Multiple endocrine neoplasia type 2 and autoimmune polyendocrine syndromes (type 1 diabetes mellitus and Graves’ disease) in a 16-year-old male with Kabuki syndrome

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Abstract. Multiple endocrine neoplasia type 2A (MEN2A) is caused by germline pathogenic variants in the RET proto-oncogene and is characterized by medullary thyroid cancer (MTC), pheochromocytoma, and hyperparathyroidism. Autoimmune polyendocrine syndromes (APS) are defined as multiple endocrine gland insufficiency associated with loss of immune tolerance. APS type 2 (APS-2) consists of at least two of the following diseases: type 1 diabetes mellitus (T1DM), autoimmune thyroid disease, and Addison’s disease. We describe the clinical, molecular, and biochemical findings of MEN2A, APS-2, and Kabuki syndrome (KS) in a 16-year-old male. Whole exome sequencing was performed to identify the genetic cause of the pheochromocytoma and syndromic features including facial dysmorphism, developmental delay, and epilepsy. RET pathogenic variant and KMT2D pathogenic variant were identified, and he was diagnosed with MEN2A and KS. This is the first case of association between MEN2 and APS in adolescence and the second proven case in humans. In addition, this is the first report of MEN2 and APS in KS.

Key words: Multiple endocrine neoplasia type 2 (MEN2), Autoimmune polyendocrine syndrome (APS), Pheochromocytoma, RET pathogenic variant, Kabuki syndrome (KS)
is characterized by distinctive facial features, skeletal anomalies, intellectual disability, and a variable range of abnormalities such as congenital heart defects, cleft lip and/or palate; and genitourinary, gastrointestinal, and ophthalmologic anomalies [9-11]. Endocrinological anomalies of KS include premature thelarche, short stature, hyperinsulinism, adrenal insufficiency, precocious puberty, and diabetes insipidus [9, 10].

Here, we describe the clinical, molecular, and biochemical findings of a 16-year-old male with MEN2A, APS-2, and KS. To the best of our knowledge, this is the first case report of association between MEN2 and APS in adolescence and the second proven case in humans. The patient was diagnosed with MEN2A and KS by genetic test, additionally diagnosed with T1DM and Graves’ disease, and subsequently with APS-2. This is the first report in which MEN2 and APS are diagnosed simultaneously in a patient with KS.

**Case Report**

A 16-year-old male visited the emergency room due to vomiting, diarrhea, and sweating for two days. He had been born via cesarean section delivery at term gestation with a birth weight of 3,700 g. The patient was the only child of non-consanguineous healthy parents. He showed mild intellectual disability and had taken anticonvulsants since the age of eight years and an antihypertensive drug since the age of 15 years.

His height was 166.5 cm (–1.109 standard deviation score [SDS]), and his weight was 61.7 kg (–0.381 SDS). He had long and high-arched eyebrows and eversion of the lateral portion of both lower eyelids. His blood pressure was 140/98 mm Hg despite an antihypertensive drug medication, pulse rate 155 beats/minute, respiratory rate 21 times/minute, and body temperature 38.6°C. His mental status was drowsy. Breathing sounds were clear, but a gallop was noted. Complete blood count, electrolytes, and renal function were within the normal ranges. Aspartate aminotransferase (AST) was 2,676 U/L, alanine aminotransferase (ALT) 4,160 U/L, total bilirubin 5.1 mg/dL, and direct bilirubin 2.0 mg/dL. Cardiac enzyme levels (creatine kinase MB 34.99 ng/mL, troponin I 14.315 ng/mL) and lactic acid (4.2 mmol/L) were elevated. Fasting blood glucose level was 156 mg/dL, hemoglobin A1c was 7.0%, C-peptide was 3.87 ng/mL, GAD II antibody was 33.56 U/mL, TSH was 0.001 uU/mL, FT4 was 4.26 ng/dL and calcitonin was 6.2 pg/mL. Thyroglobulin Ab, thyroid peroxidase Ab, and TSH-receptor-Ab were all positive. Adrenal 21-hydroxylase antibody was negative (Table 1). Electrocardiography revealed sinus tachycardia with ST elevation in V2 to V6. Echocardiography revealed a decreased cardiac ejection fraction (LVEF 27.9% by Simpson’s method), and diastolic dysfunction without regional wall motion abnormality. Coronary aorta contrast-enhanced computed tomography (CT) angiography revealed no evidence of coronary artery stenosis but did show coarctation of the aorta. Abdominal contrast-enhanced CT showed a heterogeneously enhanced, 5.5-cm mass on the right adrenal gland (Fig. 1). An FDG PET scan showed a 52-mm-sized soft tissue mass with mild heterogeneous increase of FDG uptake in a right adrenal mass, suggestive of pheochromocytoma. Twenty-four-hour urinary catecholamine and metabolite levels were elevated, as were plasma catecholamine and metabolite levels. Thyroid ultrasonography showed diffuse parenchymal disease of the thyroid gland without focal lesions. A thyroid scan (Tc-99m) showed diffuse enlargement with increased radioactive technetium uptake.

The patient was admitted to the pediatric intensive care unit, and an alpha-blocker (phenolamine) and milrinone administration were started to treat heart failure. Methimazole was started for Graves’ disease. An oral alpha-blocker (terazosin) and beta-blocker (atenolol) were initiated, and continuous intravenous infusions of phenolamine and milrinone were tapered on the seventh in-patient day. The patient’s blood pressure remained below 120/80 mm Hg. Echocardiography revealed normal cardiac output, and AST and ALT had decreased to 48 and 82 U/L, respectively. The patient was discharged with oral medication (terazocin, atenolol) on the 12th day of admission. After three weeks of treatment with alpha blocker, the patient underwent laparoscopic right adrenalectomy with a transabdominal approach, and pheochromocytoma was confirmed by histological examination (5.5 × 2.5 cm). There was no cortical atrophy or lymphocyte infiltration in the adrenal cortex. After tumor resection, the patient had controlled blood pressure without antihypertensive medication and normal blood glucose level. HbA1c has been maintained at less than 6% by diet control without medication.

Whole exome sequencing (WES) was performed to identify the genetic cause of pheochromocytoma and syndromic features including facial dysmorphism, developmental delay, and epilepsy. Informed consent was obtained from the patient and his mother, and this research was approved by the Institutional Review Board of Samsung Medical Center (Approval no. 2012-05-080). For analysis, 3 cc of blood was obtained from the patient, and genomic DNA was extracted. Library preparation was performed using TruSight One Sequencing Panel (Illumina, Inc., San Diego, CA, USA), which enriches a 12-Mb region spanning 62,000 target exons of a total of 4,813 clinically relevant genes. Massively parallel sequencing was performed on the Illumina
NextSeq platform. Sequence reads were mapped to a UCSC hg19 standard base for comparative analysis. The result of WES revealed c.1891G>T (p. Asp631Tyr) in RET, which has been reported to be related to MEN2A [12, 13] and heterozygous variant c.14710C>T (p.Arg4904Ter) in KMT2D, which has been reported as a pathogenic variant of KS type 1 [14]. Genetic testing of the parents could not be performed because they did not provide consent. The two variants were confirmed via direct sequencing and have been previously reported as pathogenic variants according to the guidelines of ACMG. The average depth of the panel was 281X, and 100% of bases were above 10X. Finally, the patient was diagnosed with MEN2A, APS-2, and KS.

At 30 months after tumor resection, 24-hour urinary catecholamine and metabolite levels have been maintained within the normal ranges. Abdominal ultrasonography has demonstrated no abnormal masses. Calcitonin level has been monitored to determine thyroidectomy for possible MTC. Remission of Graves’ disease was obtained after six months of therapy with methimazole. Euthyroid status has been maintained through the most recent follow-up. HbA1c has been maintained at less than 6%, and the patient has no symptoms of Addison’s disease.

| Table 1 Patient laboratory findings | Measured value | Reference range |
|------------------------------------|----------------|-----------------|
| Plasma                             |                |                 |
| Creatine kinase MB                 | 34.99 ng/mL    | 0–4.87 ng/mL    |
| Troponin I                         | 14.315 ng/mL   | 0.003–0.057 ng/mL |
| NT-proBNP                          | 350,000 pg/mL  | 0–88 pg/mL      |
| Lactic acid                        | 4.2 mmol/L     | 0.7–2.5 mmol/L  |
| Hemoglobin A 1c                    | 7.0%           | 4–6%            |
| C-peptide                          | 3.87 ng/mL     | 0.69–3.59 ng/mL |
| GAD II antibody                    | 33.56 U/mL     | 0–1 U/mL        |
| Anti-insulin autoantibody          | 5.4%           | 0–7%            |
| Thyroid-stimulating hormone (TSH)  | 0.001 uIU/mL   | 0.27–4.20 uIU/mL|
| Free thyroxine (FT4)               | 4.26 ng/dL     | 0.93–1.7 ng/dL  |
| Thyroglobulin Ab                   | 431.9 U/mL     | <60 U/mL        |
| Thyroid peroxidase Ab              | 2,908.3 U/mL   | <60 U/mL        |
| TSH-receptor-Ab                    | 4.5 IU/L       | <1.0 IU/L       |
| Adrenocorticotropic (ACTH)         | 68.4 pg/mL     | 0–60.0 pg/mL    |
| Cortisol                           | 45.9 ug/dL     | 1.8–26.0 ug/dL  |
| Calcitonin                         | 6.2 pg/mL      | 1.9–9.6 pg/mL   |
| PTH                                | 46.9 pg/mL     | 11.0–62.0 pg/mL |
| Metanephrines                      | 1.32 nmol/L    | 0.05–0.48 nmol/L|
| Normetanephrine                    | 99.43 nmol/L   | 0.12–0.45 nmol/L|
| Epinephrine                        | 129.2 pg/mL    | <90 pg/mL       |
| Norepinephrine                     | 6,821.6 pg/mL  | 125–700 pg/mL   |
| Dopamine                           | 123.4 pg/mL    | <87 pg/mL       |
| 24-Hour urine                      |                |                 |
| Epinephrine                        | 43.6 ug/day    | 0–20 ug/day     |
| Norepinephrine                     | 7,600.7 ug/day | 15–80 ug/day    |
| Dopamine                           | 492.8 ug/day   | 65–400 ug/day   |
| Vanillylmandelic acid              | 8.3 mg/day     | <6.0 mg/day     |
| Metanephrines                      | 35.6 ug/day    | <229.5 ug/day   |
| Normetanephrine                    | 1,428.6 ug/day | <502 ug/day     |
Discussion

This is the first report of the coexistence of genetically confirmed MEN2 and APS in adolescence. This patient was diagnosed with MEN2A and APS-2 by RET pathogenic variant, positive GAD II antibody, as well as with Graves’ disease.

APS-1 is a rare autosomal recessive disease caused by an autoimmune regulator gene pathogenic variant (AIRE) [15, 16]. APS-1 is diagnosed when at least two of the following three conditions are present: primary adrenal insufficiency (Addison’s disease), chronic mucocutaneous candidiasis, and hypoparathyroidism [17]. APS-2 is a genetically polygenic and multifactorial disease [7, 18]. APS-2 is characterized by at least two of the following three conditions: T1DM, autoimmune thyroid disease, and Addison’s disease [19]. In this case, T1DM was diagnosed based on hyperglycemia (fasting blood glucose and HbA1c were 156 mg/dL and 7.0%, respectively) and positive GAD II antibody [20]. The C-peptide is a valuable tool in classification of diabetes but is not essential for diagnosis [21, 22]. C-peptide level less than 0.6 ng/mL is associated with a diagnosis of T1DM [21]. But C-peptide (3.8 ng/mL) was increased in the present patient. C-peptide must always be interpreted in the clinical context of comorbidities and disease duration [21]. T1DM patients with increased C-peptide level have been reported [23, 24]. It is thought that our patient showed a temporary increase in C-peptide due to increased insulin resistance by elevated catecholamine level caused by pheochromocytoma [3, 23, 25]. The patient was diagnosed with T1DM and Graves’ disease, and subsequently with APS-2. Also, APS is a marked variation in the pattern of autoimmunity [7], our patient must be monitored for Addison’s disease and various organ-specific autoimmune diseases.

The association between MEN2 and APS is rare and has not been well studied or documented in the literature. In 2020, Manso et al. described the first human with proven MEN2A and APS-2 [8]. A 25-year-old man was diagnosed with Hashimoto’s thyroiditis, pancreatic autoimmunity, and Addison’s disease without ACA or 21-hydroxylase autoantibodies (APS-2) [8]. He was diagnosed with MTC at 34 years of age, and he had a family history of pathogenic variant, c.1900T>G (p. Cys634Gly) in RET [8]. At age 41 years, he developed T1DM [8]. At 55 years, he was diagnosed with bilateral pheochromocytoma without any clinical symptoms on routine follow-up for MEN2A [8]. Pathology revealed bilateral pheochromocytoma and concomitant bilateral cortical atrophy with lymphocytic infiltrate, compatible with autoimmune adrenalitis [8]. The authors suggested that adrenal medullary tumors can develop even on an adrenal gland with cortical atrophy due to autoimmune adrenalitis [8]. In addition, two cases of pheochromocytoma and APS have been reported. In 2007, Murao et al. reported a 45-year-old woman with slowly progressive T1DM, Hashimoto’s disease (APS-2), and pheochromocytoma [26]. In 2008, García et al. reported a 78-year-old woman who developed pheochromocytoma after diagnosis of Addison’s disease at 46 years of age and autoimmune thyroiditis at 66 years of age (APS-2) [27]. This case was described as an association between pheochromocytoma and APS-2 without adrenal cortex autoantibodies (ACA). Our patient was diagnosed with MEN2A by identification of pathogenic variant c.1891G>T (p. Asp631Tyr) in RET, which is classified into the MTC moderate risk category in the American Thyroid Association’s 2015 revised guidelines [28]. Also, Lee, J. Y et al. reported that pheochromocytoma, MTC, and hyperparathyroidism occurred in 58.8%, 32.3%, and 2.9%, respectively of patients with c.1891G>T (p. Asp631Tyr) in RET [29]. The penetration of pheochromocytoma was higher than MTC in this pathogenic variant. Pheochromocytoma was likely the first symptom of MEN2 in our patient. This symptom indicates the need for continuous monitoring for subsequent development of MTC and hyperparathyroidism. As shown in the above cases and in the present case (Table 2), MEN2 or pheochromocytoma can be related to APS.

Murao et al. suggested that catecholamines may contribute to autoimmune antibody production because T helper 1 cytokines and interleukin-12 are associated with

![Image](https://via.placeholder.com/150)

**Fig. 1** Preoperative imaging showed a 5.5-cm right pheochromocytoma by abdominal CT scan coronal (arrow).
various autoimmune diseases [26]. However, pheochromocytoma was diagnosed after the APS2 diagnosis in all but our case. It is unlikely that APS was induced by pheochromocytoma. Another hypothesis is that hormonal imbalance and inflammation caused by autoimmunity regulate the expression of a proto-oncogene. Chronic inflammation increases the risk of cancer [30]. However, there is no clear evidence supporting a correlation between MEN2 and APS. Further research is needed to elucidate the mechanism.

Our patient showed facial dysmorphism, developmental delay, epilepsy, and coarctation of the aorta, findings related to KS. The c.14710C>T (p.Arg4904Ter) in \textit{KMT2D} is a pathogenic variant for KS type 1 and was identified by WES [14]. This nonsense variant is expected to cause loss of normal protein function through nonsense-mediated mRNA decay [14]. \textit{KMT2D}-related KS is inherited in an autosomal dominant pattern, while \textit{KDM6A}-related KS is inherited in an X-linked manner [10]. Autoimmune diseases including idiopathic thrombocytopenic purpura, hemolytic anemia, thyroiditis, vitiligo, and even DM have been reported in patients with KS [9, 31, 32]. However, MEN2 and APS with KS had not been reported before our case. Failure of adequate suppression of autoreactive immune cells can lead to autoimmune disease in KS [32]. In addition, KS patients have had tumors including spinal ependymoma, giant cell fibroblastoma, neuroblastoma, Wilms’ tumor, and nephroblastoma [9, 11]. Thus, a causative association of KS and malignancy or autoimmunity should be considered.

In conclusion, this is the first pediatric case genetically confirmed with MEN2A and APS-2 in KS. The present case and a literature review might support a recommendation for monitoring of the symptoms and laboratory findings of autoimmune destruction of multiple endocrine glands if MEN2 or pheochromocytoma is suspected. Further research is needed to elucidate the mechanism of the association of MEN2 and APS. In addition, we suggest monitoring of MEN2 or APS in patients with KS.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

Compliance with Ethics Guidelines

Written informed consent was obtained from the patient and his parents. The Institutional Review Board at Samsung Medical Center approved this study (IRB file number: 2012-05-080).

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Table 2

| Case [Ref. no.] | Sex | Family history of MEN | Gene | Pheochromocytoma or MEN2 clinical finding (age at diagnosis) | APS clinical finding (age at diagnosis) |
|-----------------|-----|-----------------------|------|-------------------------------------------------------------|-----------------------------------------|
| 1. Murao et al. in 2007 [26] | F   | No                    | NA*  | Pheochromocytoma (45 yr)                                     | APS 2—Slowly progressive type 1 DM, Hashimoto’s thyroiditis (before 45 yr) |
| 2. T Garcia et al. in 2008 [27] | F   | NA*                   | NA*  | Pheochromocytoma (78 yr)                                     | APS 2—Addison’s disease (46 yr), Hashimoto’s thyroiditis (66 yr) |
| 3. Manso et al. in 2020 [8]    | M   | Yes (MEN2A)           | RET  | MEN2A—Medullary thyroid cancer (34 yr), bilateral pheochromocytoma (55 yr) | APS 2—Addison’s disease, Hashimoto’s thyroiditis (25 yr), type 1 DM (41 yr) |
| 4. Present case in 2022        | M   | No                    | RET  | MEN2A—Pheochromocytoma (16 yr)                               | APS 2—Graves’ disease, type 1 DM (16 yr) |

* NA = not available, † Mutated gene

MEN, multiple endocrine neoplasia; APS, autoimmune polyglandular syndrome.
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