requires larger amounts of calcium and phosphorus than that of adults [12], so pubertal growth may be considered as

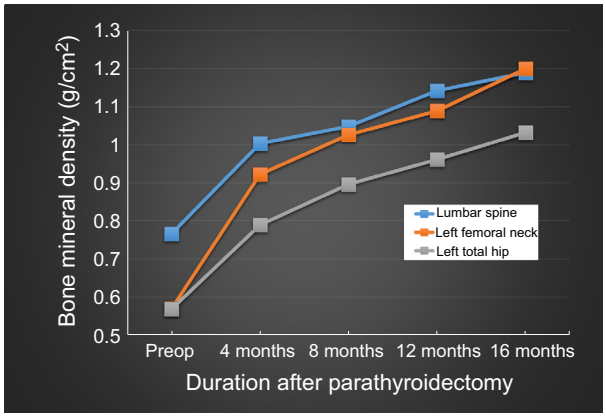

Figure 4. Rapid recovery of regional bone mineral density after parathyroidectomy.

one of the risk factors of bone lesions of PHPT. Considering HBS, previous reports demonstrated that the risk factors of HBS are higher preoperative levels of serum calcium, PTH, and ALP [6, 13, 14]. In addition, patients with a radiological evidence of skeletal involvement developed a higher rate of HBS (25–90%) compared to the patients without it (0–6%) [15–17]. Patients with a single adenoma of >2 g developed higher rate of HBS (68.8%) compared with patients with a single adenoma of <1 g (14.3%) [7]. In this case, the patient fulfilled all these previously described risk factors, so abundant infusion of calcium and magnesium with oral calcitriol supplementation should be prepared before parathyroidectomy. As for the correlation between histopathology and incidence of HBS, 80% of the adolescent with PHPT had a single adenoma [9], which was comparative to that of adult (88.6%) [10, 18], and there are no available data indicating the relationship between histopathology and incidence of the development of HBS [6, 7].

The critical point in the treatment of adolescent PHPT is early diagnosis [9], although there were several difficulties in the diagnosis in this case. Firstly, PHPT is very rare in adolescent. Secondly, brown tumors are more common in the ribs, clavicle, pelvic bones, and mandible than in long bones [3, 14], and often found as a solitary tumor [15–17]. Moreover, extremely high serum calcium and ALP levels led us to speculate a metastatic bone tumor during the initial stage.

Severe pain in the affected lesions may be caused by the extensive bone resorption induced by excessive PTH, and this pain could not be reduced by a painkiller, but rapidly decreased after parathyroidectomy. In addition, a rapid bone union was observed after parathyroidectomy, so consideration of internal fixation should be minimized to avoid redundant invasion.

Conclusions

We experienced a rare case of adolescent PHPT associated with multiple fractures of long bones and prolonged severe postoperative HBS. The diagnosis of multiple osteolytic disease of adolescent, serum intact-PTH levels should be measured considering the possibility of PHPT; and abundant intravenous calcium and magnesium infusion with oral calcitriol supplementation should be prepared for the treatment of HBS, immediately after parathyroidectomy.

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Conflict of Interest

The authors declare that they have no competing interests.

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