Case Report

Somatic HRPT2 Mutation (Arg234X) of Parathyroid Carcinoma Associated with Slipped Capital Femoral Epiphysis: A First Case Report

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A 14-year-old boy was admitted to the orthopedic clinic of Rajavithi Hospital complaining of pain in the left hip. A year earlier, pain had developed in his left joint and had gradually increased in intensity in both hips. A month before he was referred, radiographs obtained at another hospital showed bilateral slipped capital femoral epiphysis (SCFE). The patient's biochemical laboratory data showed hypercalcemia, hypophosphatemia, and a high level of intact parathyroid hormone (iPTH) compatible with primary hyperparathyroidism. HRPT2 gene analysis found heterozygosity for c.700 C>T mutation (Arg234X) of HRPT2 gene at exon 7. This is the first report in the literature about somatic mutation of the HRPT2 gene of parathyroid carcinoma associated with slipped capital femoral epiphysis.

Keywords: *HRPT2, Parathyroid carcinoma, Slipped capital femoral epiphysis (SCFE)*

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Primary hyperparathyroidism (PHP) is an unusual disease in children and adolescents. Associations between PHP and slipped capital femoral epiphysis (SCFE) are rare, and so far only six cases have been reported in the literature[1-6]. The cause of SCFE is unknown, but it is most probably caused by multiple factors including local trauma, obesity overcoming the physeal plate, inflammatory factors, endocrine abnormalities, hypothyroidism, panhypopituitaryism, gonadal conditions, renal osteodystrophy, and growth hormone therapy. The possibility of endocrine abnormalities should certainly be considered when a child presents with bilateral SCFE. In Thailand, bilateral SCFE with hormonal dysfunction is rare, and only seven cases (9 hips) of this condition in Ramathibodi Hospital have been reported: five boys (average age 12.5 years) and two girls (average age 13 years)[7]. No endocrine disorder was observed in any of these cases. Herein, we report the first case of PHP due to parathyroid carcinoma with novel somatic mutation (Arg234X) associated with SCFE in the literature.

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Case Report

A 14-year-old boy presented in the orthopedic clinic of Rajavithi Hospital with left hip pain. A year earlier, pain had developed in his left joint and had gradually increased in intensity in both hips. A month before he was referred, radiographs obtained at another hospital showed bilateral slipped capital femoral epiphysis (SCFE). The patient was the first of his parents' two sons; his brother did not have the condition. A diagnosis of nephrolithiasis had been made 4 months earlier, when the patient had been suffering

from right flank pain for two months. On examination, he appeared well: his height was 148 cm, his weight was 37 kg, and he was noted to have normal developmental milestones. His gait was antalgic, he had pain with internal rotation of the left hip, and he had a limited range of passive and active motion of the left hip. Measurement of his legs showed that they were of equal length at 77 cm. His vital signs, including temperature, appeared normal. Examination of the thyroid gland showed a nodule of about 3.5 cm in diameter with cystic consistency; he had no lymphadenopathy. Other examinations were normal: pubic hair was in Tanner stage 2, and the 3 cm diameter of both testes was appropriate for his age. The results of routine laboratory tests are shown in Table 1 and those of hormonal tests are shown in Table 2.

Table 1. Result of routine laboratory tests

Laboratory	Value
Complete blood count	
White blood cell counts	9,600
Neutrophils	80%
Lymphocyte	20%
Hemoglobin	12.8
Hematocrit	38.6
Platelets	452,000
Urine analysis	
Specific gravity	1.005
pH	7
Protein	Negative
Glucose	Negative
Ketone	Negative
RBC	0-1
WBC	0-1
Crystal	Negative
Blood chemistry	
Fasting blood sugar (mg/dL)	91
Blood urea nitrogen (mg/dL)	8
Creatinine (mg/dL)	0.6
Calcium (mEq/L)	17.1
Phosphate (mEq/L)	2.3
Magnesium (mEq/L)	1.9
Sodium (mEq/L)	136
Potassium (mEq/L)	4
Chloride (mEq/L)	101
Bicarbonate (mEq/L)	23
Albumin (mg/dL)	4.2

Imaging studies were performed during the admission period. Radiographs of the hips and pelvis showed bilateral slipped capital femoral epiphysis. Radiographs of both hands showed subperiosteal bone resorption (Fig. 1A). Three-Dimensional Computed Tomography (3D-CT) scanning of the hip suggested slipped capital femoral epiphysis (Fig. 1B). He had hypercalcemia, hypophosphatemia, and a high level of intact parathyroid hormone suggesting primary hyperparathyroidism. Magnetic resonance imaging of the neck after gadolinium revealed an oval mass in the left thyroid lobe. The mass was slightly hypersignal on T1W, hypersignal on T2W with homogenous enhancement measuring 1.7 by 3 cm in size with cystic appearance (Fig. 2A), and there was no neck lymph node enlargement. Sestamibi parathyroid scan for pre-operative parathyroidectomy was performed. These scans also showed increased uptake in the left upper pole of the thyroid gland (Fig. 2B).

Two weeks after the initial evaluation, when the hips had been pinned, the patient was referred to Otolaryngology-Head and Neck for surgery, and fine needle aspiration of neck mass was performed. The

Table 2. Results of hormonal test

Endocrine laboratory value	Value	Reference
Thyrotropin (TSH) (mIU/L)	1.43	0.27-4.20
Free thyroxin (FT_4) (ng/dl)	1.02	0.93-1.7
Triiodothyronine (T_3) (ng/dl)	1.46	0.8-2.0
Intact parathyroid hormone (iPTH) (pg/ml)	1,164	15-65
Follicle-stimulating hormone (FSH) (mIU/ml)	3.70	1.5-12.4
Luteinizing hormone (LH) (mIU/ml)	3.40	1.7-8.6
Testosterone (T) (nmol/l)	10.50	9.9-27.8
Urine 24 hour vanillylmandelic acid (VMA) (mg/d)		<10
I	5.90	
II	5.10	
III	4.10	

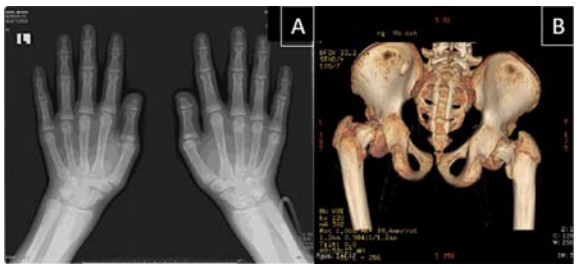

Fig. 1 Radiographs of parathyroid carcinoma patient: A) picture showing both hands subperiosteal bone resorption, B) three-dimensional computed tomography (3D-CT) scanning of the hip suggesting slipped capital femoral epiphysis.

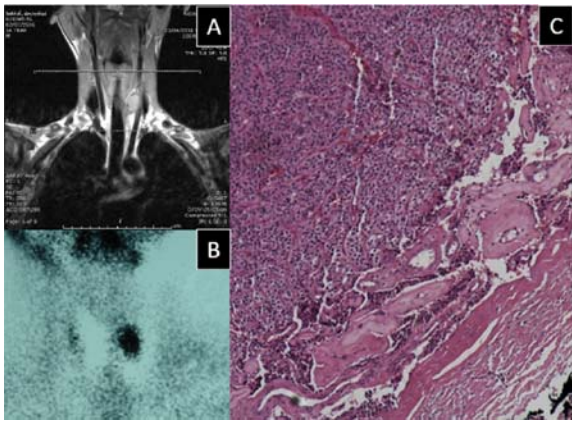

Fig. 2 A) Magnetic resonance imaging (T1W) showing hypersignal homogenous enhancement in left thyroid lobe. B) Sestamibi parathyroid scan showing increased uptake in left thyroid lobe. C) Parathyroid mass in left thyroid lobe showing parathyroid carcinoma with capsular invasion.

diagnostic cytology showed epithelium neoplasm (either thyroid or parathyroid in origin). Left thyroid lobectomy, left parathyroidectomy, central nodes dissection and partial thymectomy were carried out because the surgeon suspected parathyroid carcinoma. Surgery is the most effective therapy for parathyroid carcinoma, with complete resection of the primary lesion. The pathologic results showed parathyroid carcinoma with capsular invasion (Fig. 2C).

Parathyroid tissue was frozen in liquid nitrogen immediately after surgical removal and stored at -80°C or below. Peripheral blood was collected into EDTA anti-coagulant tubes and stored at -80°C. DNA was extracted from the frozen tissue and peripheral blood leucocytes according to standard procedures. RNA was extracted from the frozen tissue using TRI

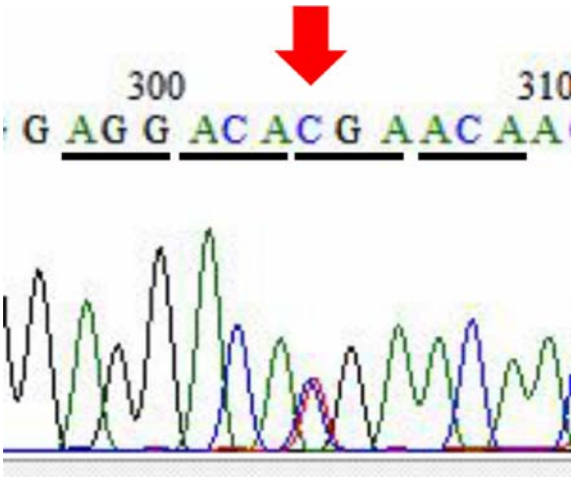

Fig. 3 Somatic heterozygote mutation of HRPT2 gene at c.700 C>T mutation (Arg234X).

Reagent (Sigma-Aldrich Corporation, St. Louis, MO) in accordance with the manufacturer's protocol. Real time polymerase chain (20 µl) reaction (RT-PCR) by SyBrGreen® Roche® used primer specific sequences for HRPT2, each designed to target on the basis of a full search of the GenBank database (www.ncbi.nlm.nih.gov) with sensitivity of 93.0% and specificity of 100.0%. We found only somatic mutation at c.700 C>T mutation (Arg234X) in exon 7 of the HRPT2 gene. We double checked by direct sequencing this mutation in forward and reverse PCR products to confirm this mutation (Fig. 3).

On the fourth day after the operation, the patient developed hypocalcemia. He was treated intravenously with calcium gluconate and orally with vitamin D and recovered in two days. At follow-up visits after 3 months, 6 months and 1 year, the calcium, phosphorus and parathyroid levels were in the normal range and manual palpation failed to detect any nymph nodes. His parents' HRPT2 mutation was negative.

Discussion

Parathyroid carcinoma accounts for less than 1% of patients with primary hyperparathyroidism, and it is more common in Japan (accounting for 5% of patients with primary hyperparathyroidism) than in western countries. In 1999, the National Cancer Data Base reported 286 cases of parathyroid carcinoma, the largest series to date. At present, parathyroid carcinoma has been found in only 711 cases, as reported in the literature. In our recent report we found 15.38% (4/26 cases)[8].

The pathogenesis of the parathyroid

hormone on slipped capital femoral epiphysis was introduced by Crabb et al[9], and Barling et al[10] claim that PTH receptors are found in large numbers in the hypertrophied cells zone. This is the same zone where the slipping of the upper femoral epiphysis occurs. Kawashima et al[11] recently proved that PTH plays a significant pivotal role in the induction of various metalloproteinases in ossifying cartilage by controlling cartilage matrix degradation during endochondral bone formation. The increased and decreased values of PTH in patients without hyper- or hypoparathyroidism are what may trigger the slipping process.

The markedly elevated levels of PTH observed in this patient are compatible with the diagnosis of long-standing primary hyperparathyroidism due to parathyroid carcinoma, which has been hypothesized as a cause of bilateral slipped capital femoral epiphysis. Further investigation in this patient should include genetic testing of parathyroid carcinoma in order to attempt to detect germline mutations in familial genetic inheritance such as Cyclin D1 or PRAD1 (parathyroid adenoma 1), RB (retinoblastoma), p53 tumor suppressor gene and HRPT2 (parafibromin).

In HRPT2 mutation, a recent reviewed study[12] found that prevalence of HRPT2 in parathyroid carcinoma was 77% compared with 0.8% in parathyroid adenoma, and these results are similar to those of our recent report[8] which found 100% in parathyroid carcinoma and 0.095% in parathyroid adenoma. Fortunately, we found novel somatic mutations in this patient that may describe a phenotype of slipped capital femoral epiphysis. We were not familiar with the mechanism of HRPT2 and the slipping process of femoral epiphysis. However, based on our findings above, parathyroid pathogenesis could be the cause of this process. We need further investigation into the slipping process and multi-gene involvement in order to prove this hypothesis.

What is already known on this topic ?

Primary hyperparathyroidism in children is unusual disease.

Slipped capital femoral epiphysis (SCFE) with primary hyperparathyroidism should be considered for hormonal dysfunction but do not found any endocrine disorder in previous report in Thailand.

What this study adds ?

Bilateral SCFE with primary hyperparathyroidism is rare disorder.

HRPT2 mutation is tumor suppressor gene in parathyroid carcinoma.

The novel somatic mutation of HRPT2 in parathyroid tissue that drive PTH level plays in ossifying cartilage in hypertrophied cells zone during bone growth development and may trigger the slipping process of femoral necks.

Potential conflicts of interest

None.

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รายงานผู้ป่วยมะเร็งต่อมพาราไทรอยด์ที่มาด้วยอาการหัวกระดูกต้นขาเคลื่อนหลุดที่มีการกลายพันธุ์ของจีน HRPT2 จากเนื้อเยื่อ: รายงานผู้ป่วยรายแรกของประเทศไทย

สถิตย์ นิรมิตรมหาปัญญา, ชัยชาญ ดีโรจนวงศ์, วีระศักดิ์ ศรินนภากร, ทองคำ สุนทรเทพวรากุล, สาริณี ปิงสุทธิวงศ์, พรเอก อภิพันธ์, ยุทธนา แสงสุดา

รายงานผู้ป่วยเด็กชายอายุ 14 ปี เข้ารับการรักษาที่แผนกกระดูกโรงพยาบาลราชวิถี ด้วยเรื่องปวดบริเวณข้อสะโพกซ้าย โดยเมื่อประมาณ 1 ปีก่อนมีอาการปวดบริเวณสะโพกซ้ายและมีอาการรุนแรงเพิ่มขึ้นเรื่อยจนกระทั่งปวดสะโพกทั้งสองข้าง ก่อนส่งตัวมารักษา 1 เดือน ตรวจพบความผิดปกติจากภาพฉายรังสีบริเวณหัวกระดูกขาท่อนบน (femur) ทั้งสองข้างเลื่อนออกจากแนวกระดูก ผลตรวจทางห้องปฏิบัติการพบแคลเซียมในเลือดสูงฟอสฟอรัสในเลือดต่ำและฮอร์โมนพาราไทรอยด์สูงเข้าได้กับโรคต่อมพาราไทรอยด์ทำงานมากผิดปกติชนิดปฐมภูมิ ตรวจพบการกลายพันธุ์ของจีน HRPT2 แบบ Heterozygous ตรงตำแหน่ง c.700 C>T (Arg234X) ของ exon7 บนจีน HRPT2 ซึ่งเป็นรายงานผู้ป่วยรายแรกที่พบการกลายพันธุ์จากเนื้อเยื่อร่างกาย (somatic mutation) ที่ได้รับการวินิจฉัยว่าเกิดจากมะเร็งต่อมพาราไทรอยด์ร่วมกับหัวกระดูกขาท่อนบน (femur) ทั้งสองข้างเลื่อนออกจากแนวกระดูก