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Original Article

A Case of Primary Hyperparathyroidism in Childhood Found by a Chance Hematuria

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Abstract. A 10-yr-old boy visited Minoh City Hospital complaining of gross hematuria. Laboratory investigations revealed hypercalcemia, hypophosphatemia, and elevated serum levels of parathyroid hormone. A stone was found in the right ureter with drip infusion pyelography. A parathyroid adenoma was successfully diagnosed with computed tomography, ultrasonography, and methoxy-2-isobutyl isonitrile (MIBI) scintigraphy. Multiple endocrine neoplasia was ruled out by normal results of endocrine laboratory examinations. Extracorporeal shock wave lithotripsy was performed to treat the urolithiasis, and the parathyroid adenoma was surgically removed. Primary hyperparathyroidism is rare in childhood; however, this case suggests that gross hematuria is an important sign of hyperparathyroidism.

Key words: hyperparathyroidism, hematuria, calcium, phosphate, bone mineral density

Introduction

Primary hyperparathyroidism is characterized by hypercalcemia and hypophosphatemia caused by increased secretion of PTH. This disease is rare in children. In Japan, from 1980 through 1989, primary hyperparathyroidism was diagnosed in 1241 patients, of whom 3% were younger than 10 yr (1). To our knowledge, the youngest patient with primary hyperparathyroidism caused by adenoma was 9 yr old (2–4). On the other hand, kidney stones are present in more than half of cases of primary hyperparathyroidism in patients younger than 30 yr (2), which suggests that kidney stone is an important sign of primary hyperparathyroidism. Hypercalcemia with hypophosphatemia is a hallmark of primary hyperparathyroidism. However, serum phosphate levels are regulated by many factors, including dietary intake. Serum phosphate levels sometimes remain in the normal range in patients with primary hyperparathyroidism. Here, we present a boy with gross hematuria because of urolithiasis derived from hypercalcemia caused by a parathyroid adenoma. In this case, serum phosphate levels were slightly low in the presence of increased serum levels of PTH.

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Case Report

A 10-yr-old boy visited Minoh City Hospital complaining of painless gross hematuria. We failed to detect urolithiasis with abdominal ultrasonography, and the hematuria soon resolved. Five months later, the patient returned to the outpatient clinic of the department of pediatrics after a second episode of gross hematuria. This time, a stone was discovered in the right ureter with drip infusion pyelography. There was no evidence of hydronephrosis. At the same time, laboratory investigations revealed hypercalcemia, hypophosphatemia, and elevated serum levels of PTH. These findings suggested the presence of hyperparathyroidism. The past medical history and familial history indicated no evidence of urolithiasis or hypercalcemia. One month later, the patient visited again, complaining of right flank pain and was admitted to the division of urology for treatment of urolithiasis.

On physical examination, no abnormal signs were found. The right flank pain was intermittent and was not associated with tenderness. Laboratory investigations showed an elevated serum calcium level of 11.5 mg/dl (normal range, 8.9–10.7 mg/dl), a low serum phosphate level of 3.3 mg/dl (normal range, 3.6–5.6 mg/dl), an elevated serum intact-PTH level of 225 pg/ml (normal range, 15–50 pg/ml), an elevated serum $1,25(OH)_2D$ level of 152 pg/ml (normal range, 25–45 pg/ml), and a normal serum 25-(OH)D level of 23.4 ng/ml (normal range, >20 ng/ml). Endocrinological investigations revealed a normal serum epinephrine level of 0.03 ng/ml (normal range, <0.17 ng/ml), a serum norepinephrine level of 0.10 ng/ml (normal range, 0.15–0.57 ng/ml), a serum dopamine level of less than 0.02 ng/ml (normal range, <0.03 ng/ml), a serum calcitonin level of 32 pg/ml (normal range, 15–86 pg/ml), a serum gastrin level of 75.3 pg/ml (normal range, 40–140 pg/ml), a urine homovanillic acid level of 4.9 μg/mg·cr (normal range, 1.6–5.5 μg/mg·cr), and a urine vanillylmandelic acid level of 3.9 μg/mg·cr (normal range, 1.2-4.9 μg/mg·cr). These findings ruled out multiple endocrine neoplasia (MEN). A spot urine test showed an elevated calcium/creatinine ratio of 388 mg/g·Cr (normal range, <250 mg/g·Cr) and a normal fractional excretion of calcium of 2% (normal range, >1%). Familial hypocalciuric hypercalcemia (FHH) (5) was unlikely because of the normal fractional excretion of calcium.

The patient had normal renal function, as shown by a normal serum blood urea nitrogen concentration of 16 mg/dl and a serum creatinine level of 0.4 mg/dl. Examination of metabolic bone markers showed an elevated serum bone-specific alkaline phosphatase (BAP) level of 179.1 U/l (normal range, 80–100 U/l) and an elevated urine N-terminal telopeptide of type I collagen crosslinks (NTx) level of 2330 nmol BCE/mmol·Cr (normal mean value, 450 nmol BCE/mmol·Cr). Dual energy X-ray absorptiometry (DXA) showed a low bone mineral density at the L2–4 vertebrae (0.497 g/cm^2; Z score = –3.2). When he was 10 yr and 7 mo, his height and body weight were 137 cm (–0.4 SD) and 32 kg respectively. The tubular reabsorption of phosphate (%TRP) was calculated to be 91% (normal range, 85–90%), and the ratio of the renal tubular maximum reabsorption of phosphate to the glomerular filtration rate (Tmp/GFR) was 3.9 mg/dl (normal range, 2.3–4.3 mg/dl). The nephrogenic cyclic adenosine monophosphate (cAMP) level was 2.76 nmol/100 ml GFR (normal range, 1.42 ± 0.71 nmol/100 ml GFR).

Ultrasonography on admission revealed urolithiasis of the right ureter with hydronephrosis of the right kidney. Extracorporeal shock wave lithotripsy was performed twice. The stones disappeared, and the hydronephrosis resolved.

Cervical ultrasonography revealed a 15 × 10 × 3 mm low echoic lesion in the part of behind the right thyroid gland (Fig. 1). Cervical computed tomography showed a low-density

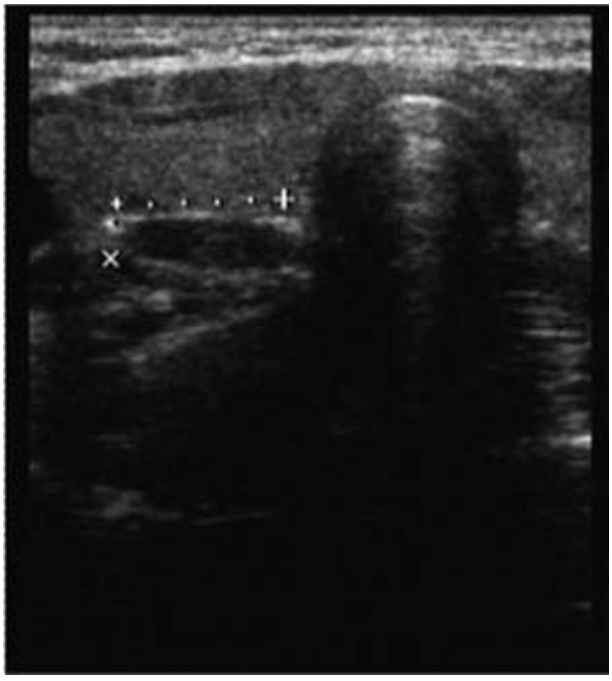

Fig. 1 Cervical ultrasonography (transverse) showed a 15 × 10 × 3 mm low echoic lesion in the posterior part of the right thyroid gland.

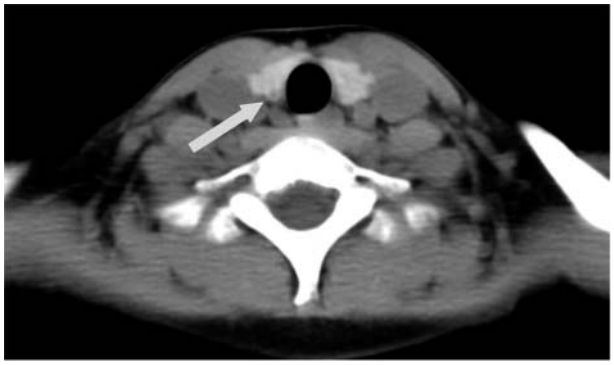

Fig. 2 Cervical CT showed a low-density nodule in the posterior part of the right thyroid gland without infiltration to surrounding organs.

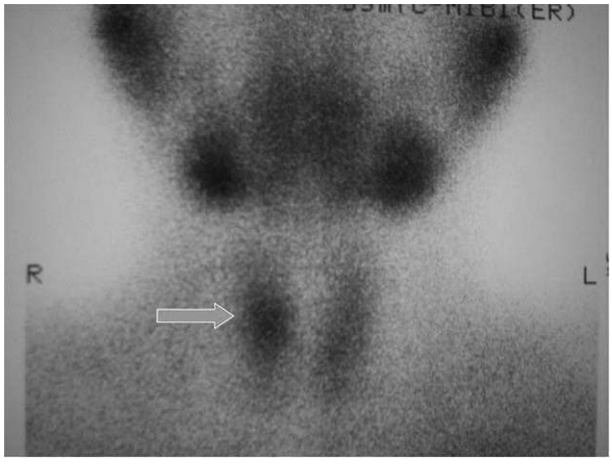

Fig. 3 MIBI scintigraphy showed a focus of MIBI accumulation in the right part of thyroid gland.

nodule at the same location without invasion of the surrounding organs (Fig. 2). Methoxy-2-isobutyl isonitrile (MIBI) scintigraphy showed a focus of MIBI accumulation in the right part of the thyroid gland (Fig. 3). However, abdominal ultrasonography showed no abnormal signs. On the basis of these findings, parathyroid adenoma was diagnosed.

Parathyroidectomy was performed without complications. Pathological examination revealed that the chief cells had proliferated homogeneously with a trabecular pattern and an alveolar pattern. This finding was compatible with parathyroid adenoma. There was no evidence of malignancy.

On the first postoperative day, the patient complained of numbness of the hands and legs. At that time, the serum calcium level had decreased to 8.2 mg/dl, and thus we administered an injection of calcium gluconate. The numbness resolved immediately, and the serum calcium increased to 9.5 mg/dl. The patient was discharged on the fifth postoperative day without complications.

Nine months after the operation, the serum PTH level had increased to 102 pg/ml. However, the laboratory studies showed normal serum calcium (8.9 mg/dl), normal serum phosphate levels (5.0 mg/dl), elevated %TRP (95%) and Tmp/GFR (5.7 mg/dl). Serum BAP and urine NTx levels improved to 138 U/l and 751 nmol

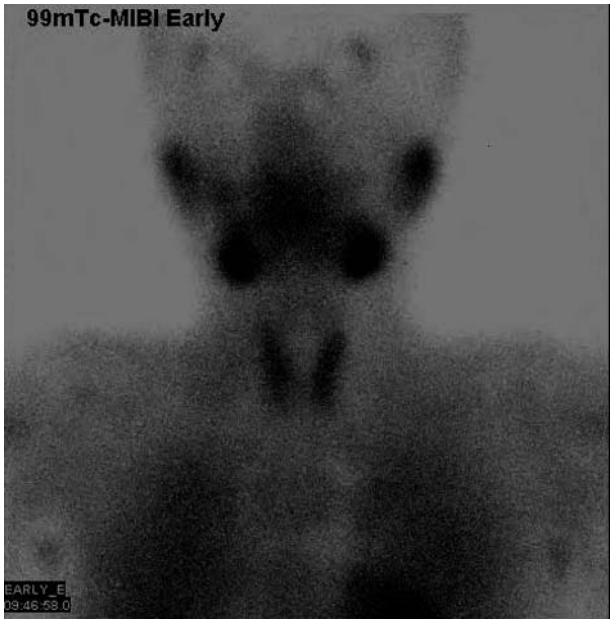

Fig. 4 MIBI scintigraphy after surgery showed no MIBI accumulation.

BCE/mmol·Cr, respectively. The DXA scan showed an increase in bone density in the lumbar spine (L2–4) to 0.555 g/cm^2 (Z score = –2.7). Contrast-enhanced computed tomography showed no signs of parathyroid adenoma, and MIBI scintigraphy revealed no abnormalities (Fig. 4). Recent laboratory studies (10 months after the operation) showed a decrease of the serum level of PTH to 54.3 pg/ml, a normal serum calcium of 9.4 mg/dl, and a low urine calcium creatinine ratio of 0.047. Serum phosphate level became normal (5.3 mg/dl). Tmp/GFR and %TRP values were 5.7 mg/dl and 94.8%, respectively. These values were slightly increased compared to the laboratory data on admission.

Discussion

Primary hyperparathyroidism is most frequent in the sixth decade of life in postmenopausal women (6). In Japan, from 1980 through 1989, primary hyperparathyroidism was diagnosed in 1241 patients, of whom 38 (3%) were younger than 10 yr (1). Of the 30 patients with primary hyperparathyroidism diagnosed at our hospital from 1981 through 2005, 2 patients, including the present patient, were younger than 10 yr (7). In childhood, primary hyperparathyroidism might be caused by several endocrinopathies with a genetic basis, such as MEN type 1 or 2 (6). In our patient, results of endocrinological investigations ruled out MEN.

Urolithiasis is much less common in children than in adults, with an incidence 0.7 to 1.6% in Japan (8). Children with urolithiasis may have metabolic abnormalities, including cystinemia, oxalosis, and primary hyperparathyroidism. The incidence of renal stone diseases was higher in the 1970s to 1980s than in recent years. This high incidence was probably because the disorder is currently recognized earlier while still asymptomatic. Nevertheless, urolithiasis remains a major complication of primary hyperparathyroidism (9). In one report, 6% of children with urolithiasis had primary hyperparathyroidism (10). On the other hand, urolithiasis is present in more than 50% of patients with primary hyperparathyroidism who are younger than 30 yr (2). Therefore, metabolic disease should be included in the differential diagnosis of urolithiasis in children.

The skeletal disease known historically as *osteitis fibrosa cystica* is characterized by subperiosteal resorption of the distal phalanges. In our patient, we could not find any skeletal abnormalities. Bone demineralization is a common complication of hyperparathyroidism, which is reported to improve 1 to 3 yr after parathyroid surgery (11). In our patient, low bone mineral density in the lumbar spine (0.497 g/cm^2; Z score = –3.2) was observed before parathyroidectomy. Nine month after surgery, DXA values had significantly increased to 0.555 g/cm^2 (Z score = –2.7).

PTH levels are suppressed in most cases of hypercalcemia, except those with hyperparathyroidism and FHH (12). FHH is an

autosomal dominant disorder caused by a mutation of the calcium-sensing receptor. Half the calcium-sensing receptors in the parathyroid gland are defective, and, thus the parathyroid glands are not aware of the normal serum calcium concentrations. This results in increased PTH release at normal calcium concentrations. A deficiency in calcium-sensing receptors in the kidneys causes the renal tubules to avidly reabsorb calcium as a result of the perception that the serum calcium level is low. Therefore urinary calcium levels are extremely low, with most patients having a fractional excretion of calcium less than 1%. This value is lower than in patients with primary hyperparathyroidism (5). In our patient, several spot urine tests showed normal fractional excretion of calcium, ruling out FHH.

In primary hyperparathyroidism, the serum phosphate tends to be below or in the lower part of the normal range because of the decreased %TRP and Tmp/GFR. In our patient, serum phosphate levels were slightly low (3.3 mg/dl); however, both %TRP and Tmp/GFR were normal (%TRP = 91%, Tmp/GFR = 3.9 mg/dl). Low phosphate intake stimulates tubular phosphate reabsorption (13). This regulation is independent of changes in PTH levels, extracellular fluid volume, or the level of serum calcium (13). Also, variations in phosphate intake showed inverse modulation in the maximum rate of phosphate transport by the proximal tubule phosphate cotransporter (Npt2) within hours (13). In our case, the parathyroid adenoma was of moderate size, and the serum PTH levels were not extremely high. Thus, the low phosphate intake in our patient might have increased phosphate reabsorption, which led to the normal %TRP and Tmp/GFR in the presence of increased serum PTH levels. Since discharge, the patient's serum phosphate levels have been normal in contrast to the slightly elevated %TRP and Tmp/GFR levels. These changes were thought to be derived from parathyroidectomy.

At nine months after the operation, the patient's serum PTH level increased transiently to 102 pg/ml, however, there was no evidence of recurrent hyperparathyroidism judging from laboratory data and image studies. At ten months post-op., the serum PTH level decreased spontaneously to 54.3 pg/ml, and we thought that the recurrence of hyperparathyroidism was implausible.

Since discharge, the patient's serum calcium level has remained within the normal range, although the urine calcium creatinine ratio was low. Also the moderate size of the parathyroid adenoma led us not to give calcium and vitamin D to the patient, because hungry bone is usually caused by a large parathyroid adenoma.

In conclusion hyperparathyroidism producing gross hematuria is rare in childhood. However, this case suggests the possible presence of hyperparathyroidism in children with urolithiasis or gross hematuria caused by urolithiasis.

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