【 CASE REPORT 】

Carney Complex Complicated with Primary Pigmented Nodular Adrenocortical Disease without Cushing's Syndrome Recurrence for Five Years after Unilateral Adrenalectomy

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Abstract:
We herein report a case of Carney complex (CNC) complicated with primary pigmented nodular adreno-cortical disease (PPNAD) after unilateral adrenalectomy. A 44-year-old woman was admitted to our hospital for PPNAD surgery. She had previously undergone surgery for cardiac myxoma and had a *PRKAR1A* mutation with no family history of CNC. She had Cushing's signs, but her metabolic abnormalities were mild. Adrenal insufficiency due to poor medication adherence was a concern, so she underwent unilateral adrenalectomy. Cushing's signs improved postoperatively and without recurrence for five years. Treatment plans for PPNAD should be determined based on the patient's condition, medication adherence, and wishes.

Key words: Carney complex, primary pigmented nodular adrenocortical disease, unilateral adrenalectomy, Cushing's syndrome

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Introduction

Carney complex (CNC) is a syndrome characterized by benign tumors and is associated with skin pigmentation, myxomas inside and outside the heart, and endocrine disorders. CNC is an autosomal dominant genetic disorder with mutations in the *PRKAR1A* gene that encodes the regulatory subunit type 1A of cyclic adenosine monophosphate-dependent protein kinase (1). While CNC is a rare disease, its early diagnosis and treatment are important, as it leads to serious and occasionally fatal complications, such as cardiac myxoma (2).

Primary pigmented nodular adrenocortical disease (PPNAD) is a complication of CNC (3). It is characterized by nodular hyperplasia of the adrenal cortex and hyperpigmentation of each nodule due to the accumulation of lipofuscin. PPNAD causes Cushing's syndrome due to hypercortisolism and leads to various disorders, including metabolic abnormalities and osteoporosis. Because PPNAD is usually a bilateral disease, bilateral adrenalectomy is needed to cure hypercortisolism (4). However, after bilateral adrenalectomy, steroid replacement therapy is mandatory, and a certain number of patients develop adrenal crisis, which is sometimes fatal (5). Therefore, unilateral adrenalectomy may be considered if there is concern about medication adherence and the handling of sick days.

However, there are only a few case reports in the literature of unilateral adrenalectomy for PPNAD (4, 6-10). In particular, very few cases have been described with a detailed clinical postoperative course.

We herein report a case of CNC complicated with PPNAD without recurrence of Cushing's syndrome for five years after unilateral adrenalectomy.
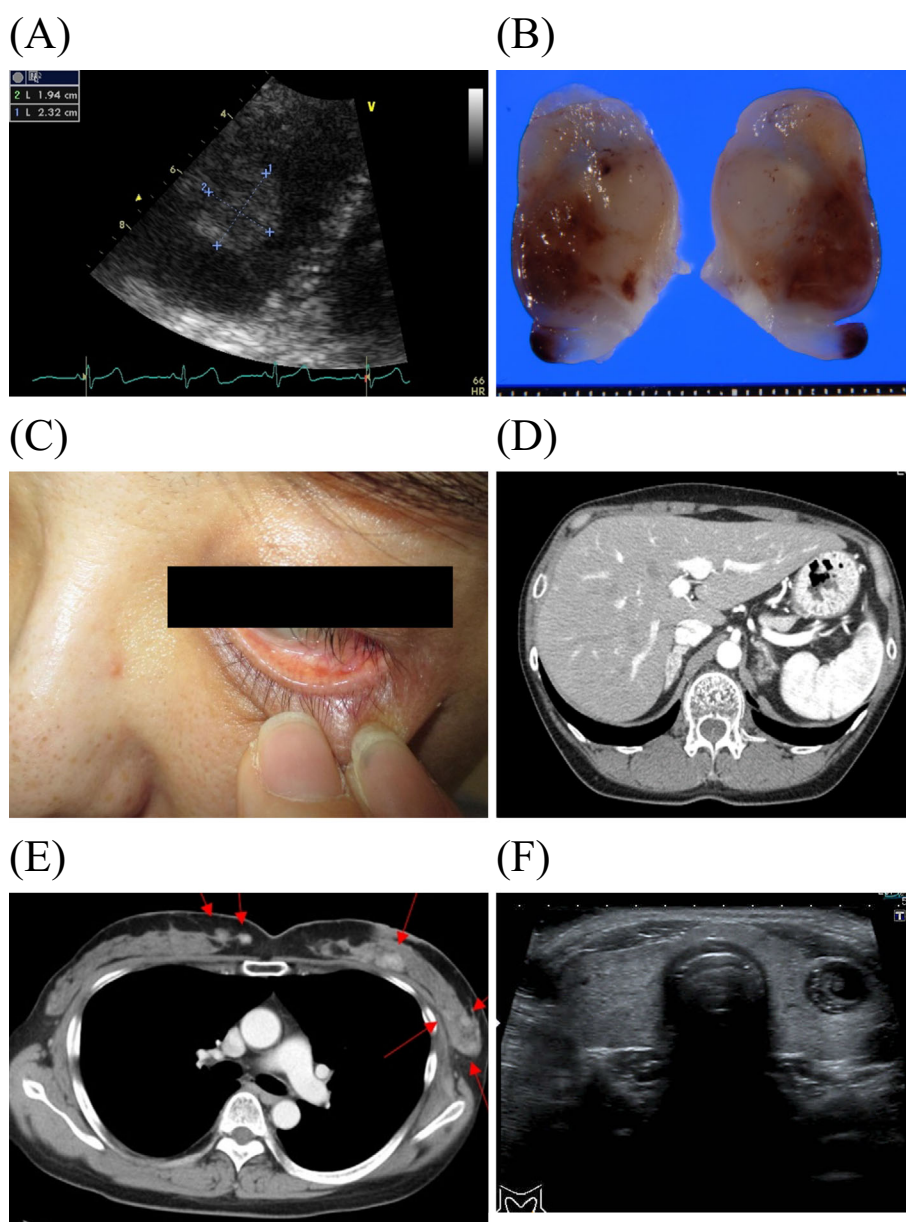
Case Report

A 44-year-old woman was admitted to our hospital for

Figure 1.   Clinical symptoms indicating Carney complex. (A) Cardiac myxoma on echocardiography. (B) Cardiac myxoma specimen. (C) Mass on the left eyelid conjunctiva. (D) Computed tomography image of the adrenal nodule. (E) Breast tumors on computed tomography. The red arrows indicate breast tumors. (F) Thyroid tumor on echocardiography.

PPNAD surgery. She had a history of excised benign skin tumors all over her body since 10 years old. She had been diagnosed with hypertension at 42 years old. At 44 years old, a local doctor discovered a cardiac tumor on an echocardiogram and referred her to a general hospital for surgery. She underwent cardiac surgery, and the pathological diagnosis was cardiac myxoma (Fig. 1A, B). During hospitalization, CNC was suspected because of various findings, such as skin pigmentation, a mass on the left eyelid conjunctiva (Fig. 1C), adrenal (Fig. 1D) and breast tumors (Fig. 1E) on computed tomography (CT), and a thyroid tumor on echography (Fig. 1F). PPNAD was suspected because she had Cushing's signs, such as moon face, a buffalo hump, and subcutaneous hematomas. She was referred to

our hospital, which has significant experience with adrenal diseases, for the diagnosis of Cushing's syndrome and surgery. The patient had no family history of endocrine disorders, and neither her parents nor her children had any obvious symptoms suggestive of CNC. Her two children underwent general laboratory blood and hormonal tests and echocardiography, but no abnormalities were found.

Her consciousness was clear. A physical examination revealed the following findings: body temperature, 36.4 °C; blood pressure, 124/79 mmHg; and pulse rate, 78 beats per minute. She was 158 cm tall and weighed 52.8 kg (body mass index, 21.1 kg/m²). Her abdominal circumference was 70 cm. She had brown pigmentation on her face and a 2-mm mass on the left eyelid conjunctiva. She had Cushing's

Table 1. Laboratory Data on Admission.

Parameter	Value	Unit	Parameter	Value	Unit
WBC	7,800	/μL	T-cho	227	mg/dL
Neutrophil	77.0	%	HDL-C	52	mg/dL
Eosinophil	1.5	%	LDL-C	142	mg/dL
HGB	13.2	g/dL	TGL	162	mg/dL
PLT	27.3	×10⁴/μL	FPG	70	mg/dL
AST	31	U/L	HbA1c	5.4	%
ALT	78	U/L			
ALP	341	U/L	Urinary analysis		
LDH	299	U/L	Blood	(-)	
γ-GTP	24	U/L	Protein	(-)	
BUN	11	mg/dL	Glucose	(-)	
CK	0.67	U/L			
CRE	0.8	mg/dL			
Na	139	mEq/L			
K	3.9	mEq/L			
Cl	104	mEq/L			
Ca	9.3	mg/dL			
P	3.2	mg/dL			
CRP	0.11	mg/dL			

WBC: white blood cell count, HGB: hemoglobin, PLT: platelet, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, γ-GTP: gamma-glutamyl transpeptidase, BUN: blood urea nitrogen, CK: creatine kinase, CRE: creatinine, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, P: phosphorus, CRP: C-reactive protein, T-cho: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TGL: triglycerides, FPG: fasting plasma glucose, HbA1c: glycated hemoglobin

signs, such as moon face, buffalo hump, thinning of the skin, and numerous subcutaneous hematomas. Her heart sounds were regular, and no murmurs were detected. Her thyroid was not palpable, and her abdomen was flat and soft. She took 10 mg of amlodipine for hypertension.

Laboratory data revealed elevated liver enzyme levels and hypertriglyceridemia (Table 1). There were no abnormalities in the blood count, renal function, or electrolyte levels. Fasting blood glucose and HbA1c levels were within normal ranges. An endocrinological examination revealed that adrenocorticotropic hormone (ACTH) secretion was suppressed both in the early morning and late at night, and the circadian cortisol rhythm was disrupted (Table 2). Dehydroepiandrosterone sulfate production was suppressed, and her urinary free cortisol (UFC) level was mildly elevated. An overnight dexamethasone suppression test showed a paradoxical response with rising plasma cortisol levels. Growth hormone (GH) and insulin-like growth factor 1(IGF-1) levels were within normal ranges. The 75-g oral glucose tolerance test showed no suppression of GH secretion and borderline diabetes.

CT showed a 20-mm nodule on the left adrenal gland (Fig. 1D), with no apparent nodule found on the right side. T1-weighted magnetic resonance imaging (MRI) showed a left adrenal nodule with a high signal intensity (Fig. 2A). Adrenal scintigraphy using ^{131}I-adosterol revealed a bilateral adrenal uptake (Fig. 2B). Dual-energy X-ray absorptiometry showed a decreased bone mineral density with young adult

Table 2. Endocrinological Examination Findings.

Parameter	Value	Unit	Parameter	Value	Unit
ACTH (8 am)	<2	pg/mL	Dexamethasone suppression test		
Cortisol (8 am)	19.4	μg/dL	1 mg		
ACTH (23 pm)	<2	pg/mL	ACTH	<2	pg/mL
Cortisol (23 pm)	20.0	μg/dL	Cortisol	18.5	μg/dL
DHEA-S	6.0	μg/dL	8 mg		
PRA	2.9	ng/mL/h	ACTH	<2	pg/mL
PAC	59.0	pg/mL	Cortisol	26.4	μg/dL
TSH	0.29	μIU/mL			
FT4	1.1	ng/dL	75 g OGTT		
GH	1.95	ng/mL	PG at 0 min	87	mg/dL
IGF-1	224	ng/mL	PG at 30 min	135	mg/dL
LH	2.73	mIU/mL	PG at 60 min	172	mg/dL
FSH	12.81	mIU/mL	PG at 120 min	184	mg/dL
PRL	13.89	ng/mL	GH at 0 min	1.21	ng/mL
TRACP-5b	227	mU/dL	GH at 30 min	1.0	ng/mL
Intact PINP	39.1	ng/mL	GH at 60 min	2.42	ng/mL
Urinary free cortisol	111	μg/day	GH at 120 min	1.79	ng/mL

ACTH: adrenocorticotropic hormone, DHEA-S: dehydroepiandrosterone sulfate, PRA: plasma renin activity, PAC: plasma aldosterone concentration, TSH: thyroid-stimulating hormone, FT4: free thyroxine, GH: growth hormone, IGF-1: insulin-like growth factor-1, LH: luteinizing hormone, FSH: follicle-stimulating hormone, PRL: prolactin, TRACP-5b: tartrate resistant acid phosphatase-5b, PINP: N-terminal propeptide of type I procollagen, OGTT: oral glucose tolerance test, PG: plasma glucose
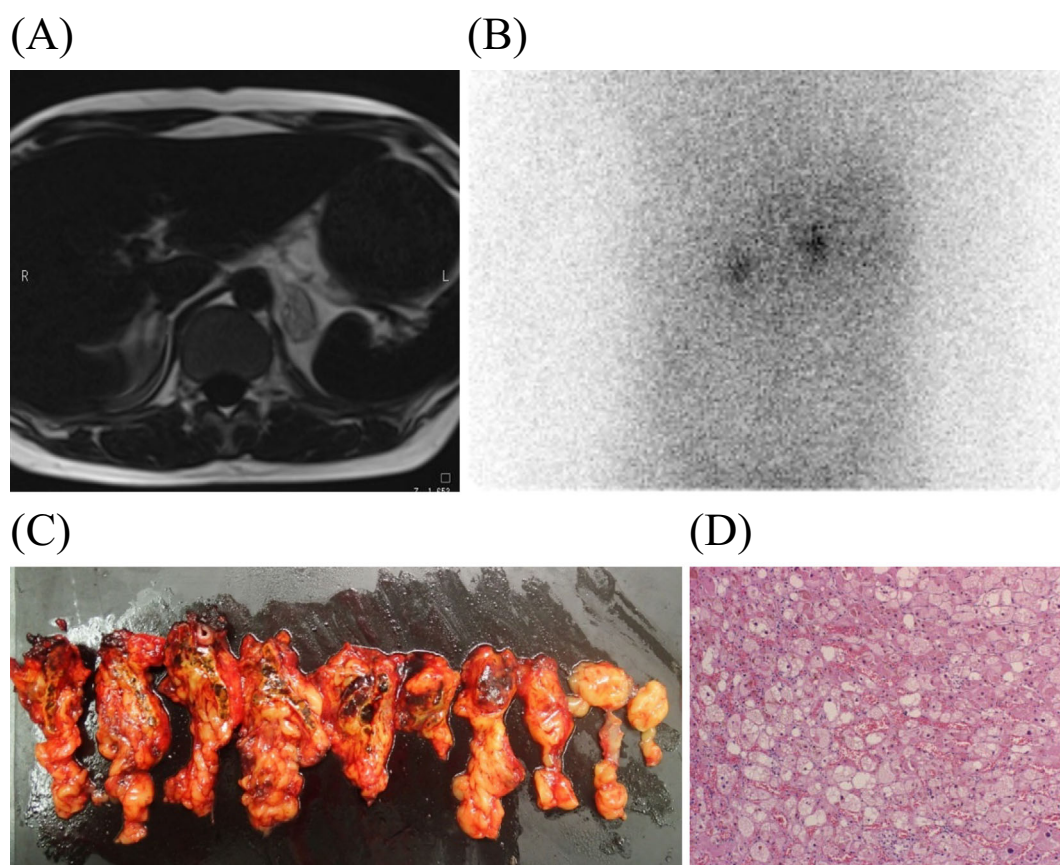
Figure 2. Imaging and pathological findings of primary pigmented nodular adrenocortical disease. (A) Magnetic resonance imaging showing a left adrenal nodule with a high intensity on T1-weighted imaging. (B) ^{131}I-adosterol scintigraphy showing a bilateral adrenal uptake. (C) Surgically removed specimen of the left adrenal nodule. Numerous dark-brown nodular lesions were observed in the atrophic adrenal cortex. (D) Hematoxylin and Eosin staining of the specimens. The nodules were composed of cells with cytoplasm containing brown lipochrome.

mean values of 67% for the femoral neck and 74% for the lumbar vertebrae. Brain MRI showed no tumor in the pituitary gland.

Based on these results, PPNAD was suspected to be the cause of her Cushing's syndrome. Although bilateral total adrenalectomy and steroid replacement therapy were necessary for a complete cure, both the patient and doctors were concerned about this treatment plan because she was unsure about taking oral medication regularly. Given her relatively mild metabolic abnormalities, previous reports that showed long-term improvement of Cushing's signs with unilateral adrenalectomy (9), and the patient's wishes, laparoscopic total left adrenalectomy was performed (Fig. 2C).

Although the ^{131}I-adosterol uptake was comparable in the left and right adrenal glands, we chose to perform total adrenalectomy for the left adrenal gland, given that the adrenal nodule was found only on the left side and considering a previous report (6). Numerous dark-brown nodular lesions were found in the atrophic adrenal cortex, which confirmed the diagnosis of PPNAD. A microscopic examination showed that the nodules were composed of cells with cytoplasm containing brown lipochrome (Fig. 2D). Postoperatively, she received steroid replacement therapy, which was

tapered off, and no symptoms of adrenal insufficiency occurred. With the patient's written consent, we searched for *PRKAR1A* mutations in the peripheral blood and adrenal tissue and found the c.491_492delTG mutation (p.Val164fsX4) in both samples.

After surgery, a prescription for a small dose of metyrapone (500 mg/day 250 mg after lunch and 250 mg before sleeping) was started. Her UFC levels had decreased by about 25% at 1 year after surgery (Table 3). Her Cushing's signs, such as moon face, buffalo hump, thinning of the skin, and extensive subcutaneous hemorrhaging, were markedly improved and have not recurred to date (Fig. 3). No elevation of her serum cortisol level, suppression of ACTH secretion, or metabolic abnormalities have since been observed, and her bone mineral density has been increasing with a course of oral bisphosphonates (Table 3). The right adrenal gland has shown no marked change on imaging. The prescription of metyrapone has been continued with the same dosage and timing as started, since her condition is stable and she feels fatigued when the dose is increased. Although GH was not suppressed during the oral glucose tolerance test (OGTT), we considered the onset of acromegaly to be negative because of the normal range of IGF-1 levels

Table 3. Clinical Course before and after Unilateral Adrenalectomy.

	Before Surgery	12 Months	24 Months	36 Months	48 Months	60 Months
Body weight (kg)	52.8	50.0	52.0	52.6	53.5	51.0
ACTH (pg/mL)	<1.0	<1.0	2.1	12.5	4.6	12.8
Cortisol (μg/dL)	19.4	8.3	9.9	5.5	11.3	8.5
Cortisol 23:00 (μg/dL)	20	55		3.2		
Urinary free cortisol (μg/day)	111	25.3		18.2		
ALT (U/L)	78	18	15	16	15	15
TGL (mg/dL)	162	70	134	112	112	75
HDL-C (mg/dL)	52	57	46	48	63	61
LDL-C (mg/dL)	142	120	118	98	102	137
HbA1c (%)	5.4	5.4	5.6	5.3	5.3	5.4
Femoral neck BMD (%YAM)	67		69	71		71
Lumbar BMD (%YAM)	74		92	99		100

ACTH: adrenocorticotropic hormone, ALT: alanine aminotransferase, TGL: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, HbA1c: glycated hemoglobin, BMD: bone mineral density, YAM: young adult mean

(A)

(B)

(C)
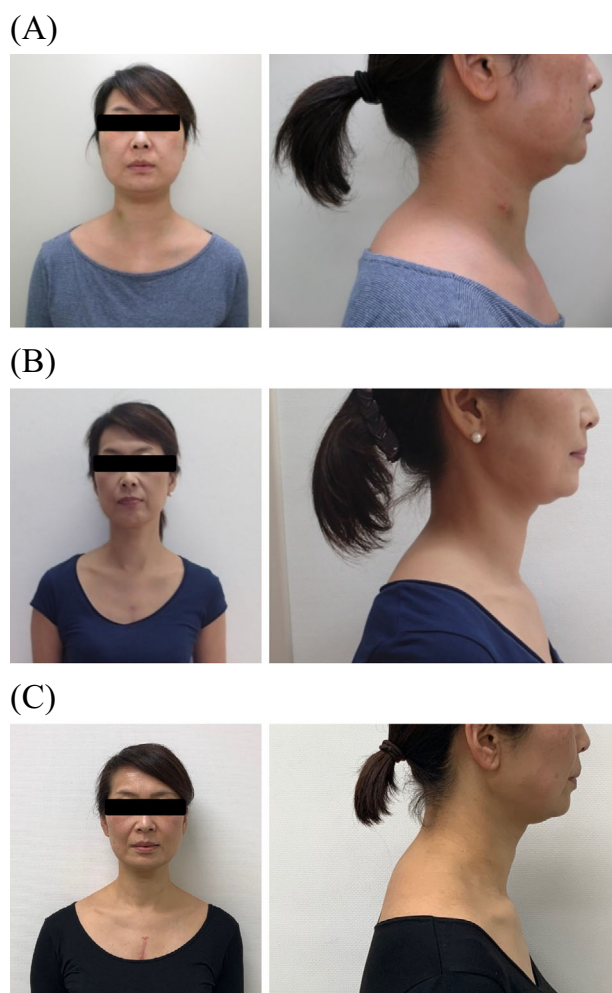
Figure 3. Longitudinal changes in Cushing's sign. (A) Before surgery. The patient had a moon face and a buffalo hump. (B) Twelve months after surgery, her Cushing's signs had disappeared. (C) Sixty months after surgery, her Cushing's signs have not recurred.

and the absence of acromegaly symptoms and pituitary tumors on imaging. During follow-up, there has been no increase in her IGF-1 level nor symptoms of acromegaly. Her mammary tumors and goiter were followed by specialists, but no malignancies were found. The patient provided her written informed consent for this case report.

Discussion

We herein report a case of unilateral adrenalectomy for PPNAD secondary to CNC. There has been no obvious recurrence of Cushing's syndrome in the five years since surgery.

Ninety percent of PPNAD occurs as a complication of CNC [11], and 25% of CNC patients have PPNAD [12]. PPNAD causes Cushing's syndrome, which is characterized by the presence of various disorders, such as glucose intolerance, dyslipidemia, hypertension, osteoporosis, and susceptibility to infection. As PPNAD is a bilateral disease, bilateral adrenalectomy is the necessary curative treatment [4]. However, after bilateral adrenalectomy is performed, the body no longer produces glucocorticoids and mineralocorticoids, and replacement therapy with oral medication is necessary. Patients with a poor understanding of replacement therapy are at risk of developing adrenal insufficiency [13, 14]. In our case, the patient had been prescribed antihypertensive medication prior to admission, but she sometimes forgot to take the medication. The patient was aware of this issue and thus did not feel confident in remembering to take her medication every day after surgery. Therefore, we recommended unilateral adrenalectomy and informed the patient of the possibility of residual Cushing's syndrome after surgery.

According to previous reports and to the best of our knowledge, 26 cases of unilateral or partial adrenalectomy for PPNAD have been reported (Table 4) [4, 6-10]. Although the postoperative follow-up period has varied and

Table 4.   Reported Cases of Unilateral or Partial Bilateral Adrenalectomy for Primary Pigmented Nodular Adrenocortical Disease.

Reference number	Number of patients	Mean follow-up (Range, Months)	Number of recurrence
4	3	80 (12-384)	3 (one underwent contralateral adrenalectomy)
6	13	47 (16-113)	1 (contralateral adrenalectomy after 2 mo)
7	1	9	No
8	1	9	No
9	6	120 (12-792)	3 (three underwent contralateral adrenalectomy after 3, 10, and 25 y)
10	2	24 (18-36)	No

cases are thus not uniformly comparable, recurrence was observed in seven cases, and contralateral adrenalectomy was required in five cases. Since the degree of cortisol excess and metabolic abnormalities in these cases are not clear from the literature, it is difficult to determine in which cases unilateral adrenalectomy would be appropriate as the first choice. In our case, the metabolic abnormalities were not considered severe because although the patient had borderline diabetes, she did not require treatment with medication. Thus far, no recurrence of Cushing's syndrome has been observed with the use of a small amount of metyrapone. However, since there are reports of patients requiring surgery on the opposite side more than 10 years after undergoing surgery (9), we need to continue to carefully observe the progress of the disease in our patient.

Although CNC is an autosomal dominant genetic disorder, 30% to 50% are reportedly solitary cases (3, 15). The c.491_492delTG pathogenic variant, which was detected in this case, was confirmed to be *de novo* and likely represented "hot spots" (1). Our patient had had a history of skin tumors throughout her body since her teenage years that were repeatedly removed, but CNC was never suspected. Although she had been experiencing changes in her body shape for two years prior to her visit, she considered this to be due to aging. In the present case, cardiac myxoma presented the opportunity for the discovery of CNC. If left untreated, cardiac myxoma can cause embolism and sudden death (2, 16). For the early detection of CNC, the disease needs to be widely recognized among general clinicians, allowing the existence of isolated cases to be identified. It should also be recognized that various endocrinological phenotypes can exist in CNC, even within the same family, due to the presence of gene modifiers and other factors, such as nonsense-mediated messenger ribonucleic acid decay (17-19).

In conclusion, we encountered a case of unilateral adrenalectomy for CNC complicated with PPNAD without recurrence of Cushing's syndrome for five years after surgery. Although PPNAD is a bilateral disease, the treatment plan should be determined with due consideration of the degree of cortisol excess, the degree of metabolic abnormalities, medication adherence, and the patient's wishes. Further studies are needed to determine which patients are suited for unilateral adrenalectomy as the first choice for treatment.

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