ELSEVIER Case Report

A Patient with Primary Hyperparathyroidism Associated with Familial Hypocalciuric Hypercalcemia Induced by a Novel Germline *CaSR* Gene Mutation

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We report a patient with familial hypocalciuric hypercalcemia (FHH) associated with primary hyperparathyroidism (PHPT) and incidental papillary thyroid carcinoma. The patient showed hypercalcemia, high parathyroid hormone (PTH) levels and low urinary calcium excretion. A computed tomography (CT) scan revealed an enlarged parathyroid gland. Ultrasonography (US) and aspiration cytology revealed microcarcinoma of the left lobe of the thyroid gland. Screening studies of his family revealed that four of five family members had hypocalciuric hypercalcemia and normal PTH level. Sequencing analysis of the calcium sensing receptor gene revealed a novel heterozygous mutation (3193delA) in the patient and his family members with hypercalcemia, but one with normocalcemia. The patient underwent total thyroidectomy, central node dissection and extirpation of the enlarged parathyroid gland. Surgery is not indicated for FHH; however, FHH may be accompanied with parathyroid adenoma causing PHPT, as reported here, for which surgical treatment is indicated. [*Asian J Surg* 2009;32(2):118–22]

Key Words: calcium sensing receptor, familial hypocalciuric hypercalcemia, papillary thyroid carcinoma, primary hyperparathyroidism

Introduction

Familial hypocalciuric hypercalcemia (FHH) is one of the calcium homeostasis disorders characterised by mild to moderate hypercalcemia, generally accompanied with no symptoms, inherited as an autosomal dominant trait.[1,2] Surgery is not indicated for this entity. In 1993, it was reported that the cause of FHH was a heterozygous inactivating mutation in the calcium sensing receptor (CaSR) gene.[3] Since then, a large number of inactivating mutations in the *CaSR* gene associated with FHH have been reported.[4] Moreover, it is suggested that mutations in genes in at least two other distinct locations (19p and 19q) are causative of FHH.[5,6] In respect to the degree of hypercalcemia, the clinical features of FHH are similar to those of mild primary hyperparathyroidism (PHPT). Thus, differential diagnosis between FHH and PHPT is clinically important, although it may be somewhat difficult.

Here, we show the very rare case of a patient with FHH associated with parathyroid adenoma causing PHPT and papillary thyroid carcinoma, and describe the clinical features of this rare but clinically important association.

Case report

A 76-year-old Japanese man visited a local hospital complaining of weight loss. For a whole body examination a ^{18}F-fluoro-2-deoxyglucose positron emission

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Table 1. Laboratory data of the proband

	Preoperation	Postoperation	Normal
Ca (mg/dL)	11.2	10.7	8.2–10.2
Albumin (g/dL)	4.2	4.4	3.8–5.2
Ionized Ca (mEq/L)	2.96	ND	2.24–2.58
Phosphorus (mg/dL)	2.8	2.2	2.5–4.5
Intact PTH (pg/mL)	135	54	15–70
Alkaline phosphatase (IU/L)	134	184	105–340
Creatinine (mg/dL)	1.3	1.4	0.5–1.3
Cl (mEq/L)	106	101	98–110
Uric acid (mg/dL)	9.4	7.3	3.0–7.0
FECa	0.005	0.004	
NTx (nmol BCE/mmol Cr)	13.7	ND	13.0–66.2
BAP (U/L)	14.2	ND	13.0–33.9

Fractional excretion of calcium (FECa) was calculated by the following formula: (urinary calcium/urinary creatinine)/(serum calcium/serum creatinine). PTH = parathyroid hormone; NTx = N-telopeptides; BAP = serum bone-specific alkaline phosphatise; ND = not determined.

tomography scan was performed, revealing a focus with increased uptake in the right lobe of the thyroid gland. Thus, he was referred to our hospital in June 2006. He experienced repeated episodes of urolithiasis. His son had a history of asymptomatic hypercalcemia. Ultrasonography (US) of the neck showed a 27 × 20 mm nodule in the right and a 7 × 5 mm nodule in the left lobe of the thyroid gland. Laboratory data of the patient are shown in Table 1. Serum concentration of calcium, intact PTH and ionised calcium was increased. Fractional excretion of calcium (FECa) was below 0.01. Thyroid function was normal. The bone mineral density of the lumbar spines and femoral neck showed 1.300 g/cm^2 (T score, 0.8; Z score, 2.3) and 0.876 g/cm^2 (T score, –0.5; Z score, 0.8), respectively. Bone turnover markers, urinary type I collagen cross-linked N-telopeptides (NTx) and serum bone-specific alkaline phosphatase (BAP) were within normal range. Computed tomography (CT) scans of the neck revealed a tumour posterior to the left lobe of the thyroid gland, suggesting left lower parathyroid enlargement (Figure 1A), as well as thyroid tumours in both lobes. ^{99m}Tc-sestamibi (MIBI) parathyroid scintigraphy showed MIBI accumulation in the left lower pole of the thyroid gland (Figure 1B). Fine needle aspiration biopsy of the left thyroid nodule revealed papillary thyroid carcinoma.

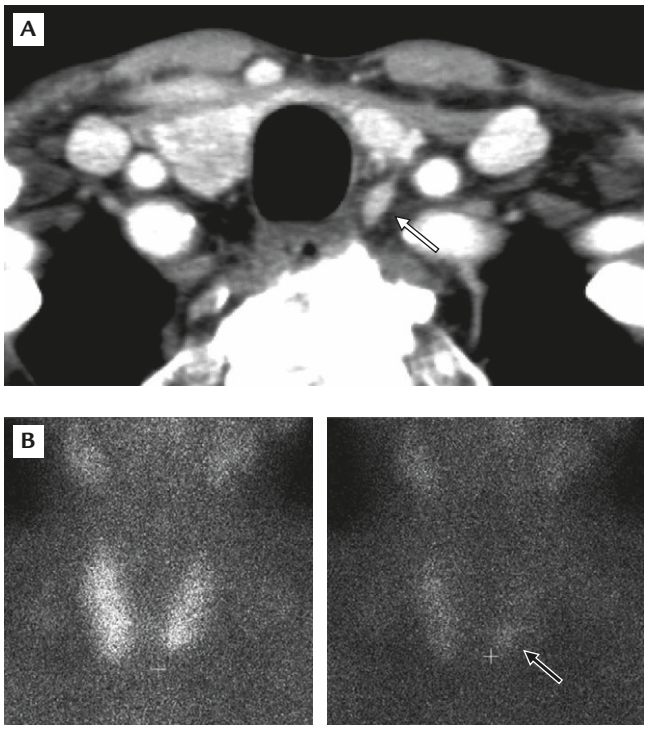

Figure 1. (A) Computed tomography scan showed a homogeneous, enhancing mass (arrow) posterior to the left lobe of the thyroid gland. (B) MIBI scintigraphy. Early-phase (left panel) and delayed-phase (right panel) scintigrams show a focus of uptake in inferior aspect of the left thyroid lobe (arrow).

The patient was suspected to have primary hyperparathyroidism; however, because of low FECa and his family history, we also considered the possibility of FHH and we therefore analysed his *CaSR* gene. Sequencing analysis of the *CaSR* gene was approved by the ethics committee of Kuma Hospital, and informed consent was obtained from all patients before samples were collected. Sequencing analysis of the coding region of the *CaSR* revealed a heterozygous novel mutation, 1-bp deletion at

nucleotide 3193 in exon 7 (3193delA), leading to a premature stop codon (Figure 2).

The screening study of his family members revealed hypercalcemia with inappropriately normal intact PTH and low FECa in his son, daughter, grandson and granddaughter (Table 2, Figure 3). They had the same mutation in the *CaSR* gene as the patient. The *CaSR* gene mutation was not detected in one of his grandsons, whose serum calcium and PTH levels were normal.

The patient was admitted in September 2006 with a preoperative diagnosis of papillary thyroid carcinoma associated with FHH and PHPT. A total thyroidectomy and central compartment lymphadenectomy were carried out. At the same time, one enlarged parathyroid gland behind the inferior pole of the left thyroid lobe was resected. The upper parathyroid glands on the both side looked normal in size and shape and were preserved in situ in order to avoid hypoparathyroidism after surgery. The right lower parathyroid gland could not be found during the surgery. The parathyroid tumour was bean-shaped, reddish-brown and 393 mg in weight, and a normal parathyroid rim was observed. Microscopically, closely packed chief cells with enlarged hyperchromatic nuclei were arranged in uniform sheets and cords (Figure 4). A rim of fat cell-rich glandular tissue was seen at the periphery of the adenoma (Figure 4A). Four months after surgery, his serum calcium and intact PTH level decreased, although his serum calcium level remained mildly hypercalcemic (Table 1). Serum uric acid was decreased to normal range after surgery. Eighteen months after surgery, the bone mineral density of the lumbar spines and femoral neck showed 1.341 g/cm^2 (T score, 1.1; Z score, 2.7) and 0.876 g/cm^2 (T score, –0.5; Z score, 0.8), respectively.

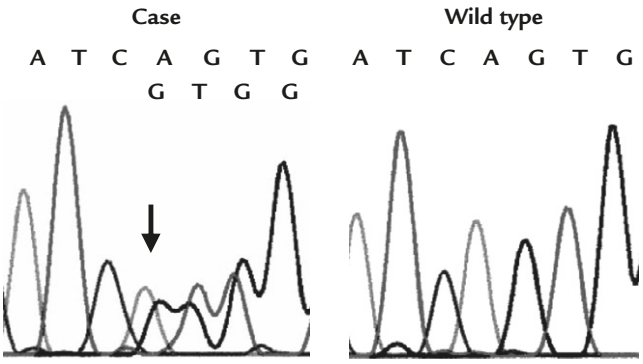

Figure 2. Sequencing analysis of exon 7 of the *CaSR* gene. A heterozygous 3193delA (arrow) was detected in this case.

Discussion

Clinically, it may be difficult to distinguish FHH from PHPT. PHPT occurring in patients with FHH can be very confusing; however, accurate diagnosis is critical, since surgical treatment is indicated for PHPT, but not for

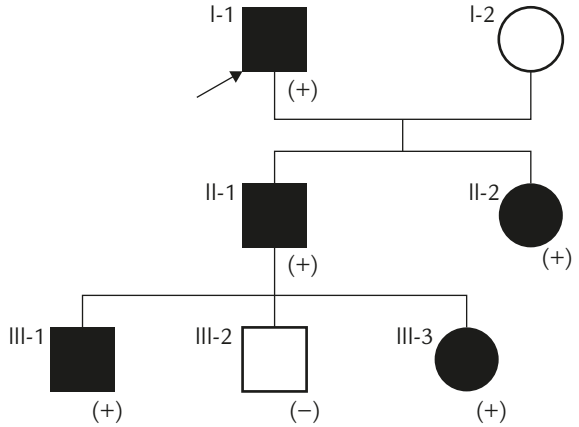

Figure 3. Pedigree of the family with FHH. Circles and squares represent females and males, respectively. Solid symbols represent hypercalcemia cases. The arrow indicates the proband. The presence (+) or absence (–) of the *CaSR* mutation in the family members are shown.

Table 2. Characteristics of FHH family members

Pedigree no.	I-1 (proband)	II-1	II-2	III-1	III-2	III-3
Ca (mg/dL)	11.2	11.5	11.5	11.5	9.6	11.2
Albumin (g/dL)	4.2	5.0	4.9	4.7	4.5	4.8
Ionized Ca (mEq/L)	2.96	ND	ND	ND	ND	ND
Phosphorus (mg/dL)	2.8	ND	ND	2.8	4.7	3.0
Intact PTH (pg/mL)	135	58	64	46	28	36
FECa	0.005	0.01	0.006	0.007	ND	0.007
Genotype of the *CaSR* locus	wt/mut	wt/mut	wt/mut	wt/mut	wt/wt	wt/mut

PTH = parathyroid hormone; FECa = fractional excretion of calcium; ND = not determined; wt = wild type; mut = mutant (3193delA).

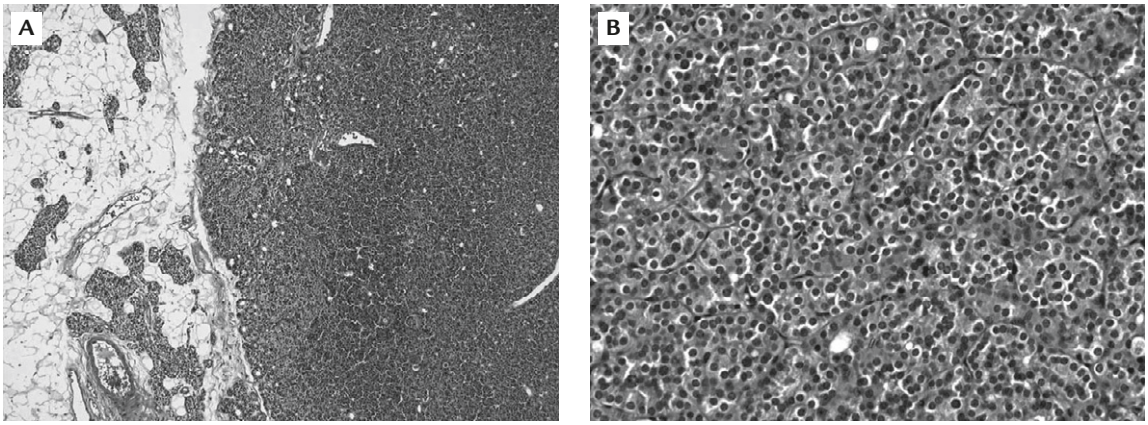

Figure 4. (A) Microscopic appearance of parathyroid tumor showing a normal rim adjacent to the tumour at low magnification. (B) Parathyroid adenoma at high magnification.

FHH. The low FECa level in this patient and the family history of asymptomatic hypercalcemia in his son were clues to the diagnosis of FHH, and a family screening study supported the diagnosis of FHH. The most convincing evidence was obtained by gene analysis of *CaSR* in this family. A novel *CaSR* gene mutation was found, which clearly segregated five hypercalcemic individuals with low FECa values and one normocalcemic family member.

The CaSR regulates renal tubular calcium excretion. Patients with an inactivating mutation of the *CaSR* gene display an increase in renal tubular calcium reabsorption. Consequently, their urinary calcium excretion is reduced, independent of PTH secretion. This probably explains why FECa remained low in the present patient, although he showed increased intact PTH and serum calcium levels. On the other hand, it is not clear the reason why bone turnover markers remained normal in the patient despite an increased intact PTH level. As was seen in the present patient, symptoms may be obscured by CaSR mutation in PHPT. This is consistent with a previous report that reported that an extremely high calcium level caused only mild symptoms in a FHH patient with parathyroid adenoma.[7]

In FHH patients, many mutations are reported in the *CaSR* gene. Most of the reported mutations are a single base substitution resulting in a missense or nonsense mutation. These inactivating mutations cluster at the N-terminal extracellular and transmembrane domain,[4] indicating that these regions are critical for the function of CaSR protein.[8] The deletion mutation in the intracellular domain, as founded in the present family, is rare. This novel deletion mutation leads to truncation of the intracellular domain of CaSR protein. We did not perform functional analysis of the truncated proteins; however, the presence of the heterozygous mutation was clearly associated with FHH phenotype in this family, speculated that this novel mutation is an inactivating mutation of the *CaSR* responsible for FHH.

Pathologically, mild hyperplasia may be present in the parathyroid gland of FHH patients,[9] however, the parathyroid gland from the proband showed chief cell adenoma with a rim of normal parathyroid tissue. The serum intact PTH level of the proband before surgery was greater than those of the affected family members. After extirpation of the parathyroid adenoma, the serum intact PTH level decreased to the normal range, although the serum calcium level remained mildly increased; thus, it is reasonable to think that the proband in this case was FHH associated with PHPT.

FHH associated with PHPT is extremely rare.[7,10] Papillary thyroid carcinoma is probably incidentally associated with FHH in this patient. The association of hyperuricemia and hyperparathyroidism has been noted.[11] Indeed, hyperuricemia of the present patient was improved after surgery. It is possible that the cause of urolithiasis in the patient was a preoperative increase in the level of uric acid due to PHPT. Hypercalcemia in FHH is generally asymptomatic, and a consensus has evolved that parathyroidectomy should be avoided in FHH. In this case, the parathyroid adenoma was resected by central compartment lymphadenectomy for papillary thyroid carcinoma. Since the patient had only mild hypercalcaemia and no hypercalciuria, parathyroidectomy for adenoma would be considered unnecessary. However, since FHH was associated with papillary thyroid carcinoma in this case and he had repeated urolithiasis resulting from hyperuricemia, surgery

was performed. Reduced *CaSR* expression or function may lead to parathyroid cellular proliferation,[12] and we should consider that PHPT can occur in patients with FHH.

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