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A Typical Korean Case Of Carney Complex

Hyun Dae Yoon, M.D. and Ho Sang Shon, M.D.

Department of Internal Medicine, Catholic University of Daegu School of Medicine, Daegu, Korea

Carney complex is a multiple neoplasia syndrome, inherited in an autosomal dominant manner, that is characterized by lentigines, cardiac myxoma, and numerous endocrine and other tumors, including primary pigmented nodular adrenocortical disease. Here, we describe a typical case of Carney complex in a 27-year-old female who exhibited spotty skin pigmentation on the lips, oral mucosa, fingers, and toes and several manifestations of Cushing's syndrome due to primary pigmented nodular adrenocortical disease. She also had pituitary adenoma, breast tumor and thyroid nodule. Only a few cases of this disorder have been reported in the Korean literature. All of them, however, had only two components of Carney complex: composed of skin pigmentation and primary pigmented nodular adrenocortical disease. Therefore, the present case seems to be the first true case of Carney complex reported in Korea.

Key Words : Multiple primary neoplasms, Adrenal cortex neoplasm, Cushing syndrome

INTRODUCTION

Carney complex is a very rare multiple neoplasia syndrome with cardiac, endocrine, cutaneous, and neural tumors, as well as a variety of pigmented lesions of the skin and mucosa[1, 2]. Most cases are familial, but sporadic cases have also been reported[1]. Carney complex has also been considered a form of multiple endocrine neoplasia, because Carney complex patients frequently present more than two endocrine tumors[3]. In the Korean literature, however, all of the reported cases had only one endocrine tumor, such as primary pigmented nodular adrenocortical disease (PPNAD)[4, 5]. We report here a case of Carney complex with multiple endocrine tumors.

CASE REPORT

A 27-year-old woman was admitted to evaluate the cause of secondary amenorrhea and recent weight gain. Her menstruation was very irregular and stopped a year ago. She had also gained 10 kg in the last two years. Her past medical history did not show anything significant. On admission, her blood pressure was 150/90 mmHg, pulse rate, 78/min, body temperature, 36.8℃, respiratory rate, 20/min, height 168.8 cm, and body weight was 67 kg. On physical examination, she had a moon face central obesity, and hypertrichosis. She also had many spotty skin and mucosal pigmentation on her lips, oral mucosa, fingers, and toes (Figure 1).

Laboratory studies included WBC 9700/mm^3 with 77% neutrophils and 14.7% lymphocytes and platelet 300×10^3/mm^3. Her liver and renal function test results were normal. Concentrations of Na and K were 144 mEq/L, 4.1 mEq/L, respectively. Blood sugar after fasting was 100 mg/dL, and LH was 2.6 mIU/mL (1.1-7.0), FSH 4.0 mIU/mL (6.3-24), estradiol 24.3 pg/mL (30-400), and testosterone 1.30 ng/mL (0.14-0.76).

Looking at her history and physical examination, we suspected cushing's syndrome. The levels of plasma ACTH and cortisol at 8 AM were 12.38 pg/mL and 27.8 ug/dL. The levels of plasma cortisol at 4 PM and midnight were 26.3 ug/dL and 27.5 ug/dL, respectively. The 24 hour urine-free cortisol was 902 ug/day, and the level of 17-ketosteroid slightly increased, while that of DHEA-S was within normal range. The results of low and high dose dexamethasone suppression test were shown in Table 1. The 24 hour urine-free cortisol excretion was not suppressed by the low and high dose dexamethasone suppression test. Abdominal CT scan was done under the impression of adrenal Cushing's syndrome. A 2.3×1.7 cm-sized well defined homogenous mass was seen in the left adrenal gland (Figure 2). However, at this time, we could not explain her skin pigmentation.

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• Correspondence to : Hyun Dae Yoon, M.D., Department of Internal Medicine, Catholic University of Daegu, 3056-6, Daemyeong 4-dong, Daegu, 705-718, Korea Tel : 82-53-650-4026, Fax : 82-53-651-4009, E-mail : hdyoon@cu.ac.kr

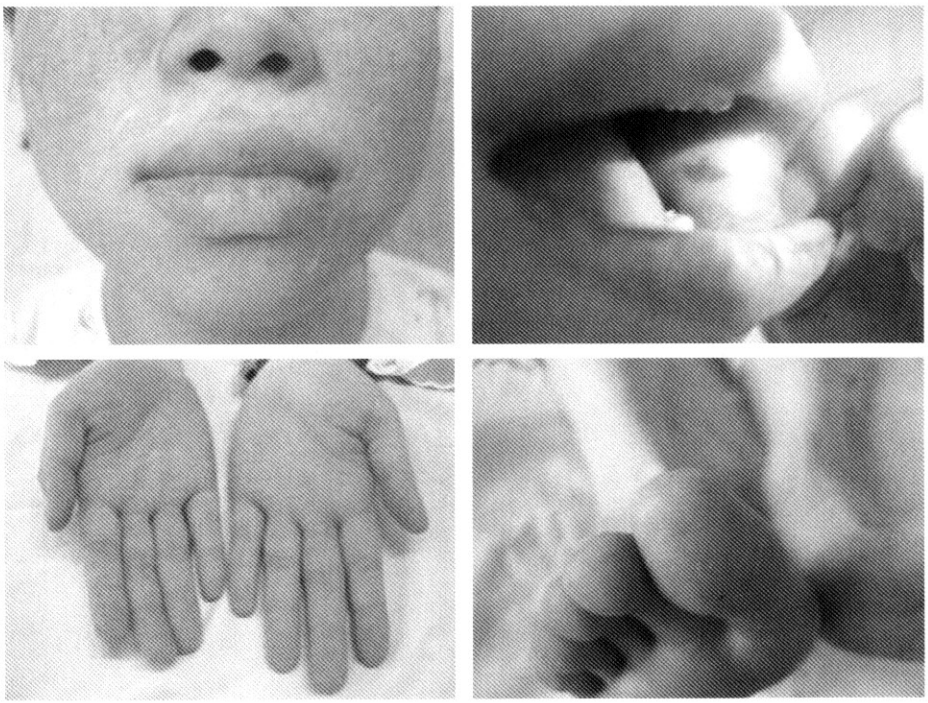

Figure 1. Pigmented skin and mucosal spots on the lips, oral mucosa, fingers and toes.

Table 1. low and high dose dexamethasone suppression test

	baseline	low dose	high dose
serum cortisol (7-21 ug/dL)	27.8	24.5	23.8
24 hr urine free cortisol (20-90 ug/day)	902	547.2	572
24 hr urine 17-OHCS (2.4-6.4 mg/day)		11.39	10.34

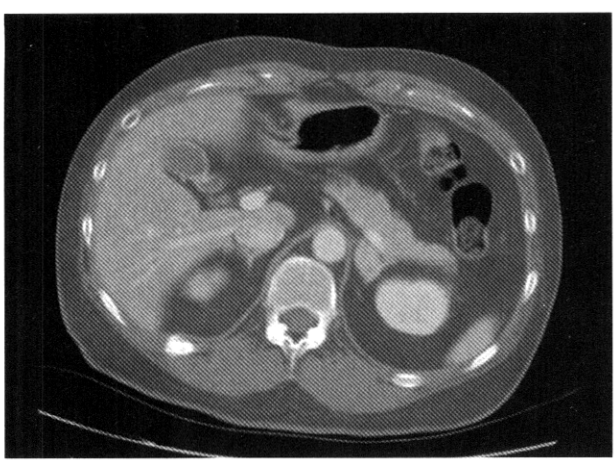

Figure 2. Adrenal CT shows 2.3×1.7 cm sized well defined homogenous mass in the left adrenal gland.

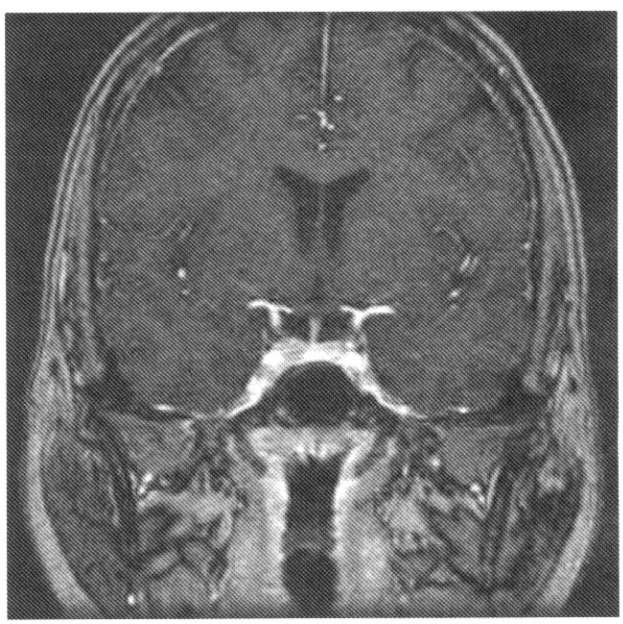

Figure 3. Magnetic resonance imaging shows focal low signal intensity lesion in right inferior portion of pituitary gland.

Although the abdominal CT scan findings were not typical of PPNAD, echocardiography was performed to search for cardiac myxoma, so that Carney complex could be excluded since right adrenal gland atrophy was not identified. However, the result turned out negative, prompting us to perform

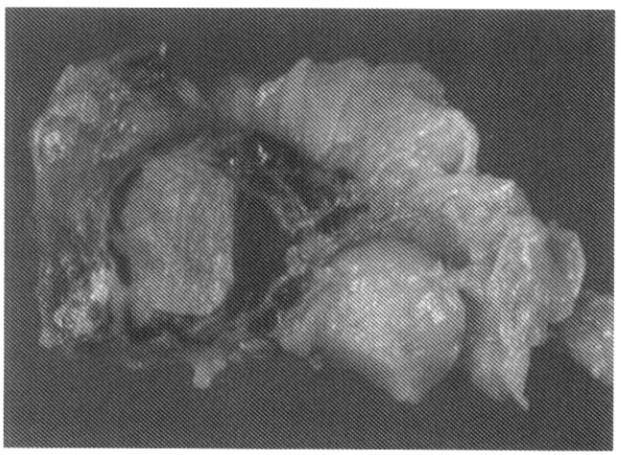

Figure 4. The cut surface of surgical specimen shows golden yellowish colored dominant nodule with multiple black pigmented small nodules.

pituitary fossa MRI to exclude the diagnosis of adrenal nodular hyperplasia due to pituitary Cushing's disease. We also measured the cathecholamine metabolites to exclude ectopic Cushing's syndrome due to pheochromocytoma. The levels of vanylmandelic acid and metanephrine had not increased. However, there was a microadenoma in the inferior portion of the right pituitary gland (Figure 3). At that time, baseline levels of all pituitary hormones were found to be within normal range (growth hormone: 0.63 ng/mL, prolactin: 15 ng/mL, TSH 0.94 uIU/mL, free T4 1.0 ng/dL). Jugular vein ACTH sampling was performed to rule out pituitary Cushing's disease, but the ACTH level of the right jugular vein did not increase at twice the level of the peripheral vein (right jugular vein: 28.16 pg/mL, peripheral vein: 17.37 pg/mL). We planned to resect the left adrenal gland only because abdominal CT findings and echocardiographic findings were not typical of

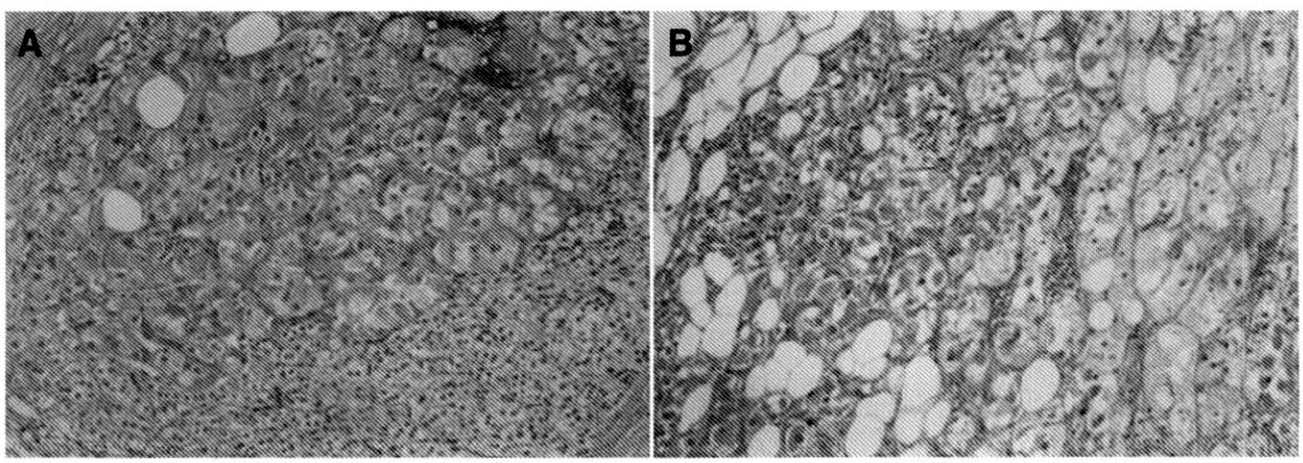

Figure 5. Microscopic finding shows cortical nodules composed of eosinophilic cells containing large bizzare nuclei and abundant acidophilic cytoplasm. The nodules are circumscribed but not encapsulated (A). Extracapsular nodules are noted at periadrenal fat. Abundant lipofuscin pigments are noted at tumor cytoplasma (B), (H&E stain, ×200).

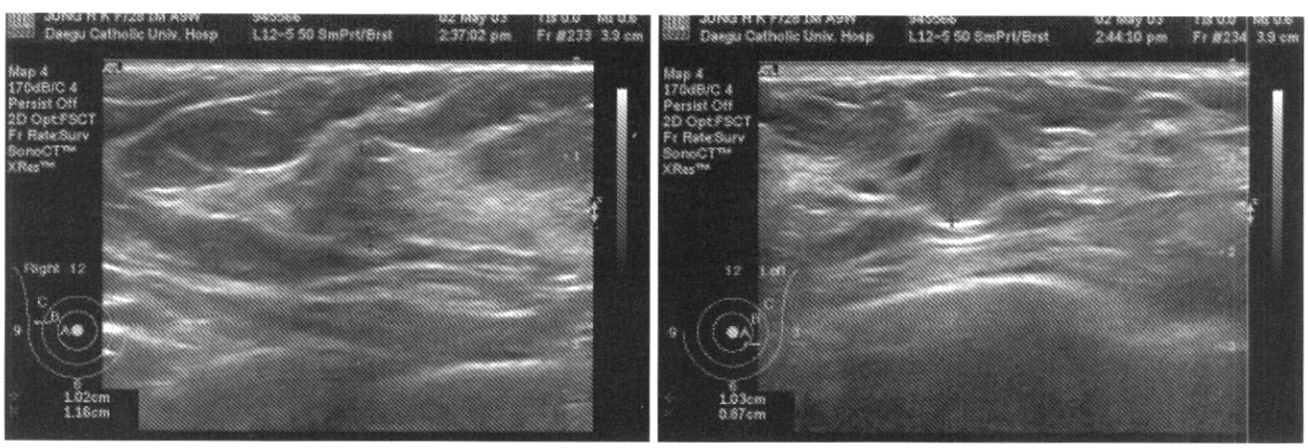

Figure 6. The ultrasonographic finding of breast shows multiple benign appearing hypoechoic masses in both breasts.

Table 2. 75 g oral glucose tolerance test

	glucose (mg/dL)	Growth hormone (ng/mL)
baseline	86	1.13
30min	111	0.45
60min	79	7.51
90min	132	10.94
120min	147	3.45

PPNAD, and because pituitary Cushing's disease was not definitively ruled out by inferior petrosal sinus sampling. Left adrenalectomy was performed, and the cut surface of the surgical specimen showed a golden yellowish colored dominant nodule with multiple black pigmented small nodules (Figure 4). On microscopic findings, variable multiple cortical nodules were noted and extracapsular nodules were also noted at periadrenal fat and abundant lipofuscin pigments were noted at the tumor cytoplasm (Figure 5). We concluded that Cushing's syndrome resulted from PPNAD and further studied whether she had other components of Carney complex. She mentioned that her father and grandmother also had the same skin pigmentation on the lips and oral mucosa, but we did not perform studies on her family. The 75 g oral glucose tolerance test and the measurement of IGF-1 were performed to exclude growth hormone secreting pituitary adenoma. The level of IGF-1 increased (721.6 ng/mL), but the level of growth hormone was suppressed during the oral glucose tolerance test (Table 2). Ultrasonography of the thyroid showed a 0.3 cm sized hypoechoic nodule at the right thyroid, while ultrasonography of the breasts showed multiple hypoechoic masses on both breasts (Figure 6). However, the patient refused breast biopsy. We concluded with a final diagnosis of Carney complex including spotty skin pigmentation, Cushing's syndrome due to PPNAD, nonfunctioning pituitary adenoma, and other suggestive findings such as breast and thyroid masses. After operation, the levels of plasma cortisol and 24 hour urine-free cortisol were normalized. However, 6 months after operation, 24- hour urine-free cortisol increased slightly (129.6 ug/day), causing us to consider resecting the contralateral adrenal gland.

DISCUSSION

Carney complex, discovered in 1985, is a multiple neoplasia syndrome that is inherited in an autosomal dominant manner that is composed of cardiac, endocrine, cutaneous, and neural tumors, as well as a variety of pigmented lesions of the skin and mucosa[1, 2]. It may be viewed as a form of multiple endocrine neoplasia, because affected patients often have tumors in two or more endocrine glands, including PPNAD, growth hormone and prolactin- producing pituitary adenoma, testicular neoplasm, thyroid adenoma or carcinoma, and ovarian cysts[3, 6]. Most cases are familial and the median age at detection is 20[1]. The major clinical manifestations of Carney complex are spotty skin pigmentation, heart myxoma, skin myxoma, PPNAD, large cell calcifying sertoli cell tumor (LCCSCT), acromegaly, psammomatous melanotic schwannoma (PMS), thyroid nodules or cancer and breast ductal adenoma. The diagnostic criteria for Carney complex have been recently reviewed[1] (Table 3).

Table 3. Diagnostic criteria for Carney complex

1. spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)
2. myxoma (cutaneous and mucosal)
3. cardiac myxoma
4. Breast myxomatosis or fat suppressed magnetic resonance imaging findings suggestive of this diagnosis.
5. PPNAD or paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle's test
6. Acromegaly due to GH-producing adenoma
7. LCCSCT or characteristic calcification on testicular ultrasonography
8. Thyroid carcinoma or multiple, hypoechoic nodules on thyroid ultrasonography, in a young patient
9. Psammomatous melanotic schwannoma
10. Blue nevus, epithelioid blue nevus (multiple)
11. Breast ductal adenoma (multiple)
12. Osteochondromyxoma

Supplemental criteria:

1. Affected first-degree relative
2. Inactivating mutation of the PRKAR1A gene

To make a diagnosis of Carney complex, a patient must either: 1) exhibit two of the manifestations of the disease listed, or 2) exhibit one of the manifestations and meet one of the supplemental criteria.

Lentigines and blue nevi observed in faces, eyelids, ears, and lips are the most frequent sign of the complex. They were observed in half of the patients before the evolution of the other components[7]. After the pigmented skin lesions, cardiac myxomas are the most common component of Carney complex. They are often multiple, occur in all heart chambers, have no predilection for a particular gender or age group, and recur quite frequently[7]. Classic sites for skin myxomas included the eyelid, external ear canal, breasts, and the genital areas[8].

Among the endocrine tumors, PPNAD was the most frequent manifestation of the disease, occurring in about one quarter of the patients[9]. In our case, we had many difficulties in finding the cause of Cushing's syndrome. According to

hormonal studies and abdominal CT findings, we suspected adrenal Cushing's syndrome. However, we could not explain her skin pigmentation with adrenal Cushing's syndrome. Although we suspected PPNAD, abdominal CT finding and echocardiographic finding were not typical of PPNAD, as CT scanning of adrenal glands in PPNAD generally shows normal or slightly enlarged glands without evidence of mass[10]. We also performed gastrointestinal endoscopy to search for gastrointestinal tumors so that we could rule out other systemic disease accompanied by hyperpigmentation, such as Peutz-Jeghers syndrome. However, all our results were negative while, surprisingly, pituitary microadenoma was detected, causing us a lot of confusion. The possibility of pituitary Cushing's disease as a cause of her Cushing's syndrome was low since the ACTH level of the right jugular vein did not increased twice as much as that of the peripheral vein. Nonetheless, we could not rule out pituitary Cushing's disease because the inferior petrosal sinus sampling was not performed due to technical reasons, and also since the sensitivity of jugular vein sampling without CRH administration in diagnosing pituitary Cushing's disease was low[11]. We could not definitively exclude the possibility of pituitary Cushing's disease until the typical findings for PPNAD, without any evidence of adrenal cortical hypertrophy, were found microscopically. In general, the biochemical findings of PPNAD include 1) no suppression of urinary corticosteroid excretion after high dose dexamethasone test 2) no response to metyrapone or ACTH administration and 3) undectable, low, or normal plasma levels of ACTH[5]. The characteristic pathological features of PPNAD include 1) decreased, normal, or slightly enlarged adrenal glands 2) multiple small-sized (<4 mm) unencapsulated pigmented cortical nodules and 3) atrophy of the internodular cortex (this distinguishes these glands from the nodular hyperplasia of pituitary dependent Cushing's disease, in which the cortical tissue between the nodules is hyperplasitc)[12]. However, Travis et al[12], as in our case, described a very unusual pathologic finding of PPNAD: macronodules of up to 3 cm. Since bilateral adrenalectomy is warranted as a treatment, recognition of PPNAD before operation is very important. However, it was very difficult to have a clear preoperation diagnosis in our case. As shown in our case, extracapsular nodules are commonly seen in PPNAD[12], which initially cause confusion for pathologists in differentiating PPNAD with adrenal carcinoma.

Among male Carney complex patients, LCCSCT is the most common endocrine abnormality, LCCSCT is almost always benign and only rarely is this tumor is associated with aromatization, gynecomastia and precocious puberty[13]. Clinically evident acromegaly is a relatively infrequent manifestation. However, asymptomatic elevation of GH and IGF-I levels, as well as subtle hyperprolactinemia, may be present in up to 75% of the patients[14]. In our case, although 75 g OGTT was negative, we are following the patient up for the possible development of growth hormone secreting pituitary adenoma.

Female patients with Carney complex often have multiple breast masses with variable imaging appearances that probably represent myxoid fibroadenomas or ductal adenomas. These lesions all demonstrate benign characteristics and should not prompt multiple biopsies[15]. However, we could not confirm the histologic diagnosis of breast mass because the patient refused biopsy.

Thyroid gland abnormalities, mostly benign non hormone-secreting follicular adenomas, were found in over two-thirds of patients. Papillary and follicular carcinoma also may occur[16]. Additional unusual manifestations include psammomatous melanotic schwannoma, breast ductal adenoma, and osteochondromyxoma (a rare bone tumor). The most common cause of death in Carney complex is heart-related disease[1].

Recently, two genetic loci have been identified for Carney complex, on chromosome 2 in band p16 and chromosome 17 in bands q22-24. This second locus contains the gene encoding the regulatory subunit of the protein kinase A (PRKAR1A), which has been shown to be mutated in almost half of the Carney complex patients. PRKAR1A acts as a classic tumor suppressor gene[9]. Testing for PRKAR1A mutation is not recommended at present for patients with Carney complex, but may be advised for detection of affected patients in families with known mutations of this gene, so that unnecessary medical surveillance of noncarriers can be avoided[1]. For established Carney complex patients, the following studies are generally recommended on a yearly basis, echocardiogram, urinary free cortisol, serum IGF-1 levels, testicular ultrasonography in male patients; thyroid and pelvic ultrasonography and breast imaging in female patients[1].

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