RET 유전자변이로 확진된 제2A형 다발성내분비샘종 남자 환자에서 발병한 크롬모세포종

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Pheochromocytoma Developed in a Boy with Multiple Endocrine Neoplasia Type 2A Confirmed by the *RET* Proto-Oncogene Mutation

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A 9-year-old boy presented with increased sweating and abdominal pain. His mother and uncle had been diagnosed with bilateral pheochromocytoma and medullary thyroid carcinoma. Magnetic resonance imaging of the boy's abdomen revealed a 7.5 cm×7.0 cm×6.0 cm mass with a thick peripheral enhancing wall and fluid-fluid level at the right suprarenal region. His ^{123}I-meta-iodobenzylguanidine (MIBG) scan showed a large mass with increased MIBG uptake in the right adrenal gland. The levels of serum norepinephrine, urine epinephrine/norepinephrine, metanephrine, and vanillylmandelic acid were elevated. He, his mother, and two sisters tested positive for the known mutation of multiple endocrine neoplasia type 2A, Cys634Tyr in *RET* proto-oncogene. Laparoscopic tumor excision and right adrenalectomy were performed. Final diagnosis was pheochromocytoma with malignant behavior, based on adrenal gland scoring scale. However, there was no overt metastasis. After surgery, his symptoms resolved and abnormal laboratory tests were normalized.

Key Words: Pheochromocytoma, Multiple endocrine neoplasia, *RET* proto-oncogene, Child

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Introduction

Pheochromocytoma is a rare catecholamine-secreting tumor originating from the chromaffin tissue. Its frequency is approximately 1 per 100,000 (0.4-9.5 per million), with a peak incidence in the thirties and forties [1]. Only 10-20% of this tumor arise in children and adolescents, indicating its rarity in pediatric age [2]. Approximately 10% of pheochromocytomas are correlated with familial syndromes, inherited as autosomal dominant inheritance, including multiple endocrine neoplasia (MEN), von Hippel-Lindau disease (VHL), and neurofibromatosis type 1 (NF1) [1]. Herein we present the first Korean pediatric case of pheochromocytoma in a boy with MEN 2A confirmed by the *RET* proto-oncogene mutation (Cys634Tyr).

Case Report

A 9-year-old boy was admitted for having increased sweating and intermittent cramping abdominal pain for 2 months. He had a family history of bilateral pheochromocytoma and medullary thyroid carcinoma (MTC) (mother and maternal uncle). His blood pressure was 100/60-110/70 mmHg (normal range, 100-120/60-75 mmHg), and his heart rate was slightly elevated, around 80-105 beats per min (normal range, 60-95 beats per min). His body weight was 23 kg (10-25 percentile) and height was 131 cm (50-75 percentile).

An abdominal ultrasonogram showed a well-defined complex mass in the right suprarenal region. Abdominal computed tomography showed a thick-walled cystic mass sized 7.6 cm×6.2 cm×5.9 cm, and fluid-fluid level at the right suprarenal region. Magnetic resonance imaging of the abdomen confirmed a well-demarcated and complex 7.5 cm×7.0 cm×6.0 cm mass, with a thick peripheral enhancing wall and fluid-fluid level at the right suprarenal region (Fig. 1). An ^{123}I-meta-iodobenzylguanidine (MIBG) scan showed a large mass with increased MIBG uptake in the right adrenal gland (Fig. 2). Laboratory tests results were serum epinephrine level 0.129 ng/mL (normal range, <0.3 ng/mL), serum norepinephrine level 8.590 ng/mL (normal range, <0.8 ng/mL), 24 hr urine epinephrine 27.3 μg/day (normal range, 0-20 μg/day), 24 hr urine norepinephrine 577.9 μg/day (normal range, 15-80 μg/day), 24 hr urine metanephrine 13.588 mg/day (normal range, <0.8 mg/day), and 24 hr urine vanillylmandelic acid 31.5 mg/day (normal range, <8 mg/day). Sanger sequencing for the *RET* proto-oncogene (NM_020975.4) was performed for the patient and his family members, using the primers RET_ex11F, AGCCATGAGGCAGAGCATAC and RET_ex11R, ACACAGCGCCCTATGGAAAT. The known mutation of *RET* (exon 11; c.1901G>A; p.Cys634Tyr) associated with MEN 2A was found in the patient, his mother and his two sisters. The pedigree of the family and the Sanger sequencing result of the patient are shown in Fig. 3A and B.

Even though his blood pressure was in normal range, we suspected pheochromocytoma on the basis of his family history and clinical manifestations. Thus the patient was given an alpha-blocking agent (doxazocin 1 mg, 0.04 mg/kg) for 14 days, followed by alpha- and beta-blocking agents (doxazocin 2 mg, 0.08 mg/kg and atenolol 10 mg, 0.4 mg/kg) for 4 days before the operation. Despite the preoperative medication, his systolic blood pressure was elevated to 180 mmHg when the adrenal vein was dissected during surgery, but within 30 minutes after surgical resection, the blood pressure returned to normal.

The resected adrenal gland revealed an 8.0 cm sized pheochromocytoma with features of potentially malignant behavior, based on the adrenal gland scoring scale (PASS score). The tumor showed large nests or diffuse growth

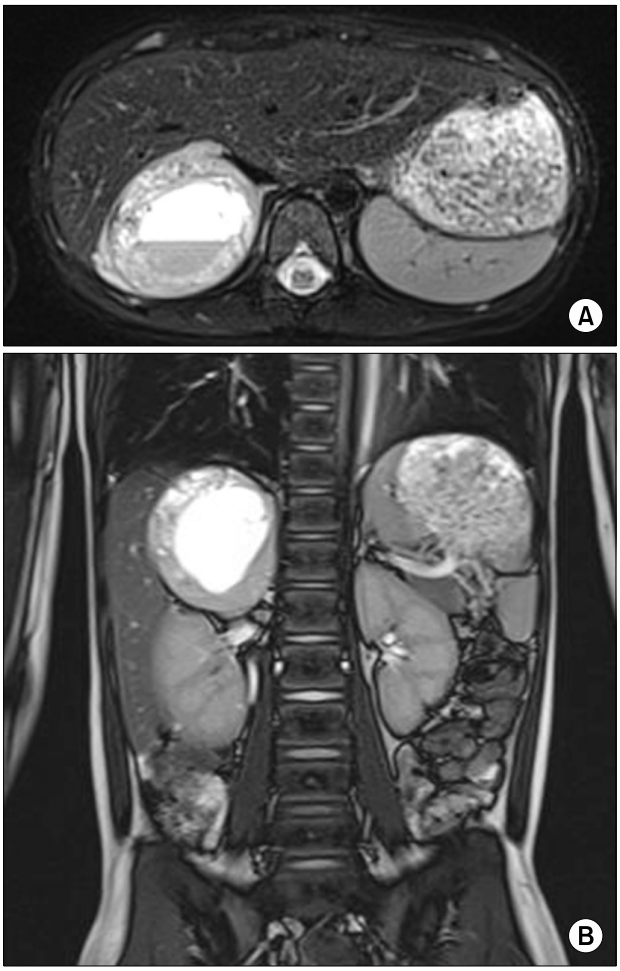

Fig. 1. Magnetic resonance image reveals a well-demarcated, complex mass measuring 7.5×7.0×6.0 cm, with a thick-walled peripheral enhancing wall and fluid-fluid level at the right suprarenal region.

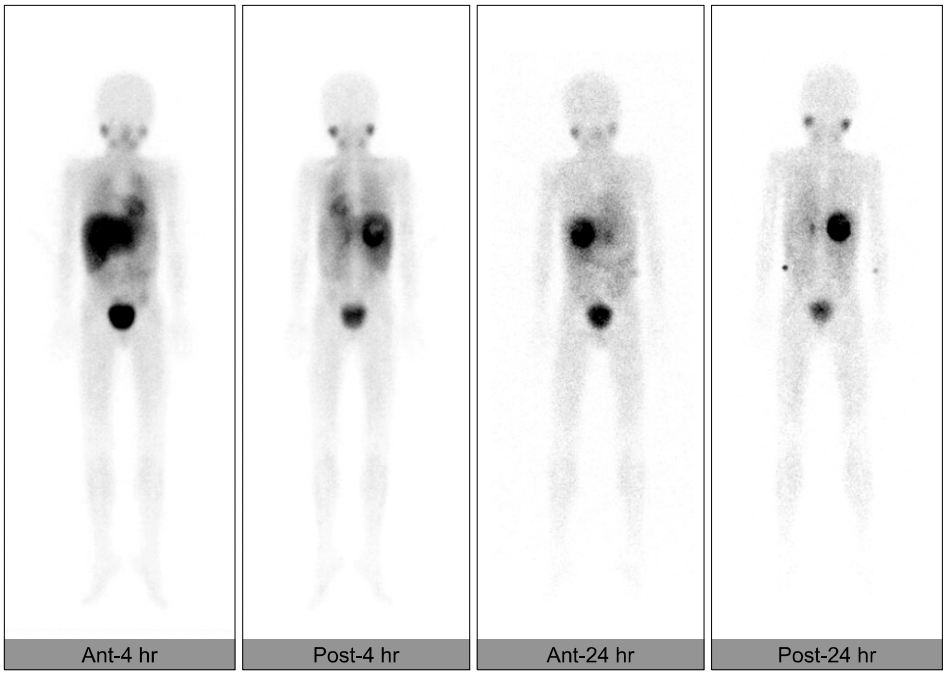

Fig. 2. An ^{123}I-meta-iodobenzylguanidine (MIBG) scan reveals a large mass (7 cm) with increased MIBG uptake in the right adrenal gland.

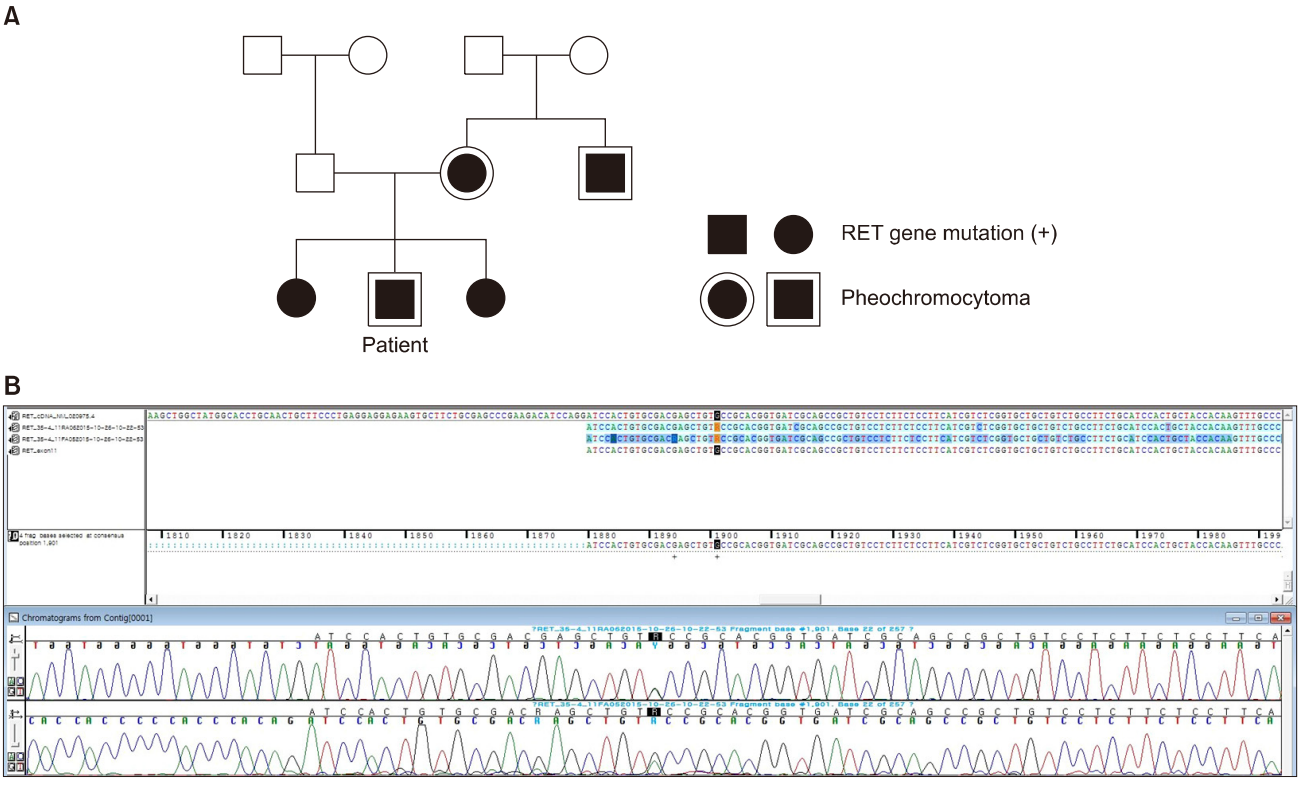

Fig. 3. The pedigree and the Sanger sequencing of RET proto-oncogen. The pedigree of the patient's family shows multiple endocrine neoplasia (MEN) 2A with medullary thyroid carcinoma and pheochromocytoma (A). Sanger sequencing for the *RET* proto-oncogene (NM_020975.4) was performed, and the known mutation of *RET* (exon 11; c.1901G>A;p.Cys634Tyr) associated with MEN 2A was found in the patient, his mother, and two sisters (B).

2/2, central or confluent tumor necrosis 2/2, high cellularity 2/2, atypical mitotic Figures 2/2, vascular invasion 1/1, and a PASS score of 9 (Fig. 4). Because of malignant behavior of the tumor suggested by the pathologic findings, positron emission tomography (PET) was performed after surgery. PET did not reveal abnormal fluorodeoxyglucose uptake in the right adrenal gland bed, and did not show any hypermetabolic lesions suggesting lymph node or distant metastasis. Immediately after surgery, the patient's symptoms were resolved and the results of laboratory tests were normalized. One year and 3 months after tumor removal, the patient remains free of symptoms. Periodic monitoring of imaging studies and endocrine/biochemical markers are continuing, with consideration of prophylactic thyroidectomy.

Discussion

MEN 2A is a familial cancer syndrome consisting of MTC, pheochromocytoma, and primary hyperparathyroidism, caused by an autosomal dominant mutation of *RET* proto-oncogene [1]. MEN 2B is characterized by MTC, pheochromocytoma, mucosal neuromas, intestinal ganglioneuromas, and marfanoid habitus [2]. Nearly 100% of the MEN 2A patients develop MTC, about 50% of the patients develop pheochromocytoma, mainly after the age of 10 years, and 10-30% develop hyperparathyroidism [3].

The diagnosis of pheochromocytoma is confirmed by biochemical evidence of elevated catecholamine production, usually corroborated by radiologic studies [1]. In Korean and Canadian single institute retrospective studies, increased plasma or urine catecholamine also contributed to the diagnosis of the pheochromocytoma [4,5]. There were 3 VHL cases and 2 NF cases but no MEN case among 16 children with pheochromocytoma in the Korean study [5]. To our knowledge, this case is the first Korean pediatric pheochromocytoma associated with MEN 2A. Mutations of the *RET* proto-oncogene can cause pheochromocytoma by increasing adrenergic metabolism. The *RET* gene locates on the chromosome 10 long arm (10q11.2) with 16 exons, of which 10, 11, 13 and 16 are primarily associated with pheochromocytoma [3]. In case of our patient, the *RET* mutation (exon 11; c.1901G>A; p.Cys634Tyr) was found. It is well known genetic mutation associated with MEN 2A [6]. The clinical findings of the present patient's family included MTC and pheochromocytoma, but no evidence of neuroma or marfanoid habitus, thus consistent with MEN 2A. In Korea, two children with MEN 2 whose parents had MTC have been reported previously [7]. Although there was no symptom in both of two children, a screening test showed that they have the same mutations in of *RET* as their parents. Subsequently one of the children received prophylactic total thyroidectomy.

Patients with catecholamine secreting tumors present with paroxysms of severe hypertension or tachycardia, gastrointestinal dysfunction, or skeletal-related events [3-5]. In this case, the boy had experienced headache, perspiration, and abdominal discomfort. Perioperative mortality rate of patients with pheochromocytoma has dropped 45% to <3%

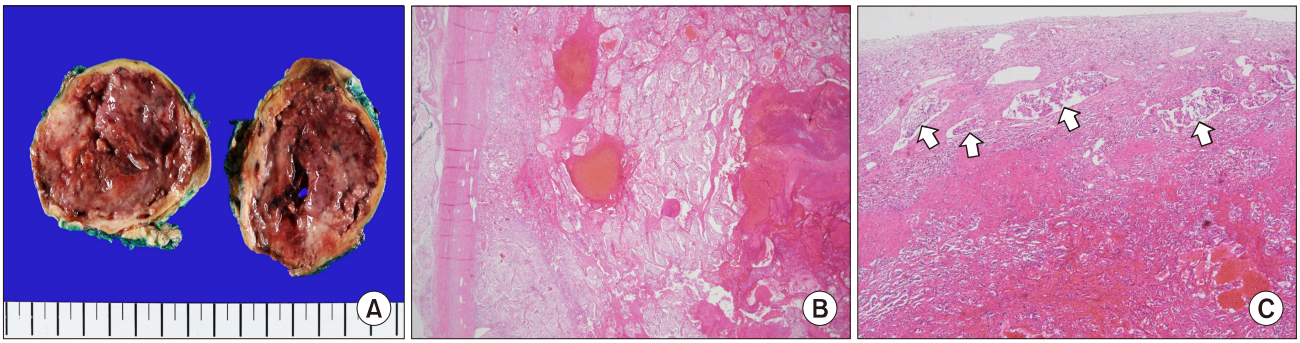

Fig. 4. The mass is relatively well encapsulated and the cut surface is reddish brown and shows a central hemorrhage and necrosis (A), and microscopically a characteristic 'zellballen' pattern or trabecular arrangement (B) and vascular invasion (C, white arrow) (H&E ×40 manification).

since the introduction of the alpha-adrenergic blocking agents in 1967 [5]. Surgical removal should be done after successful prevention the effects of catecholamine excess. Phenoxybenzamine, a long-acting, nonselective alpha-adrenergic blocker has been the mainstay of pharmacologic therapy. The alpha-adrenergic blocker should be initiated for 10-14 days prior to surgery [8]. Beta-adrenergic blockade is indicated in cases of cardiac arrhythmias or tachycardia [5]. Despite aggressive pharmacologic loading with phenoxybenzamine, intraoperative hypertension (systolic blood pressure, >170 mmHg) was reported in patients during induction of anesthesia or tumor manipulation [4,5], because complete alpha-adrenergic blockade is not possible.

The treatment of malignant pheochromocytoma includes surgical resection, successful pharmacological control of catecholamine-medicated symptoms, systemic chemotherapy, and radiotherapy [1,9]. For patients with no evidence of metastatic disease by workup, complete surgical removal should be undertaken [1,9]. In cases with sufficient uptake of ^{123}I-MIBG, targeted radiation therapy is an option as an adjuvant therapy after surgery, or it can be done for patients with metastatic disease for whom surgery is not feasible [1,10]. Adjuvant chemotherapy should be used for the patients with progressive disease despite of radionuclide treatment, negative MIBG-scan or no response to ^{131}I-MIBG [10]. Neoadjuvant therapy can play a role in rendering very large tumor amenable to surgical intervention [1]. As new effective medical treatment modality, cytostatic therapies achieve its antineoplastic activity by interfering with specific targeted molecules needed for carcino-genesis and tumor growth [10]. In the present case, even though the pathologic features showed malignant behavior by PASS score, additive radionuclide treatment or adjuvant chemotherapy was not undertaken because there was no clinical metastasis and the tumor was completely excised.

Depending on the genetic background and location, approximately 6-10% of pheochromocytoma tumors are malignant. Virtually all pheochromocytomas in MEN type 2, more than 90% of those in VHL, and almost 90% of those in NF appear to be benign [11]. Pheochromocytoma is more frequently associated with familial syndromes and a lower incidence of malignancy in children than in adults (3.5% vs. 3-14%) [12]. Although there is no universal accepted time interval to screen pheochromocytoma recurrence after surgery, plasma and urinary catecholamine levels are performed annually for a period of 10 years [13]. Biochemical markers are useful in assessing tumor response, relapse, and progression [9]. In the present case, the patient will be followed by periodic urine/plasma catecholamine studies, ^{123}I-MIBG scans, and thyroid ultrasonogram. The preventive thyroidectomy also will be considered.

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