A case of Carney complex in a Korean patient is presented. The patient had the characteristics of Carney complex including skin lesions, positive family history, and multiple myxomas including a superficial angiomyxoma in the perianal area. An extensive genetic analysis revealed a novel mutation in the protein kinase A type I-a regulatory subunit (PRKAR1A) gene, but not in the phosphodiesterase type 11A (PDE11A) gene. This is the first case wherein extensive genetic studies were performed in a patient with Carney complex in Korea.

Key Words: Carney complex; PRKAR1A; PDE11A; Superficial angiomyxoma

CASE REPORT

A 19-year-old woman was admitted due to slowly progressing right hemiparesis. At the time of admission, apart from a slightly drowsy mental status, her presentation was unremarkable with stable vital signs and no past medical history. On physical examination, she had multiple tiny brown pigmented macules on her face and abdomen, and a bean-shaped brownish papule on the axilla and left upper arm. She also had groups of brownish papules on both nipples (Fig. 1). Her mother and elder sister had a history of cardiac myxoma.

Magnetic resonance imaging (MRI) of the brain demonstrated diffuse hemorrhagic infarction in the middle cerebral artery territory. Echocardiography showed a 3 × 2.5 × 2 cm echogenic mass in her left atrium (Fig. 2). The cardiac mass was resected through an open thoracotomy, and the masses on both nipples
were also excised during the operation. The histologic diagnosis of all three masses was myxoma. Her multiple myxomas, skin pigmentation, and familial history of cardiac myxoma were compatible with CNC. Upon evaluation for endocrinologic derangement, the laboratory data including adrenocorticotropic hormone, cortisol, estradiol, and testosterone were within the normal range. Follow-up was planned for the patient with regular echocardiography and ultrasonography (US) on her breasts and thyroid glands.

During 5 years of follow-up, US demonstrated several iso-choic or hypoechoic nodules in both of her breasts. US-guided core needle biopsy of these lesions revealed fibroadenomas. The number of nodules on her breasts gradually increased, and numerous nodules of various sizes were found on her breasts and axilla. Her thyroid glands had several tiny cystic nodules on both lobes, but the overall number or size of the nodules remained unchanged.

Most recently, the patient was admitted due to a perianal mass that she had for 1 year. It did not cause any pain, tenderness, or dyschezia. MRI demonstrated a $6.7 \times 5.8 \times 4.0$ cm round mass occupying the subcutaneous soft tissue, abutting the inferior border of the internal sphincter. The mass showed a low signal intensity on T1-weighted imaging (WI) and a bright high signal intensity on T2WI, and on fat suppression T2WI. With gadolinium enhancement, the mass revealed multiple enhancing internal septa (Fig. 3). With the presumptive diagnosis of a malignant mucinous neoplasm, surgical resection was performed. Grossly, multiple thin fibrous septa were identified within the gray to white gelatinous surface. Histologic examination of the tumor showed a multilobular growth of myxoid stroma and loosely deposited spindle cells. The thin fibrous septa traversed the tumor parenchyma. Occasional prominent arborizing blood vessels were also identified (Fig. 4). These findings were consistent with superficial angiomyxoma.

DNA was extracted using a QIAamp DNA mini kit (Qiagen,
Fig. 3. (A-C) Magnetic resonance imaging demonstrated a 6.7 × 5.8 × 4.0 cm multilocular cystic mass with multiple septa in the perianal area. The mass shows a bright high signal intensity on both T2-weighted imaging (T2WI) and fat suppression T2WI.

Fig. 4. Grossly, the mass is well circumscribed and has a gray to white, gelatinous cut surface with multiple thin fibrous septa (A). Histologically, the tumor shows a multilobular appearance with an infiltrative border (B). The fibrous septa traverse the tumor into multiple lobules (C). Spindled to stellate-shaped tumor cells are loosely deposited in a myxoid stroma. Prominent vasculature is identified in this area (D).

Hilden, Germany) from the perianal specimen. Polymerase chain reaction was performed using a thermal cycler (GeneAmp PCR System 9600, Perkin-Elmer, Wellesley, MA, USA) for which the primers of 10 exons of PRKAR1A, exon 16 of myosin, heavy chain 8, skeletal muscle, perinatal (MYH8), and 7 exons of PDE11A were prepared (Table 1). The cycle sequenc-
Table 1. Primer sequences

| Gene   | Exon | Sequence                  |
|--------|------|---------------------------|
| PRKAR1A| 1A   | F 5'-AGT CGG CCA CCT GTC ATC T-3' |
|        |      | R 5'-CAC TTC TCG TTC CAG CAG TC-3' |
|        | 1B   | F 5'-CAT TGA GTG CAG TAG CGG AA-3' |
|        |      | R 5'-ATG TGA CGG CTC AGC TC-3' |
|        | 2    | F 5'-GTC ATG CAC TTC TCT GTT GC-3' |
|        |      | R 5'-ATC TCC TCA TCT TCC CCA CA-3' |
|        | 3    | F 5'-CAT GCC GAA GGA GTA TCT TT-3' |
|        |      | R 5'-ATG GAA GGT CCA CCC TG-3' |
|        | 4A   | F 5'-CAG GTT GCA AAC GTG AAA TG-3' |
|        |      | R 5'-CTG CGA TAA AGA GCG AA-3' |
|        | 4B   | F 5'-AGC CAA AGC CAT TGA AAA GA-3' |
|        |      | R 5'-GCC TCC TCT CCA GTA ACA AT-3' |
|        |      | F 5'-TTG CTT GAT TTT CTT TCC CC-3' |
|        |      | F 5'-ATT CTT ATT GCT CGG AAG CG-3' |
|        | 5    | F 5'-ATC TTG GAT CGG TCC AGC TC-3' |
|        |      | R 5'-ATT CTT ATT GCT CGG AAG CG-3' |
|        | 6    | F 5'-TCA TTT ACC TGG TCA AAC ATC ACC-3' |
|        |      | R 5'-TCT TAA ATT GCT CGG AAG CG-3' |
|        | 7    | F 5'-GGG ATA ATA TTG GCA GAA AA-3' |
|        |      | R 5'-AAG CCT TTT CCC AAC TCC AT-3' |
|        | 8    | F 5'-AGA ATG TTG AAT GGG CAT GGG-3' |
|        |      | R 5'-TTC GCC CAC TCT TCT CCT AT-3' |
|        | 9    | F 5'-CAG CTC GGG TTC GAG ATG-3' |
|        |      | R 5'-TTC CTC CTA GGA GCC AAA AA-3' |
|        | 10   | F 5'-GCT ATG TTC TCT TTC TGG TC-3' |
|        |      | R 5'-AAC AGA GGA GGA GCG ATG-3' |
| MYH8   | 1    | F 5'-CAA TTG AAC CCT CAC AGA TGC TGC-3' |
|        |      | R 5'-TGTC TGG AGG ACA ACA AGT TCA TG-3' |
|        | 2    | F 5'-ATT ACT GGT GGG GCT GAA CA-3' |
|        |      | R 5'-GTTC GCT GTA TGC CAG ATG-3' |
|        | 3    | F 5'-TGG GGT GCT GAA CCA ACT AC-3' |
|        |      | R 5'-GAG AAT TTA GTC TAC AAG GGA TG-3' |
|        | 4    | F 5'-GTC TTC TGC CCA CAG CAA GA-3' |
|        |      | R 5'-ATG GTT TTC CCA GTC TTT TG-3' |
|        | 5    | F 5'-ATG TTG AGA ACC CCA ACA GG-3' |
|        |      | R 5'-TGG TGG AGG ACA ACA AGT TCA TG-3' |
|        | 6    | F 5'-TAT GTC ACC CCC CCA CCT GC-3' |
|        |      | R 5'-TCA ATC GAT CTC TGA ATG TTT TGA A-3' |
|        | 7    | F 5'-TTG ATT GTG ATT TGC GAA GG-3' |
|        |      | R 5'-GCG TGA AAA GTG CCT CAC AA-3' |
|        | 8    | F 5'-GCG AGT TCT CAT TCT CCT CA-3' |
|        |      | R 5'-TTT GCT TGT CCT TGC CGT TG-3' |

PRKAR1A, protein kinase A type I-a regulatory subunit; MYH8, myosin, heavy chain 8, skeletal muscle, perinatal; PDE11A, phosphodiesterase type 11A.

Fig. 5. Genetic analysis finds a novel deletion mutation (c.537delA) in the PRKAR1A gene in exon 6. This results in a frameshift mutation, and introduced a premature stop codon downstream in exon 7.

DISCUSSION

Over 500 patients of diverse ethnicity with CNC from all continents have been registered by the National Institutes of Health (NIH)-Mayo Clinic (USA) and the Cochin Hospital (France), and though this is the largest registry for CNC to date, it does not include patients from a Korean heritage. One case of a sporadic form of CNC in a Korean patient that manifested as a rare psammomatous melanotic schwannoma has been reported, in which molecular studies demonstrated a loss of heterozygosity at the 17q22-24 locus. However, to our knowledge, our case is the first case of CNC in a Korean patient where extensive genetic studies have been performed.

CNC is diagnosed in patients with at least two of the main criteria. In the present case the patient had the characteristics of CNC including skin pigmentation, cardiac myxoma, cutaneous myxoma, breast fibroadenoma, and blue nevus. Cardiac myxomas are the most common noncutaneous lesions occurring in the context of CNC. The mass can occur in multiples with recurrences, and it does not have a predilection for the left atrium though it did occur in the left atrium of the present case.

A study of 353 patients in the CNC consortium found that CNC can be further classified into 3 subgroups based on the PKA R-Ia (PRKAR1A) gene mutation status and the presence of primary pigmented nodular adrenocortical disease (PPNAD). Although CNC shows vast genetic heterogeneity, the disease can be grouped based on phenotype to genotype correlation. According to this subclassification, the carriers of the PRKAR1A mutation were grouped as CNC1, and this phenotype correlated with disease occurrence at a younger age with a higher frequency of myxomas, schwannomas, and thyroid and gonadal tumors than those without the mutation. Based on these crite-
ria, the present case would be classified as CNC type 1 given the PRKAR1A mutation. CNC type 2 shows a strong linkage to the short arm of chromosome 2 (2p16), but is beyond the context of this paper and was not further studied.

The PRKAR1A gene encodes the type IA regulatory subunit of the cAMP-dependent protein kinase, or PKA. To date, a total of 117 different PRKAR1A mutations have been identified (online database: http://prkar1a.nichd.nih.gov) in 387 unrelated families of various ethnic origins. PRKAR1A mutations are spread along the entire coding sequence without predilection for a particular exon, although several ‘hot spots’ for sequence changes have been identified. Not surprisingly, the novel mutation found in our patient occurred in exon 6, which encompasses part of the cAMP functional domain. The previously mentioned CNC consortium also found that although numerous pathogenic variants have been identified, the majority of PRKAR1A defects were premature stop codons generated by nonsense or frameshift mutations. The instability introduced from the premature stop codon leads to nonsense mRNA mediated decay and results in either an absence or reduction in the mutant protein level. Much like the majority of the PRKAR1A mutations that have been identified, the mutation type of the novel mutation found in our case is a premature stop codon. Interestingly, the premature stop codon did not result directly from the amino acid change in exon 6, but rather downstream in exon 7 due to the frameshift change.

However, despite these extensive genetic studies on PRKAR1A, its role in this complex is largely unknown. Given the multiple interactions with major signaling pathways and sometimes opposing effects on cellular functions, PRKAR1A is not a tumor suppressor gene in its classic sense. Thus, the exact role of PRKAR1A in tumorigenesis remains an area for further investigation.

Among the endocrinologic manifestations of CNC, the most common involves the adrenal gland, more specifically in the form of PPNAD. This is a rare cause of Cushing’s syndrome that is pituitary-independent but adrenal-dependent. The genetic mutation culprit linked to PPNAD has been identified as protein-truncating mutations of PDE11A. PDE11A is expressed by zona fasciculata cells in the adrenal cortex that mainly produce cortisol. CNC patients without PPNAD had PDE11A sequence variants not significantly different in frequency from healthy controls. Not surprisingly, our patient did not have PPNAD, but had PDE11A sequence variations that are commonly found in the control group of healthy adults.

Another unique aspect of this case was the indolent perianal mass. Previous case series have failed to establish CNC in patients with superficial angiomyxoma, thus concluding that CNC is only weakly linked to these types of myxomas. Superficial angiomyxomas, also called cutaneous myxomas, that have been previously described in association with CNC were often small (less than 1 cm in diameter) and occurred most commonly in the eyelids, ears, and nipples. Superficial angiomyxomas could range from very small sessile papules to large pedunculated polypoid masses. The present case is noteworthy because the superficial angiomyxoma was large and occurred in the deep internal anal sphincter area, which is an unusual location.

In conclusion, the presence of multiple myxomas and lentigines should be an indication to clinicians to further investigate for the presence of CNC. Numerous advancements in genetic studies have helped identify the PRKAR1A mutation as the culprit. As of now, several hundreds of various genetic mutations in PRKAR1A have been identified including our novel deletion mutation (c.537delA) in exon 6. Despite the numerous genetic mutations identified in recent years, new treatment for the disease remains to be elucidated. Understanding how the diverse mutations converge into a common syndrome of phenotypes may be critical in elucidating a cure.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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